Intermittent vs. Continuous Pulse Oximetry in Infants Hospitalized for Bronchiolitis: A Randomized Controlled Trial

Supplement 1 Protocol Documents

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3. Statistical Analysis Plan Final with summary of changes (page 25)

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Trial registration: Registered at www.clinicaltrials.gov NCT02947204

Protocol version: December 5, 2019

Funding: This study is funded through a peer reviewed grant from the Canadian Institutes of Health Research (CIHR). The funders have no role in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

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Summary

BACKGROUND This research protocol focuses on bronchiolitis, a leading cause of infant hospitalization and cumulative expense for the health care system. Supportive management, such as oxygen supplementation and monitoring, is the major focus of care, as active medical treatment is not effective. Oxygen saturation monitoring may be performed on an *intermittent* (e.g. every 4-6hrs) or *continuous* basis for stable infants hospitalized with bronchiolitis. Observational studies find that the use of *continuous* monitoring is associated with overuse of supplemental oxygen and longer hospital stay. Based on this low quality evidence, practice guidelines state that clinicians may choose not to use continuous monitoring and practice variation exists due to a lack of RCTs.

SPECIFIC AIMS Primary: To determine if *intermittent* vs *continuous* oxygen saturation monitoring will reduce length of hospital stay in infants with bronchiolitis. Secondary: To determine differences in other outcomes - effectiveness, safety, acceptability, and cost.

METHODOLOGY

Design: multi-centre, pragmatic, parallel group, 1:1, two arm superiority RCT.

Population: Previously healthy infants (4 weeks-2 years) hospitalized with bronchiolitis who are clinically stable, will be recruited from 6 hospitals – 3 children's hospitals (SickKids, Children's Hospital of Eastern Ontario, McMaster Children's) and 3 community hospitals (North York General Hospital, Trillium Health Partners, Credit Valley Site, Lakeridge Health).

Interventions: Randomization to *intermittent* (every 4hrs) or *continuous* oxygen saturation monitoring. In keeping with local clinical practice guidelines, CPS and AAP guidelines, an acceptable oxygen saturation target of ≥90% will be used for both groups.

Outcome: Primary: time from randomization to hospital discharge. Secondary: duration of oxygen supplementation, number of medical interventions, parent anxiety, parental days missed from work, nursing satisfaction, ICU admissions, unscheduled return to care within 15 days of discharge, mortality and cost-effectiveness.

Sample Size: 210 (105 per group) will provide the power to detect a 12-hour difference in median length of stay between groups.

Analysis: Wilcoxon rank-sum test will compare the median length of stay between groups.

EXPECTED OUTCOMES This pragmatic RCT will inform the ideal oxygen monitoring strategy, improve quality of care, reduce inappropriate care and reduce the burden to families.

BACKGROUND

Bronchiolitis definition, epidemiology, burden of disease: Bronchiolitis is an acute lower respiratory tract infection that affects infants and young children less than 2 years of age resulting in a viral upper respiratory prodrome followed by tachypnea, chest retractions, and diffuse crackles, wheeze, or both. [1] Pathologically it is characterized by small airways inflammation and edema. Bronchiolitis is caused by infection with seasonal viruses, most commonly respiratory syncytial virus (RSV). [2] This acute viral illness is self-limited, however infants may experience significant distress during the illness due to cough, fast and laboured breathing, irritability and feeding difficulties.[3]

Epidemiologic studies have shown that bronchiolitis is common, associated primarily with short term morbidity, high health care resource utilization and low mortality.[1, 4] About one third of infants less than 2 years develop bronchiolitis, and of these, one in ten require hospitalization. [1, 5] It is the most common lower respiratory tract infection in infants and, in developed countries, it is a leading cause of infant hospitalization. Risk factors associated with bronchiolitis-related morbidity and hospitalizations include premature birth (< 36 weeks gestation), pre-existing cardio-respiratory disease, neurologic disease, immunosuppression, and younger age (< 6 weeks old). [6] Of all infants hospitalized with bronchiolitis, approximately 3% will require pediatric intensive care unit (PICU) admission, and, of those without risk factors, less than 1% will require PICU admission.[7,8] In-hospital mortality is very low, estimated at 0.03% in all infants hospitalized with bronchiolitis and 0.01% in those without risk factors. *Thus, poor outcomes in otherwise healthy infants hospitalized for bronchiolitis are very uncommon.*

Bronchiolitis hospital inpatient management: Management of bronchiolitis includes both *active medical treatment* and *supportive management*. Clinical practice guidelines (CPG) from the American Academy of Pediatrics (AAP) and Canadian Pediatric Society (CPS) for the diagnosis and treatment of bronchiolitis were published in 2014.[1,12] Recent meta-analyses of the large body of evidence [randomized clinical trials (RCTs)] have shown evidence of minimal effectiveness for a range of *active medical treatments,* specifically drug therapies including steroids and inhaled bronchodilators.[13-17] Thus, the focus of inpatient management is on *supportive management* which includes monitoring vital signs and hemoglobin oxygen saturation, oxygen supplementation for hypoxia, and nutritional and/or fluid supplementation through nasogastric feeds or intravenous fluids for inadequate feeding by mouth.

Local standard of care for inpatient management bronchiolitis: At the proposed study centres, The Hospital for Sick Children (SickKids), the Children's Hospital of Eastern Ontario (CHEO), McMaster Children's Hospital, North York General Hospital (NYGH), Trillium Health Partners, Credit Valley site and Lakeridge Health, Oshawa the recommended management of bronchiolitis is in keeping with these guidelines. Specifically, routine diagnostic studies (i.e. chest x-rays, blood cultures, blood gases, nasopharyngeal swabs for viral identification) and pharmacotherapy (i.e. steroids, scheduled bronchodilators, antibiotics) are not recommended. Standardization of care (local guidelines and/or physician order sets) supporting these practices exists at the study centres (see Appendix 1 Care Map).

Oxygen saturation monitoring: Over the past two decades, noninvasive oxygen saturation (SpO_2) monitoring (called pulse oximetry) has become widely available; it has become common clinical practice to utilize oxygen saturation monitoring in the initial assessment of acutely ill patients.[18] Pulse oximetry measures oxygenation by determining absorbance of infrared light through tissues and thereby estimating the saturation of oxygen in blood.[18,19] A pulse oximetry probe is placed on a patient's finger or toe. The results of pulse oximetry readings are used by

clinicians to determine the need for further investigations, therapies, and supplemental oxygen therapy. For hospitalized patients, oxygen saturation monitoring can be performed using intermittent (e.g. readings obtained for 2 minutes at intervals of 4-6 hours) or continuous (e.g. readings displayed continuously at the patient's bedside monitor) strategies.

Oxygen saturation monitoring was introduced into bronchiolitis care without health technology assessment. For infants with severe acute illness (i.e. ICU admission, severe respiratory distress, apnea) continuous oxygen saturation monitoring is used; however, for infants hospitalized with less severe illness both strategies are used. Common nursing practice includes documenting the oxygen saturation level at routine intervals (for example, every four hours) along with other vital signs (heart rate, respiratory rate, blood pressure and temperature). For this reason, oxygen saturation level has been termed the 'fifth vital sign'.[19] In addition, the nurse may be notified of low oxygen saturation levels through an alarm and/or paging system. Furthermore, the child's parents are able to view the continuous digital display of the oxygen saturation level, and hear the alarms. It is not known whether parents' experiences with continuous oxygen monitoring are associated with reassurance or anxiety.

Normal values for oxygen saturation in infants and children have not been clearly established due to a lack of robust data in infants of all ages.[18] Oxygen saturation levels vary with age and altitude. In healthy infants and children, mean oxygen saturation values at sea level have been reported to be 97-99% (-2SDs, 95-96%) and might be lower in neonates and young infants (range: 93-100%).[18] Furthermore, there is a fluctuation in oxygen saturation during a 24 hour period in children, independent of whether the child is awake or asleep, with maximal values occurring in the late afternoon and minimal values appearing in the first morning hours. A study of healthy infants and children at home has shown normal ranges of oxygen saturation to be between 95-100%.[23] However, normal saturation nadirs can be as low as 84-86%.[20-23]

Establishing 'ideal' oxygen saturation targets has been challenging given the rarity of poor health outcomes associated with too much or too little oxygen in the treatment of healthy stable infants with bronchiolitis; this contrasts from oxygen therapy in other populations. The AAP guideline for bronchiolitis suggests using a target saturation of 90%. A subsequent UK trial, found that management of hospitalized infants with bronchiolitis to a 90% target saturation or higher was as safe and effective as one a 94% target saturation or higher.[24]

Oxygen saturation monitoring and supplementation as a determinant of length of hospitalization: Using a retrospective observational study design, Unger et al. studied 102 infants hospitalized with bronchiolitis and showed that oxygen supplementation is the prime determinant of the length of hospitalization for infants with bronchiolitis, even when other symptoms, such as feeding difficulties have resolved.[25] The mean age of this population was 24 weeks and mean length of stay 72 hours (range: 6 to 371 hours). Continuous oxygen saturation monitoring was used and supplemental oxygen was discontinued when oxygen saturation levels were greater than 93% in room air. At 6 hours of admission, 70% required supplemental oxygen and oxygen supplementation resolved by 180 hours in 98% of cases. The need for oxygen supplementation was the final determinant for hospitalization in 58 patients (57%), and the average lag time, after all other issues had resolved except for oxygen supplementation was 66 hours (2.75 days). Feeding problems were the final determinant in 27 (26%) infants and feeding and oxygen problems resolved simultaneous in 13 (13%) infants.

Shroeder et al. found that in a cohort of 62 infants hospitalized with bronchiolitis on continuous oxygen saturation monitoring, 26% (n=16) continued to be hospitalized only for the purposes of oxygen supplementation after they were feeding well and had no respiratory distress or frequent

need for bronchodilators.[26] Length of stay was prolonged an average of 1.6 days (range 1.1-2.0 days) per hospitalization for these 16 patients.

McCulloh et al. conducted a trial (n=161) comparing intermittent vs. continuous pulse oximetry for nonhypoxemic infants hospitalized for bronchiolitis.[27] All infants were placed on continuous monitoring. Infants randomized to intermittent monitoring were only switched after the infants were nonhypoxemic. Length of stay was measured from the time of admission (not from the time of implementation of the intervention) and did not differ based on the oxygen saturation monitoring strategy (48.9 hours for continuous monitoring vs. 46.2 hours for intermittent monitoring; P=0.77). Several limitations of this trial include: only inclusion of nonhypoxemic infants for intermittent monitoring; an underpowered study (powered to detect an 18-hour difference in LOS); and measurement of the primary outcome before randomization. An expert commentary highlighted the need for further trials, specifically highlighting our pilot RCT which included infants with stable modest hypoxia.[28]

The two small patient based observational studies described above suggest that a significant portion of infants hospitalized with bronchiolitis, stabilized after the initial acute presentation of their illness, are well and ready for discharge except for the need for supplemental oxygen. *This has led experts to hypothesize that the easy availability of <u>continuous</u> oxygen saturation monitoring has led to an overuse of oxygen supplementation, and greater duration of hospitalization for infants with bronchiolitis.*[3,4,25,26,28-31] The one RCT suggests that intermittent oxygen saturation maybe considered in the management of infants who are nonhypoxemic.[27] However, these studies have methodologic limitations and higher quality evidence is needed to determine the best strategy for oxygen saturation monitoring and influence practice change.

The link between oxygen saturation monitoring practice, oxygen supplementation and length of hospital stay: Why would the use of <u>continuous</u> as compared with <u>intermittent</u> oxygen saturation monitoring lead to inappropriate oxygen supplementation and prolonged length of stay in stable infants hospitalized with bronchiolitis? Transient or persistent low oxygen saturation readings during the stable phase of hospitalization can be due to several reasons: (1) false positive detection due to issues such as motion artifacts, poor perfusion, skin pigmentation and probe positioning or (2) true positive detection due to ventilation-perfusion mismatch or a normal finding that healthy infants might otherwise experience (in the situation of transient low oxygen saturation levels).[18] The clinician's response to a false positive detection or a true positive detection that has little clinical consequence is often to institute or increase supplemental oxygen. This, in turn, leads to a period of further observation while receiving the increased supplemental oxygen and then a trial of oxygen supplementation weaning. With the use of <u>continuous</u> as compared with <u>intermittent</u> oxygen saturation monitoring there is a higher chance of detecting and responding to false positive readings and clinically insignificant true positive readings. The use of the <u>continuous</u> monitoring can lead clinicians (and families) to focus on the monitoring devices rather than the clinical assessment.[31] It leads to a cycle of unnecessary intervention based on a clinically insignificant low oxygen saturation reading in an otherwise stable infant. Thus, experts have postulated that the use of <u>continuous</u> oxygen saturation monitoring after clinical stabilization has lead to inappropriate oxygen supplementation and prolonged length of hospitalization.[1,3,4,31] *It is important to emphasize that the clinical context here is of otherwise healthy, stable hospitalized infants*. Even if on <u>intermittent</u> monitoring, these infants receive regular clinical assessments and oxygen saturation monitoring every 4 hours, so that any important change in their clinical status will be detected.

Clinical equipoise around the optimal strategy for oxygen saturation monitoring in stable, otherwise healthy infants with bronchiolitis is evident from the strength of recommendations in national and local practice guidelines, our pilot RCT, and current practice patterns: The recent AAP bronchiolitis guidelines[1] (2014) have recommended "clinicians may choose not to use continuous pulse oximetry for infants and children with a diagnosis of bronchiolitis". The CPS bronchiolitis guidelines (2014) state that "the issue of continuous versus intermittent monitoring of oxygen saturation is controversial. Continuous saturation monitoring may be indicated for high-risk children in the acute phase of illness, and intermittent monitoring or spot checks are appropriate for lower-risk children and patients who are improving clinically".[12] These are graded as 'weak' recommendations based on the few observational studies and expert opinion (evidence level D).

We conducted an internal pilot RCT (n=33) at SickKids comparing intermittent vs. continuous oxygen saturation monitoring in infants hospitalized with bronchiolitis and this received approval from the SickKids research ethics board (REB File No. 1000029983). There were no ethical concerns on the basis of an absence of clinical equipoise. Furthermore, we experienced great enthusiasm from clinicians (nurses and physicians) to refer their patients to the pilot RCT (70% recruitment rate). Nurses and physicians also adhered to the allocated arm (no contamination).

Discussion within the field of Pediatric Hospital Medicine through the CPS, AAP, Pediatric Research in Inpatient Settings network, and the study sites suggests that there is variability in the oxygen monitoring strategy used. Infants are usually started on continuous oxygen saturation monitoring. Some infants are transitioned to intermittent oxygen monitoring when they are clinically stable, however, continuous oxygen saturation is most commonly used throughout the hospital stay despite the rarity of poor outcomes. This is likely related to a practice culture of reliance on technology over clinical assessment. This practice culture is evident from the results of a RCT conducted by two senior investigators from our research team and published in *JAMA* (2014).[32] The RCT found that among infants presenting to an Emergency Department (ED) with mild to moderate bronchiolitis, those with an artificially elevated pulse oximetry reading were less likely to be hospitalized or receive active care than those with unaltered oximetry readings despite the same clinical status. An accompanying editorial stated that 'it is now clear that the oxygen saturation reading can influence decision making in ways that many clinicians have thought likely – overreliance on physiologic information of uncertain importance derived from a medical device".[33] *Well designed pragmatic RCTs that compare intermittent vs. continuous oxygen saturation monitoring in stable, otherwise healthy infants hospitalized with bronchiolitis are needed to close the evidence gap, change culture and effect practice change.*

Alarm fatigue and overdiagnosis with continuous monitoring: Two broad concerns around health care delivery raise further concerns around the use of continuous oxygen saturation monitoring in stable, low-risk infants hospitalized with bronchiolitis. One is a concern of the widespread overuse of physiologic monitoring devices and alarms in hospital care, the resulting alarm fatigue of staff, and the potential to compromise patient safety.[34] Second is a concern around overdiagnosis, the detection of an abnormality that does not benefit the patient, and how it may be harming children. A recent review on overdiagnosis highlighted the detection of clinically insignificant desaturations using continuous oxygen monitoring in bronchiolitis as an example of overdiagnosis in children.[35]

Feasibility of a bronchiolitis oxygen monitoring trial: *We have demonstrated feasibility of a pragmatic RCT comparing intermittent vs. continuous oxygen saturation monitoring in stable*

infants hospitalized with bronchiolitis by successfully conducting an internal pilot RCT with institutional funding (ClinicalTrials.gov NCT01646606). We established study procedures, created data collection and consent forms; obtained SickKids ethics approval; obtained support and input on the protocol from stakeholders (administration, quality improvement leaders, nursing, physicians, respiratory therapy), and presented the proposed work to knowledge users in Canada and the US. Infants (n=33; mean age: 5 months) were randomized to intermittent or continuous monitoring and all primary and secondary outcomes measured. The results of the internal pilot RCT demonstrated feasibility of the trial processes including: ascertainment of patients, clinicians and family enthusiasm to participate (70% recruitment rate); all patients receiving the allocated intervention with *no contamination*; no discontinuation of the intervention in any cases; adequacy of data collection procedures, no loss to follow-up; no adverse events occurred and no infants required PICU admission.

OVERALL GOALS

To advance health care and outcomes for hospitalized infants with bronchiolitis using patient oriented pragmatic trials as an embedded knowledge translation approach. To launch a Pediatric Hospital Research Network focusing on highly prevalent and cumulatively expensive conditions.

OBJECTIVES

Primary: To determine if *intermittent* vs *continuous* oxygen saturation monitoring will reduce length of hospital stay in hospitalized infants with bronchiolitis.

Secondary: To determine differences in other outcomes related to effectiveness, safety, acceptability, and cost.

METHODS

TRIAL DESIGN

This will be a six centre, pragmatic randomized controlled superiority trial designed with two parallel groups with a 1:1 allocation ratio with enrollment occurring over bronchiolitis seasons, November to May (Fig 1). Pragmatic trials seek to understand whether an intervention works under usual conditions.[36] This protocol follows SPIRIT guidelines[37] and was successfully implemented in a pilot RCT at SickKids demonstrating trial feasibility.

Participants, interventions, and outcomes

Study Setting: Six Ontario hospitals: SickKids; CHEO, McMaster Children's Hospital; Trillium Health Partners, Credit Valley Site, Mississauga, Lakeridge Health, and North York General Hospital (NYGH) on the General Pediatric Inpatient Units (GPIU).

Eligibility Criteria: Children admitted to the GPIU with bronchiolitis will be eligible if their clinical status is stable and not at high risk of deterioration.

Inclusion

- Clinical diagnosis of bronchiolitis as determined by the attending physician and as defined by the American Academy of Pediatrics (AAP) clinical practice guidelines (CPG)[1]: a preceding viral upper respiratory infection and increased respiratory effort.

- First episode of acute bronchiolitis. Infants with recurrent episodes may have an alternate diagnosis such as asthma.

- Age: 4 weeks to 24 months. Infants less than 4 weeks are at higher risk for requiring care in the PICU.

- Stable Clinical Status:
    - For infants receiving oxygen, clinical status must be stable for 6 hours on the GPIU as defined by all: Stable or decreasing requirement for supplemental oxygen AND a stable or decreasing respiratory rate on at least two measurements; Respiratory rate <70 breaths/minute; Heart Rate <180 beats/minute; Oxygen supplementation <40% FiO_2 or <2 L/min by nasal prongs; not on heated high flow oxygen at time of enrollment.
    - For infants in room air (i.e. no supplemental oxygen), clinical status must be stable (as defined above) for 6 hours and can be assessed from the first vital signs measured in the emergency department.
- Parent consent

Exclusion

- known risk factors for clinical deterioration including:
    - chronic medical condition: congenital heart disease that is cyanotic, hemodynamically significant requiring diuretics, and/or with pulmonary hypertension; chronic lung disease with home oxygen requirement and/or pulmonary hypertension; neuromuscular disease; immunodeficiency; hemoglobinopathy
    - premature birth (<35weeks)
    - history of apnea
    - weight < 4kg
    - receiving morphine infusions
- patient on heated high flow oxygen at time of enrollment
- ICU admission on current admission requiring mechanical or non-invasive ventilation
- No telephone available

Recruitment Strategy and Baseline Measurements: Research Assistants (RA) will assess children for eligibility 5 days a week (Monday to Friday) between 0800 and 1800. Recruitment on Saturday and Sunday is permitted if feasible. We will implement the intervention during daytime hours to simulate anticipated practice. Baseline characteristics and covariates, including those known to be associated with the length of stay will be collected prior to randomization: age, sex, history of atopy, parental cigarette smoking, treatments prior to randomization (antibiotics, salbutamol, nebulized epinephrine, steroids, intravenous fluids, nasogastric feeds), feeding adequacy, oxygen supplementation and respiratory rate at time of randomization, and duration from hospital admission to randomization.

Interventions

For children in both groups, the pulse oximetry probe will be attached to the participant (e.g. toe, finger) continuously. The target oxygen saturation for oxygen supplementation will be the same

for both groups at sites - 90%. Sites that also permit an acceptable oxygen saturation of greater than or equal to 88% while children are asleep (as indicated in their bronchiolitis CPG, order sets, or usual practice) will continue with that practice, in keeping with a pragmatic trial. The target oxygen saturations are based on recommendations from local CPGs (e.g. SickKids), national guidelines and a recent study.[1,24]

Intermittent oxygen saturation monitoring group: Oxygen saturation and vital signs will be measured intermittently at a frequency of every 4 hours by the bedside nurse through the child's hospital stay until discharge. The nurse will attach the probe to the electrical cord, which is connected to the monitor. For each measurement, the duration of monitoring will be for a minimum of 2 minutes and until a steady wave form is present on the oxygen saturation monitor, indicating a reliable measurement. The nurse will document the reading during the period. The nurse will detach the probe from the electrical cord, leaving the probe attached to the child. Hence, the child's probe will be attached to the electrical cord intermittently as well. Weaning of oxygen will be at the discretion of the attending physicians and nurses and may occur at the 4 hourly time interval; oxygen weaning may also occur at other times. If supplemental oxygen is reduced, monitoring will be for 10 minutes and then discontinued if stable until the next 4 hourly measurement.

Continuous oxygen saturation monitoring group: Oxygen saturation will be measured continuously through the child's hospital stay until discharge. The reading will be displayed on the bedside monitor in the participants' room. The oxygen saturation level at which an alarm will ring will be set at 89%. Every 4 hours the nurse will complete and document a set of vital sign measurements, including oxygen saturation level. At the completion of vital signs measurement, the nurse will not detach the electrical cord from the probe. Hence, the child's probe will be attached to the electrical cord continuously as well. Weaning of oxygen will be as usual practice and will be left to the discretion of the attending physicians and nurses.

Procedures for modifying allocated intervention

In our pilot RCT, no modifications to the allocated intervention occurred. However, the following criteria will be available for converting the group allocation of intermittent monitoring to continuous monitoring: severe tachypnea, tachycardia, apnea, clinical deterioration as assessed by the attending medical team. The infant will be converted back to intermittent monitoring when deemed clinically stable by the attending medical team.

Concomitant care permitted or prohibited

Infants at all sites will receive concomitant bronchiolitis care as outlined in a standard care map (Appendix 1). The standard care map is based on site local clinical practice guidelines.

Outcomes

Primary outcome

Length of Hospital Stay from randomization on the inpatient unit to discharge from hospital (hours): Length of hospital stay was chosen as the primary outcome as it represents a clinically meaningful outcome in the context of this acute illness for families and clinicians.[3] It is important to hospital administrators and the health care system as hospital stay accounts for a major portion of bronchiolitis associated costs.[11] Length of stay has been used as the primary outcome in inpatient bronchiolitis trials.[39,40]

Secondary outcomes

Duration of oxygen supplementation from randomization to discontinuation of supplementation (hours) will be measured from the medical record.

Medical interventions: performed from time of randomization to discharge: (a) Chest x-ray (yes/no) (b) Blood samples drawn (yes/no) and number (c) Nasopharyngeal tests for viruses (yes/no) (d) Blood culture (yes/no) (e) Bronchodilator treatments used (yes/no) and number (f) steroid administration (yes/no) (g) Nasal passage (or deeper) suctioned (yes/no) and number (h) oxygen supplementation initiated (yes/no) (i) IV fluids initiated (yes/no) and duration (j) nasogastric feeds initiated (yes/no) and duration

Time from randomization to meeting discharge criteria (hours): This will be assessed twice daily (9 am and 4pm) by a RA and defined as: no fever (temperature <38°C), no supplemental oxygen, normal respiratory rate for age [using the World Health Organization age-specific criteria (<50 breaths/min for 2-12 months, <40 breaths/min for 1 to 5 years)], and adequate feeding [defined as a feeding adequacy score of ≥ 7 on a 10 cm visual analogue scale (VAS) feeding adequacy scale].

Length of Hospital Stay from admission to the GPIU: This will be defined as the length of time (measured in hours) from physical admission on the GPIU to discharge from hospital. This has been chosen as a secondary outcome and not a primary outcome as the length of time from admission to the GPIU until randomization will not be influenced by the intervention.

Parent anxiety: Parents will rate their level of anxiety at the current time (state anxiety) every 24 hours and generally (trait anxiety) at baseline from the adult State Trait Anxiety Inventory.[41]

Number of parent work days missed from randomization to 15 days after discharge: The RA will conduct telephone follow-up with the parent.

Nursing satisfaction: The attending nurse will be asked to complete a 10 mm visual analogue scale (VAS) to measure their satisfaction with the quality of monitoring for each participant twice daily (one by the day nurse and one by the night nurse).

PICU admission and consultation after randomization.

Unscheduled return to care within 15 days of discharge: The electronic medical record will also be reviewed to determine any emergency department visits and any admissions to hospital within 15 days of discharge. Parents will be phoned after discharge to record the number of unscheduled visits to a physician's or primary care office within 15 days of discharge. Fifteen days after discharge represents approximately 23 days from onset of symptoms and will capture the range of duration of symptoms for bronchiolitis.[42]

Mortality: We will include mortality from any cause during the hospitalization and up to 15 days from discharge.

Cost-Effectiveness: We will perform a cost-effectiveness analysis (CEA) to determine the incremental costs (or savings) of intermittent compared to continuous oxygen saturation monitoring per change in hospital length of stay (in hours). We will take both a health care system and societal perspective. As there is no anticipated difference in long-term clinical outcomes from this condition or the intervention, our time horizon will be from admission to 15 days post discharge.[42] All costs, parameter estimates and ranges will be derived from study data. Standardized methods for the conduct of health economic evaluations (published by CADTH) will be followed.

Adherence to assigned intervention group: Adherence rate (proportion) and reasons for modifications will be reported for each group.

Data Collection Timeline

Data will be collected at baseline, during the hospital stay, and then by phone after 15 days post-discharge.

Assignment of Interventions

Allocation: The allocation sequence will be generated using computer-generated random numbers by the trial biostatistician. Randomization will be stratified by centre. An allocation ratio of 1:1 with random permuted blocks of varying size will be used within centre. Allocation concealment will be achieved by using a central randomization system using the REDCap randomization module. The site RA will confirm eligibility and obtain consent; then they will obtain the participant group assignment through the REDCap application. An instruction sheet for the assigned oxygen monitoring group for the attending nurse will be placed on the child's nursing flow sheet clipboard.

Blinding: Statisticians and investigators will be blind to the group allocation during the data analysis. Parents, attending nurses, physicians and research personnel involved with data collection will not be blinded to the group allocation. It is important that the clinicians receive the allocated monitoring strategy with fidelity (e.g. are aware that monitoring is intermittent and that they will not receive saturation readings more frequently) as we are interested in determining if the oxygen monitoring strategy affects their behaviour and management decisions. By taking this pragmatic approach, our estimates of effectiveness will be more applicable to usual care settings.[36,45]

Data collection, management, and analysis

Data Collection Methods: The RAs will be embedded in each inpatient unit and will collect data.

Health Service Utilization and Cost Data: At the end of the trial, decision support at each of the study sites will provide individual case-costing for each participant's hospitalization for the index admission. Direct out-of-pocket costs of caregivers/parents and productivity losses will be obtained directly from study participants. A custom data collection form has been developed to measure these costs and losses upon discharge. It will be administered to participants in both arms of the trial and can be self-administered or collected via interview with the RA. Any additional health care utilization, out-of-pocket expenses and productivity losses incurred in the 15 days after discharge will be obtained by the RA at the follow up call.

Data Management: OCHSU at SickKids and CHEO (oschu.ca) will serve as the trials and data management centre. RedCAP software will be used for data management.

Statistical methods

Sample size and recruitment duration*:* The primary outcome is length of hospital stay from time of randomization on the GPIU to discharge. Assuming a median length of hospital stay from randomization to discharge of 36 hours (from pilot data, published trials), a type 1 error rate of 0.05 (2 sided), power (1-β) of 90%, 105 subjects per group is needed to detect a clinically significant difference of 12 hours. There will be no adjustment due to loss to follow-up as this outcome is assessed in hospital. We believe that a 12 hr difference between treatment groups is a clinically meaningful difference, based on consensus with our research team, hospital administrators, and clinical experts.

Based on administrative data there are approximately 415 bronchiolitis admissions per year in total at the 6 sites. Approximately 40% will not meet the eligibility criteria and of these 30% will not be recruited due to off-season presentation (May to November) or missed, leaving 174 admissions. Assuming a conservative recruitment rate of 70% (based on pilot study), we

expect approximately 120 recruited patients per season. Thus, two 6 month seasons, each from mid November to mid May, will be needed at a minimum to recruit the 210 subjects. This seasonal definition of November to May will capture the peak months of respiratory viral infections responsible for bronchiolitis.[47] If the target sample size is reached before the end of a season, the PI in consultation with the trial biostatistician, Co-Is, and site PIs, may decide to continue the trial beyond the target of 210 patients until the end of the season. This will increase the power of the trial with minimal additional costs. This seasonal definition of November to May will capture the peak months of respiratory viral infections responsible for bronchiolitis.[47]

Statistical Analysis

Primary Outcome: Data will be analyzed according to intention to treat principles for the primary outcome. Given that the primary and most secondary outcomes are obtained during hospitalization, and mortality is rare, it is anticipated that there will be no missing data. For the outcomes measured after discharge (readmissions and parental work days missed), outcomes with the available data and lost to follow (anticipated to be less than 5 %; there was none in the pilot RCT) will be reported.

The primary outcome, length of hospital stay (hours) from randomization on the inpatient unit to discharge, will be described as the ratio of the two medians with the 95% confidence intervals. Kaplan-Meier-type survival curves will be graphed for both treatment arms. Since no censoring is anticipated, the arms will be compared using a Wilcoxon rank-sum test. Since each site will follow one of two oxygen saturation targets for all their patients, as per their usual practice ($\geq$ 90% awake and asleep *OR* $\geq$ 90% awake and 88% asleep), a treatment by target interaction will be tested to see if the treatment effect differs between targets. If any clinically important imbalances exist between treatment groups, a secondary analysis of the primary outcome will be performed adjusting for the relevant baseline characteristic(s) as a covariate(s).

Secondary outcomes To control for multiple testing, the statistical level for significance for the secondary outcomes will be set to 0.005, two-sided. For the time-to-event outcomes (oxygen supplementation, discharge criteria) a Wilcoxon rank-sum test will be applied. For count data (interventions) a Poisson model will be applied. For continuous data (parent anxiety, nursing satisfaction) a normal model for repeated observations will be applied. For binary data (PICU admission, unscheduled readmission, mortality, adherence) a Fisher exact test will be applied.

Cost-effectiveness analysis

The cost-effectiveness analysis will take both a health care system and societal perspective, with a time horizon from admission to 15 days post discharge. Costs will be adjusted for inflation and reported in 2018 Canadian dollars. Cost-effectiveness will be expressed as an incremental cost-effectiveness ratio (ICER), calculated by dividing the incremental costs between intermittent and continuous oxygen saturation monitoring by the incremental difference in hospital length of stay.[43,44] Extensive sensitivity analyses will be performed to evaluate the robustness of the results and evaluate uncertainty in assumptions. Deterministic one-way sensitivity analysis will be performed with all variables using ranges obtained from the 95% confidence intervals generated directly from study data. Probabilistic sensitivity analysis will also be performed to establish a point estimate and 95% confidence interval around the ICER.

Data Monitoring

A Data Monitoring Committee was deemed not to be necessary by the SickKids research ethics board (REB) for the pilot study; as such we are not assembling one for this current protocol. There will be no interim analysis or plans for early trial termination.

Timelines

The study will be conducted over a minimum of 5 calendar years: startup (study personnel hiring, REB applications, database development, site education); minimum three recruitment seasons including randomization and outcome assessment from November 1 - May 1, 2016-17, 2017-18 and 2018-2019; and a close-out period for analysis and manuscript preparation July 2019 – December 2020. We first will report the primary and secondary outcomes except for cost-effectiveness in a main paper, followed by a second paper where we will report results of the cost-effectiveness analysis.

ETHICS

Research Ethics Approval The study will be submitted to REB of all study sites. Study team members have completed the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans online tutorial (http://www.pre.ethics.gc.ca/english/tutorial).

Protocol Amendments Protocol modifications will be communicated to the REB at all sites.

Consent The research assistant who obtains informed consent will not have any direct role in clinical care of participants. The responsible physician or their delegate will first be approached by the research assistant to ascertain their eligibility for the study and permission to speak to the family. The research assistant then will review the study with the parents.

Confidentiality Confidentiality will be maintained throughout the study, in accordance with the Personal Health Information Protection Act (PHIPA). The data collection sheets will be kept in a locked file cabinet with access only given to study personnel. The key linking participant identity to study ID code will be kept separate from the data on a secure password protected network drive. The data collection sheets will be free of any identifying participant data and each participant will have a unique study ID code. The study data will be entered into the main study database through REDCap without any identifiable information and stored on a secure, network drive.

Declaration of Interest None of the study investigators have conflicts of interest to declare.

Access to Data All the study investigators will have access to the final trial data.

CHALLENGES AND MITIGATION STRATEGIES

In order to maximize patient recruitment, we are enrolling patients over three seasons, given that bronchiolitis incidence may vary by season, as tertiary hospitals see a higher proportion of infants with chronic health conditions who are not eligible for intermittent monitoring.

In order to mitigate challenges in trial processes, we have conducted a pilot RCT (ClinicalTrials.gov NCT01646606) comparing intermittent vs. continuous oxygen saturation monitoring (n=33; mean age: 5 months) demonstrating feasibility of trial processes including: ascertainment of patients, clinician/patient willingness to randomization (70% recruitment rate) including infants with stable modest hypoxia, all patients receiving the allocated intervention with *no contamination*, adequacy of data collection procedures, no adverse events; and estimation of the median length of stay from randomization to discharge.

Adherence to allocated arms was excellent in our pilot RCT. A similar, multi-faceted approach will be taken to support implementation of the multi-centre trial and adherence. Leadership support for the trial has been obtained at each site and this will be communicated to site staff. Tailored education for nurses and physicians will occur before and during the trial using a variety of methods (e.g. small group sessions, distribution of reference material including pocket cards). Key local opinion leaders for nurses and physicians have been engaged in the trial concept and design and will provide support. Research assistants and/or nurse educators at will provide one-on-one support for nurses and physicians.

KNOWLEDGE TRANSLATION (KT)

We have engaged knowledge users in the protocol development (CPS, AAP, clinicians) and network development [Ontario Provincial Council of Maternal and Child Health (PCMCH)]. End of grant KT activities will be conducted locally to clinical groups and incorporated into site CPGs; nationally, findings will be presented through webinars and meetings of the CPS and Society of Pediatric Nurses; internationally, findings will be presented at the Pediatric Academic Society and AAP Pediatric Hospital Medicine meetings, and through social media. We anticipate publication of findings in a high-impact general medical or pediatric journal. Knowledge users (CPS, AAP, PCMCH) have agreed to work with us on end of grant KT activities (e.g. clinical guidelines).

RESEARCH TEAM EXPERTISE

The research team brings together early, mid and senior clinician researchers trained in clinical epidemiology with a strong track record of Pediatric Hospital Medicine (Mahant, Pound, Parkin) and Emergency Medicine (Schuh) research, including observational research, RCTs and research networks (Mahant, Parkin, Schuh); excellence in clinical trials biostatistics and economic analysis (Willan, Moretti); a SPOR supported Pediatric clinical trials and data management unit (OSCHU) at the SickKids and CHEO Research Institute; health system and quality improvement leaders (Bayliss, Roy, Kanani, Tjahjadi); nursing practice leaders (Breen-Reid, Lavigne); established relationships across hospitals; and knowledge users and policy makers (AAP, Ralston; CPS, Friedman - bronchiolitis guideline authors). The research team will be organized into a *Scientific Oversight Team* (Mahant, Parkin, Schuh, Pound); *Data Management and Economics Team* (Willan, Moretti at the Ontario Child Health Support Unit); *Implementation Oversight Team* (Tjahjadi, Bayliss, Kanani, Breen-Reid); *Site Leads* (CHEO: Pound; NYGH: Kanani; Trillium: Bayliss; McMaster: Wahi, Giglia; SickKids: Mahant; Lakeridge: Sakran) and *KT Oversight Team* (Mahant, Lavigne, Roy).

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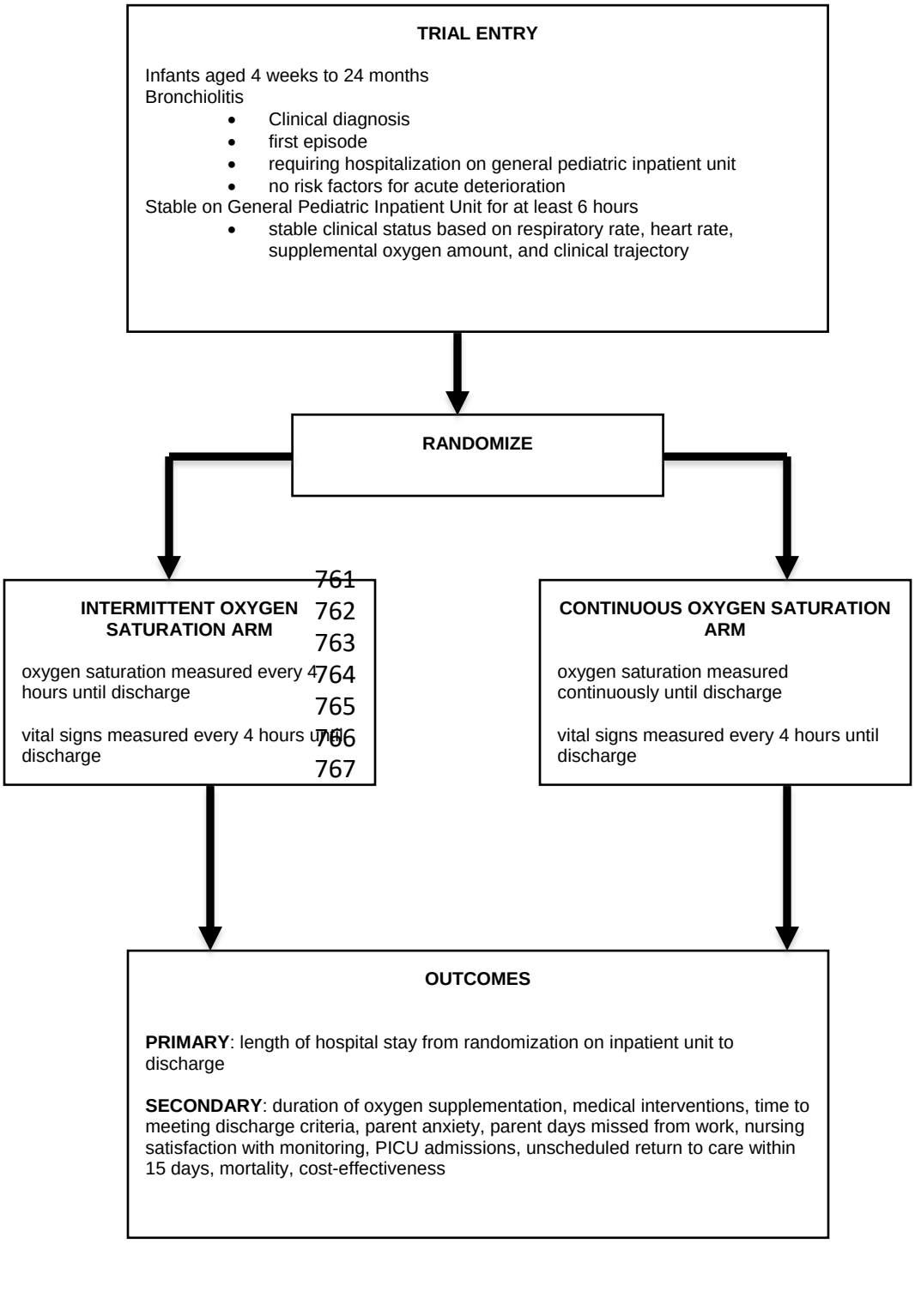
Figure 1. Trial Schematic



Appendix 1: Concomitant Care – Care Map

1.0 Assessment: Clinical history and physical examination should be the basis for a diagnosis of bronchiolitis.

2.0 Laboratory & Radiological Tests: Routine diagnostic studies such as chest x-rays, cultures, capillary or arterial blood gases and nasopharyngeal swab for viral PCR need NOT be performed to guide clinical management, to determine viral infection status or to rule out serious bacterial infections.

3.0 Management

3.1 Basic Management

The basic management of typical bronchiolitis is anchored in the provision of therapies that assure that the patient is clinically stable, well oxygenated, and well hydrated. The main benefits of hospitalization of infants with acute bronchiolitis are: the careful monitoring of clinical status with frequent reassessment maintenance of a patent airway (through positioning, suctioning, and mucus clearance), maintenance of adequate hydration, oxygenation, and parental education.

3.2 Oxygen One trial found that a 90% threshold was as effective and safe as a 94% threshold. It is suggested starting supplemental oxygen when the saturation is consistently less than 90% while breathing room air.

3.3 Bronchodilator Scheduled or serial Salbutamol aerosol therapies are not recommended. However, a single administration trial inhalation using epinephrine or Salbutamol may be considered as an option, particularly when there is a family history for allergy, asthma, or atopy. Inhalation therapy should not be repeated nor continued if there is no documented improvement in respiratory rate and effort between 15 to 30 minutes after a trial inhalation therapy.

3.4 Antibiotics Antibiotics should not be used in the absence of an identified bacterial focus.

3.5 Respiratory Therapy The infant should receive oral or nasal suctioning when clinically indicated. Routine respiratory care therapies should NOT be used, as they have not been found to be helpful. These include: (i) Cardiopulmonary (chest) physiotherapy (CPT) and (ii) cool mist therapy.

3.6 Monitoring Repeated clinical assessment should be conducted, as this is the most important aspect of monitoring for deteriorating respiratory status.

3.8 Discharge The interdisciplinary team should begin discharge planning on admission.

Bronchiolitis Discharge Criteria Checklist

- Respiratory Status respiratory status is consistently improving, tachypnea and increased work of breathing are improved. Oxygen saturation is in an acceptable range on room air (greater than or equal to 90%).

- Nutritional Status the patient is on oral feedings sufficient to prevent dehydration

- Parent & Family Education on:

- nature of illness and expected clinical course of bronchiolitis
- to call their primary care provider or return to the ED when the following signs of worsening clinical status are observed (Parent friendly language in parentheses): (1) increasing respiratory rate and/or work of breathing as indicated by accessory muscle use (i.e. breathing very fast and/or skin sucking in around the neck or ribs with each breath) (2) inability to maintain adequate hydration (i.e. unable to feed or drink by mouth or has not had a wet diaper in more than 6 to 8 hours) (3) worsening general appearance (has new symptoms not present while in the hospital such as vomiting or

fever, looks lethargic or does not respond normally to touch or sound, change in baby's colour)

- importance of handwashing before and after contact with the child to prevent spread of disease.
- eliminating exposure to environmental smoking
-

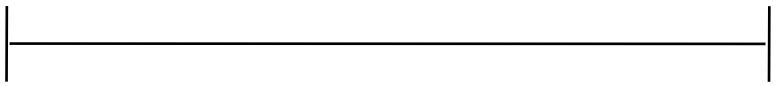
- Follow-up instructions of when to follow-up with own primary care provider (generally 1-2 days)

Parent Anxiety:
Parents rated their level of anxiety at the current time (state anxiety) every 24 hours from the adult State Trait Anxiety Inventory Please think about your own anxiety level right now. Please rate your anxiety level in the question below.

I feel at ease (state, right now)
- ❑ not at all
- ❑ somewhat
- ❑ moderately so
- ❑ very much so

Nursing satisfaction:
The attending nurse completed a 10 mm visual analogue scale (VAS) to measure their satisfaction with the quality of monitoring for each participant twice daily (one by the day nurse and one by the night nurse):

Please rate your satisfaction with the quality of the monitoring of oxygen saturation for this child on the scale below, where the left end represents not satisfied at all and the right end represents completely satisfied (mark with an 'X').

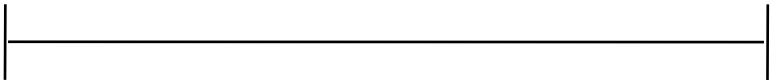


Not at all satisfied Completely satisfied

Feeding adequacy scale:

Please rate how well your child is feeding today on the scale below, where the left end represents not feeding at all and the right end represents feeding as well as when your child was healthy.

Please think about your child's **appetite**, **time spent feeding**, **how difficult it is** and **how much food or drink actually gets in your child's mouth**.



Not feeding Feeding as when healthy

Summary of Trial Protocol Changes

1. As documented in the revised protocol version date October 13, 2016, we further specified that sites that allow for an acceptable target saturation of 88% in room air while asleep can maintain that local practice as per their hospital's guidelines. We also revised the secondary analysis of the primary outcome for a treatment interaction from centre to target oxygen saturation. We did this as the oxygen saturation target is an important determinant of length of hospital stay in hospitalized infants with bronchiolitis.
2. As documented in the revised protocol version date January 18, 2017 we revised inclusion criteria for the minimum age of inclusion from 6 to 4 weeks of gestational age. We also revised the inclusion criteria to define the 6 hour period of stable clinical status for infants in room air to start from the first vital sign measurement in the emergency department. We further specified the exclusion criteria such that patient's on heated high flow oxygen at time of enrollment are excluded. We also revised the exclusion criteria to allow patients admitted after the first 24 hours of admission to the GPIU.
3. As documented in the revised protocol version date January 18, 2017 we revised exclusion criteria to further specify that patients who are admitted to the ICU on the current admission who require mechanical or non-invasive ventilation are excluded from the trial.
4. As documented in the revised protocol version date March 07, 2017 we revised the secondary outcome unscheduled return care within 15 days of discharge to indicate that the electronic medical record will be used as a data source to determine emergency department visits and admissions to hospital within 15 days of discharge.
5. As documented in the revised protocol version date May 10, 2018, we revised the sample size to indicate that if the target sample of 210 was reached before the end of the bronchiolitis season then the trial investigators may continue to recruit beyond 210 patients until the end of the bronchiolitis season. This will increase the power of the trial with minimal additional costs. We also further specified secondary outcomes, to include nasopharyngeal suctioning (yes/no) in addition to the number of times; oxygen supplementation initiated (yes/no) in addition to the duration; blood tests (yes/no) in addition to the number of times.
6. As documented in the revised protocol version date January 15, 2019, we further specified the secondary analysis of the primary outcome to indicate that if any clinically important imbalances exist between treatment groups, a secondary analysis of the primary outcome will be performed adjusting for the relevant baseline characteristic as a covariate.
7. As documented in the revised protocol version date January 15, 2019, we will report the cost-effectiveness outcome in a separate paper to the main clinical paper with reports on all other primary and secondary outcomes.
8. As documented in the revised protocol version date December 5, 2019, the secondary outcome of length of hospital stay from triage in the emergency department was revised to length of hospital stay from admission to the general pediatric inpatient unit (GPIU). The latter time frame was deemed to be more clinically relevant to an inpatient trial.

Statistical Analysis Plan

A Randomized Trial of Intermittent vs. Continuous Oxygen Saturation Monitoring in Infants Hospitalized with Bronchiolitis

ClinicalTrials.gov number, NCT02947204

Statistical Analysis Plan Version: Final. Note: 'Final' statistical analysis plan includes definitions and analyses that were established prior to unmasking of treatment groups in January 29, 2020. Please see summary of changes at the end of this document, which lists changes from the original statistical analysis plan and trial protocol.

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1 Introduction

1.1 Objectives

Primary: To determine if *intermittent* vs *continuous* oxygen saturation monitoring will reduce length of hospital stay in hospitalized infants with bronchiolitis.

Secondary: To determine differences in other outcomes related to effectiveness, safety, acceptability, and cost.

2 Study Methods

2.1 Trial Design

This will be a six centre, pragmatic, multi-centre randomized controlled superiority trial designed with two parallel groups with a 1:1 allocation ratio with enrollment occurring over bronchiolitis seasons, November to May. Pragmatic trials seek to understand whether an intervention works under usual conditions.

2.2 Randomization

The allocation sequence will be generated using computer-generated random numbers by the trial biostatistician. Randomization will be stratified by centre. An allocation ratio of 1:1 with random permuted blocks of varying size will be used. Allocation concealment will be achieved by using a central randomization system using the REDCap randomization module. The site research assistant will confirm eligibility and obtain consent; then they will obtain the participant group assignment through the REDCap application.

2.3 Sample Size

The primary outcome is length of hospital stay from time of randomization on the general pediatric inpatient unit (GPIU) to discharge. Assuming a median length of hospital stay from randomization to discharge of 36 hours (from pilot data, published trials), a type 1 error rate of 0.05 (2 sided), power (1-β) of 90%, 105 subjects per group is needed to detect a clinically significant difference of 12 hours. There will be no adjustment due to loss to follow-up as this outcome is assessed in hospital. We believe that a 12-hour difference between treatment groups is a clinically meaningful difference, based on consensus with our research team, hospital administrators, and clinical experts.

2.4 Framework

This will be a superiority trial. We will be analyzing all primary and secondary comparisons on this basis.

2.5 Statistical interim analysis and stopping rules

A Data Monitoring Committee was deemed not to be necessary by the SickKids research ethics board (REB) as we are measuring two interventions which are within the standards of usual practice. There will be no interim analysis or plans for early trial termination.

2.6 Timing of final analysis

Analysis will only be conducted after all patients have been enrolled and follow-up completed.

2.7 Timing of outcome assessments

The following outcomes are measured from randomization to discharge from hospital:

1. Length of hospital stay from randomization on the inpatient unit to discharge from hospital
2. Duration of oxygen supplementation from randomization to discontinuation of supplementation
3. Medical interventions
4. Time from randomization to meeting discharge criteria
5. Parent Anxiety
6. Nursing Satisfaction
7. PICU admission and consultation after randomization
8. Adherence to the assigned intervention group
9. Mortality

The following outcomes are measured from admission to the GPIU to discharge from hospital:

1. Length of hospital stay from admission to the GPIU

The following outcomes are measured from randomization to 15 days after discharge:

1. Number of parent work days missed from randomization to 15 days after discharge

The following outcomes are measured from discharge from hospital to 15 days after discharge:

1. Unscheduled return to care within 15 days of discharge.

3 Statistical Principles

3.1 Confidence Intervals and P values

For the primary analysis of the primary outcome, time from randomization on the inpatient unit to discharge, a two-sided P-value of <0.05 will be considered statistically significant. For all secondary outcomes, to control for multiple testing, the statistical level for significance will be set to 0.005, two-sided. Where appropriate, 95% confidence intervals (CI) will be presented.

3.2 Adherence and Protocol Deviations

Adherence rate (number and percentage) and reasons for modifications to the assigned group (i.e. intermittent or continuous oxygen saturation monitoring) will be reported for each group. Research staff at each site will assess twice daily whether infants are on the assigned oxygen saturation monitoring group. Given that this is a pragmatic trial assessing two interventions that are within the standards of usual practice, we will not consider non-adherence as a deviation in the protocol.

3.3 Analysis Populations

Data will be analyzed according to intention to treat principles for the primary and secondary outcomes.

4 Trial Population

4.1 Eligibility Criteria

Children admitted to the GPIU at the participating site hospitals with bronchiolitis will be eligible if their clinical status is stable and not at high risk of deterioration.

Inclusion

- Clinical diagnosis of bronchiolitis as determined by the attending physician and as defined by the American Academy of Pediatrics (AAP) clinical practice guidelines (CPG).
- First episode of acute bronchiolitis.
- Age: 4 weeks to 24 months. Infants less than 4 weeks are at higher risk for requiring care in the PICU.
- Stable Clinical Status:
    - For infants receiving oxygen, clinical status must be stable for 6 hours on the GPIU as defined by all: Stable or decreasing requirement for supplemental oxygen AND a stable or decreasing respiratory rate on at least two measurements; Respiratory rate <70 breaths/minute; Heart Rate <180 beats/minute; Oxygen supplementation <40% FiO_2 or <2 L/min by nasal prongs; not on heated high flow oxygen at time of enrollment.
    - For infants in room air (i.e. no supplemental oxygen), clinical status must be stable (as defined above) for 6 hours and can be assessed from the first vital signs measured in the emergency department.
- Parent consent

Exclusion

- known risk factors for clinical deterioration including:
    - chronic medical condition: congenital heart disease that is cyanotic, hemodynamically significant requiring diuretics, and/or with pulmonary hypertension; chronic lung disease with home oxygen requirement and/or pulmonary hypertension; neuromuscular disease; immunodeficiency; hemoglobinopathy

    - premature birth (<35weeks)
    - history of apnea
    - weight < 4kg
    - receiving morphine infusions
- patient on heated high flow oxygen at time of enrollment
- ICU admission on current admission requiring mechanical or non-invasive ventilation
- No telephone available

4.2 Recruitment

The CONSORT flow diagram will include total number of infants admitted with bronchiolitis who were screened, reasons for non-eligibility, the total number of eligible participants, the total number who were approached for consent, the total number who consented and were randomized, the number assigned to each treatment group, and the number of participants in the primary analysis.

4.3 Withdrawal/follow-up

If any withdrawals occur, we will report them and by group. Given that this is a pragmatic trial we will only consider withdrawals when participants (i.e. parents) ask to be withdrawn from the study (i.e. any data removed from the trial database). Parents who request their child's assigned monitoring group to change will be documented as non-adherence to the assigned group and will not be considered as a withdrawal. Patients who are transferred to the PICU will not be considered withdrawn. We will report loss to missing data due to follow-up by specific outcomes and group.

4.4 Baseline patient characteristics

We will report the following baseline characteristics: age (months), weight (kg), female sex, family history of asthma or personal history of atopy, parental cigarette smoking, management in the emergency department (antibiotic, salbutamol, nebulized epinephrine, steroid, supplemental oxygen, high flow oxygen therapy, continuous oxygen saturation monitoring, intravenous fluids, nasogastric feeds), clinical status at randomization on the inpatient unit [respiratory rate (breaths/min), heart rate (beats/min), oxygen saturation (%), Oxygen supplementation, and feeding adequacy score (out of 10)], and time from physical admission on the general pediatric inpatient unit (GPIU) to randomization (hours). For the categorical baseline characteristics, we will report the number and percentage in each group. For the age, weight, respiratory rate, heart rate, oxygen saturation, and time from physical admission on the GPIU to randomization we will report the median and interquartile range for each group. For the feeding adequacy score we will report the mean and standard deviation for each group.

5 Analysis

5.1 Outcome Analysis

Primary Outcome

Length of Hospital Stay from randomization on the inpatient unit to discharge from hospital (hours). This will be defined as the time from randomization on the inpatient unit until discharge from hospital in hours. It will be abstracted from the medical records.

Primary Analysis. The primary outcome, length of hospital stay (hours) from randomization on the inpatient unit to discharge, will be reported as the median time in hours and interquartile range by group. We will then estimate the ratio of the two medians with a 95% confidence interval. We will also estimate the difference in medians between groups with a 95% confidence interval. Kaplan-Meier-type survival curves will be graphed for both treatment arms. Since no censoring is anticipated, the arms will be compared using a Wilcoxon rank-sum test.

Secondary Analysis. (a) Since each site will follow one of two oxygen saturation targets for all their patients, as per their usual practice (≥ 90% awake and asleep *OR* ≥ 90% awake and 88% asleep), a treatment by target interaction will be tested to see if the treatment effect differs between targets. We will conduct a survival analysis using the Cox proportional hazard model comparing treatment groups that includes an interaction term for the target group. A two-sided test of significance will be applied at the 5% level. (b) If any clinically important imbalances exist between treatment groups with respect to baseline variables, a secondary analysis of the primary outcome will be performed adjusting for the relevant baseline variables as a covariate. We will conduct a survival analysis using the Cox proportional hazard model comparing treatment groups (unadjusted for the baseline characteristic) and then adjusted for the baseline characteristic. We will estimate the unadjusted and adjusted hazard ratio and 95% CI.

Secondary Outcomes

Duration of oxygen supplementation from randomization to discontinuation of supplementation (hours). This will be abstracted from the medical records. We will report the number of participants who were on supplemental oxygen at any point and stopped after randomization in each group and the median number of hours with interquartile range on supplemental oxygen for each group. For the median duration of oxygen supplementation, we will estimate the ratio of medians with 95% confidence interval. The Wilcoxon rank-sum test will be applied.

Oxygen supplementation initiated after randomization. This is defined as the number of participants who were not on oxygen supplementation at randomization and had oxygen supplementation initiated after randomization. This will be abstracted from the medical records and will be reported as the number and percentage of participants in each group who initiated oxygen supplementation after randomization. We will estimate the odds ratio with 95% CI. Fisher's exact test will be applied to determine statistical significance.

Medical Interventions. This will be defined as medical interventions performed from randomization to discharge. This will be abstracted from the medical records. For the outcomes of chest x-ray, blood test, nasopharyngeal testing for viruses, blood culture testing, bronchodilator treatment, systemic steroids, nasal suctioning, intravenous fluids initiated, nasogastric fluids initiated, we will report the number and percentage of participants in each

group who had the intervention. We will estimate the odds ratio with 95% CI for each intervention. The Fisher's exact test will be applied to determine statistical significance. For the outcomes, number of blood tests, number of bronchodilator treatments, number of nasal suctioning we will report the median number per group and interquartile range for those participants who received the intervention. We will estimate the ratio of medians and 95% CI. The negative binomial model will be applied to determine statistical significance. For the outcomes of duration of intravenous fluids (hours) and duration of nasogastric feeds (hours) from randomization to discharge, we will report the median number of hours with interquartile range for each group. Participants who did not receive nasogastric feeds or who received nasogastric feeds that were discontinued prior to randomization will not be included in this analysis. We will estimate the ratio of medians with 95% confidence interval. The Wilcoxon rank-sum test will be applied.

Time from randomization to meeting discharge criteria (hours). The time at which a participant met discharge criteria will be assessed twice daily (9 am and 4pm) by a RA and defined as: no fever (temperature <38°C), no supplemental oxygen, normal respiratory rate for age [using the World Health Organization age-specific criteria (<50 breaths/min for 2-12 months, <40 breaths/min for 1 to 5 years)], and adequate feeding [defined as a feeding adequacy score of ≥ 7 on a 10 cm visual analogue scale (VAS) feeding adequacy scale]. We will estimate the ratio of medians with 95% confidence interval. The Wilcoxon rank-sum test will be applied.

Length of Hospital Stay from admission to the general pediatric inpatient unit (GPIU) to discharge (hours). This will be defined as the length of time (measured in hours) from physical admission on the GPIU to discharge from hospital. We will report the median number of hours with interquartile range for each group. We will then estimate the ratio of medians with 95% confidence interval. The Wilcoxon rank-sum test will be applied.

Parent anxiety. Parent anxiety will be measured after randomization using the state anxiety scale which is a 4-point Likert scale (1= not at all at ease; 2=somewhat at ease; 3=moderate so at ease; 4=very much so at ease). Parents will be asked to complete this scale up to once per day. For each participant, we will first calculate the mean score across measurements from both parents, by day (day 2 to discharge), and then calculate the mean score across all days. Then we will report the mean score and standard deviation across all participants by group. We will estimate the mean difference between groups with the 95% CI. The t-test will be applied to determine statistical significance.

Number of parent work days missed from randomization to 15 days after discharge. The number of parent days missed from work will be measured by telephone follow-up with the parent(s). This includes paid and unpaid employment. Parents who don't work in paid employment and did not miss any days of unpaid work (e.g. caregiving for another child) will be recorded as missing 0 days of work. For each participant, we will first sum the total number of days missed from work by each parent, and then calculate the median number of days missed from work across both parents. Then we will estimate the median number of days missed from work and interquartile range across all participants by group. We will estimate the ratio of medians with 95% confidence interval. The negative binomial model will be applied.

Nursing satisfaction. The attending nurse will be asked to complete a 10 mm visual analogue scale (VAS) to measure their satisfaction with the quality of monitoring for each participant. We will first calculate the mean VAS score across all nurses in the day and night, and then report the mean score and standard deviation by group. We will estimate the mean difference between groups with the 95% CI. The t-test will be applied to determine statistical significance.

PICU admission and consultation. This will be defined as a PICU transfer after randomization until discharge and a PICU consultation after randomization until discharge. This will be abstracted from the medical records. We will report the number and percentage of participants in each group who had a PICU admission and/or a PICU consultation. We will estimate the odds ratio with 95% CI. Fisher's exact test will be applied to determine statistical significance.

Unscheduled return to care within 15 days of discharge. The electronic medical record will be reviewed to determine any emergency department visits and any admissions to hospital within 15 days of discharge. Parents will be phoned after discharge to record the number of unscheduled visits to a physician's or primary care office within 15 days of discharge. We will report the number and percentage of participants in each group who had an emergency department visit, admission to hospital, and unscheduled visit to a physician or primary care office within 15 days of discharge. We will estimate the odds ratio with 95% CI for each outcome separately. Fisher's exact test will be applied to determine statistical significance.

Mortality. We will include mortality from any cause. We will report the number and percentage of participants who died in each group. The odds ratio with 95% CI was not reported as there were no deaths. No statistical test was applied.

5.2 Missing Data

We will report missing data in the results. We will not perform any multiple imputation or other statistical methods to handle missing data.

5.3 Additional Analyses

We will not conduct any additional analyses.

5.4 Harms

The interventions compared in this trial are within the usual practice standards. We have collected potential harms associated with the interventions as secondary outcomes: PICU admission and consultation, unscheduled return visits within 15 days of discharge, and mortality. The analysis of these outcomes is described above in the secondary outcomes analysis section.

5.5 Statistical Software

All analyses were computed using R version 3.6.2.

5.6 References

Price, R. M. and Bonett, D. G. 2002. Distribution-free confidence intervals for difference and ratio of medians. Journal of Statistical Computation and Simulation 72(2): 119-124.

6.0 Summary of Changes to Statistical Analysis Plan

1. As documented in the revised trial protocol version date October 13, 2016 , we further specified that sites that allow for an acceptable target saturation of 88% in room air while asleep can maintain that local practice as per their hospital's guidelines. We also revised the secondary analysis of the primary outcome for a treatment interaction from centre to target oxygen saturation. We did this as the oxygen saturation target is an important determinant of length of hospital stay in hospitalized infants with bronchiolitis.
2. As documented in the revised trial protocol version date May 10, 2018, we revised the sample size to indicate that if the target sample of 210 was reached before the end of the bronchiolitis season then the trial investigators may continue to recruit beyond 210 patients until the end of the bronchiolitis season. This will increase the power of the trial with minimal additional costs.
3. As documented in the revised trial protocol version date January 15, 2019, we further specified the secondary analysis of the primary outcome to indicate that if any clinically important imbalances exist between treatment groups, a secondary analysis of the primary outcome will be performed adjusting for the relevant baseline characteristic as a covariate.
4. For the secondary outcomes of parent anxiety score and nursing satisfaction score the analysis was revised from a normal model for repeated observations to a t-test. These revisions reflected more appropriate analysis for the data.
5. For the secondary outcomes which were count data (number of blood tests, number of bronchodilator treatments, number of nasal suctioning, number of parent days missed from work) the analysis was revised from a Poisson model to a negative binomial model due to over dispersion of the data.
6. For the secondary outcome of mortality, the analysis was revised from estimating the odds ratio and 95% CI to not reporting the odds ratio and 95% CI as there were no mortalities. There was no statistical test applied.