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Intermittent vs. continuous oxygen saturation monitoring for infants hospitalized with bronchiolitis: study protocol for a pragmatic randomized controlled trial

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Keywords: bronchiolitis; pulse oximetry; randomized controlled trial; pragmatic trial; length of stay; safety; cost

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ABSTRACT

Introduction: Bronchiolitis is the most common reason for hospitalization in infants in developed countries. The main focus of hospital care is on supportive care, such as monitoring for hypoxia and supplemental oxygen administration, as active therapies lack effectiveness. Pulse oximetry is used to monitor hypoxia in hospitalized infants and is used either intermittently or continuously. Observational studies have suggested that continuous pulse oximetry use leads to a longer length of hospital stay in stable infants. The use of continuous pulse oximetry may lead to unnecessary clinical intervention due to readings that are of little clinical significance, false positive readings and less reliance on the clinical status. There is a lack of high quality evidence to guide which pulse oximetry monitoring strategy, intermittent or continuous, is superior in infants hospitalized with bronchiolitis with respect to patient and policy-relevant outcomes.

Methods and analysis: This is a multi-centre, pragmatic randomized controlled trial comparing two strategies for pulse oximetry monitoring in infants hospitalized for bronchiolitis. Infants aged 1 month to 2 years presenting to Canadian tertiary and community hospitals will be randomized after stabilization to receive either intermittent or continuous oxygen saturation monitoring on the inpatient unit until discharge. The primary outcome is length of hospital stay. Secondary outcomes include additional measures of effectiveness, acceptability, safety and cost. We will need to enroll 210 infants in order to detect a 12-hour difference in length of stay with a type 1 error rate of 5% and a power of 90%.

Ethics and dissemination: Research ethics approval has been obtained for this trial. This trial will provide data to guide hospitals and clinicians on the optimal pulse oximetry monitoring strategy in infants hospitalized with bronchiolitis. We will disseminate the findings of this study through peer reviewed publication, professional societies and meetings.

Trial Registration
Clinicaltrials.gov: NCT02947204

Keywords
Bronchiolitis, pulse oximetry, randomized controlled trial

Strengths and limitations of this study

- This pragmatic trial is addressing how to best use pulse oximetry for bronchiolitis, a common hospital condition in children
- The trial is recruiting patients in both community and specialized children's hospitals and measuring outcomes relevant to patients, clinicians and the health system so that the finds are meaningful to the real-world setting
- Clinicians and patients are not blinded to the interventions as we are interested in knowing if knowledge of the treatment arm affects behavior and management decisions.

List of Abbreviations

RCT: randomized controlled trial
GPIU: general paediatric inpatient unit
PICU: paediatric intensive care unit
ED: emergency department
AAP: American Academy of Paediatrics
CPG: clinical practice guideline
VAS: visual analogue scale
CCRT: critical care response team
RA: research assistant

INTRODUCTION

Bronchiolitis is the most common acute lower respiratory tract infection that affects infants and young children less than 2 years of age.[1] It presents with a viral upper respiratory prodrome followed by tachypnea, chest retractions, and diffuse crackles, wheeze, or both. It is a leading cause of infant hospitalization and is cumulatively expensive for the health care system.[3,4] Although the illness is self-limited, some infants require hospitalization for fast and labored breathing, hypoxia, and feeding difficulties. Systematic reviews of a large body of evidence have shown minimal effectiveness for a range of active medical treatments, specifically drug therapies including steroids and inhaled bronchodilators.[5-9] Thus, the focus of inpatient management is on supportive care, which includes monitoring vital signs, oxygen supplementation for hypoxia, and nutritional and/or fluid supplementation.

Over the past two decades noninvasive oxygen saturation (S_pO_2) monitoring, or pulse oximetry, has been widely available for identifying hypoxia.[10] Pulse oximetry can be used intermittently, such as every 4 hours, or continuously in hospitalized infants with bronchiolitis. Although pulse oximetry was introduced into bronchiolitis hospital management without health technology assessment, it has become common clinical practice to utilize continuous oxygen saturation monitoring at many centres.

Observational studies have suggested that the use of continuous oxygen saturation monitoring in stable hospitalized infants with bronchiolitis may actually unnecessarily prolong hospital stay.[11-13] It has been proposed that continuous monitoring leads to "over monitoring" in stable infants. This leads to greater false positive readings, clinicians reacting to low readings that are not clinically important and less reliance on the clinical status of the infant in decision-making around management and disposition. This then results in a longer duration of oxygen supplementation and/or prolonged observation in hospital. A randomized controlled trial conducted in the emergency department demonstrated clinician overreliance on oxygen saturation monitoring in the management of infants with bronchiolitis.[14] Experts concluded, "the art of medicine and clinical assessment should not be trumped by overreliance on a single physiologic parameter".[15]

Current clinical practice guidelines from the American Academy of Paediatrics (AAP) have recommended that clinicians "may not choose to use continuous pulse oximetry or administer supplemental oxygen if the saturation exceeds 90%".[1] Their recommendations are graded as evidence level D (expert opinion, case reports, reasoning from first principles). Subsequent to the guideline publication, the first trial comparing intermittent vs. continuous pulse oximetry monitoring was reported.[16] All infants were randomized upon admission to hospital. Infants randomized to intermittent monitoring were switched after the infants were non-hypoxemic. 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 non-hypoxemic infants for intermittent monitoring; an

underpowered study (powered to detect an 18-hour difference in LOS); and initiating measurement of the primary outcome and some secondary outcomes before randomization. An expert commentary highlighted the need for further trials.[17]

Two broad concerns around health care delivery have emerged that make this trial especially relevant. 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.[18, 19, 20] Second is a concern around overdiagnosis, the detection of an abnormality that does not benefit the patient, and how it may be harming children.[21] 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.[21] Given these broad concerns around overuse of physiologic monitoring and the evidence gap around the most effective oxygen monitoring strategy for such a common condition as bronchiolitis, high quality evidence is needed to guide best practices and healthy policy.

METHODS

Trial design

This is 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 (each season from November to May) (see Figure 1 for trial schemata). Trial recruitment commenced November 2016. This protocol follows SPIRIT guidelines (see Figure 2 for schedule of enrollment, interventions, and assessment).[22]

Rationale for choice of methods

Pragmatic randomized trials seek to answer the question "Does this intervention work under usual conditions?" and guides trial design decisions in 10 domains.[23] A pragmatic design will strengthen the generalizability and relevance of the study findings to the practice setting for which it is intended. We will include patients from both tertiary and community hospital settings; medical management will be consistent with usual clinical care; and we will be measuring outcomes that are important to patients and health care decision makers including cost. This study is embedded within the environment of the knowledge users who will promote uptake of the intervention and study findings; a study conducted in several settings of different types (community regional hospital as well as free-standing children's hospital) over more than one bronchiolitis season will also enhance generalizability and knowledge transfer.

A pilot study was conducted at one site (The Hospital for Sick Children, Toronto; clinicaltrials.gov NCT01646606). The pilot study demonstrated feasibility of the trial processes (i.e. number of eligible subjects, recruitment rate, inclusion/exclusion procedures, the acceptability of the intervention and willingness to randomize for clinicians, adherence to interventions, rates of completion of follow-up data) and provided data for sample size determination for this multi-centre trial.

Study Setting

This study will occur at three Ontario children's hospitals [The Hospital for Sick Children, Toronto (SickKids), McMaster Children's Hospital, Hamilton, and Children's Hospital of Eastern Ontario (CHEO)] and three Ontario community paediatric centre (Trillium Health Partners, Mississauga, North York General Hospital, Toronto, and Lakeridge Health) on the General Paediatric Inpatient Units (GPIU). Children with bronchiolitis are admitted to the GPIU following initial stabilization and will be eligible for the study. Children with severe bronchiolitis are admitted to the Paediatric Intensive Care Unit (PICU) and will not be eligible for the study.

Eligibility criteria

Our eligibility criteria reflects our intention of only including infants who are in a stable phase of their hospitalization and not at higher risk of deterioration.

Inclusion criteria

- Age: 4 weeks to 24 months old. Infants less than 4 weeks are at high risk for requiring care in the PICU; infants greater than 24 months do not meet the standard definitions for bronchiolitis.
- First episode of acute bronchiolitis. Infants with recurrent episodes may have an alternate diagnosis such as asthma.
- Clinical diagnosis of bronchiolitis by the attending physician as a constellation of clinical findings on history and physical exam; clinical findings include: a preceding viral upper respiratory infection, presence of wheeze on chest auscultation, and increased respiratory rate.[1]
- 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.

Exclusion criteria

The exclusion criteria are based on known risk factors for acute clinical deterioration:

- 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

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

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, society guidelines and a trial.[1,24] Nurses will measure vital signs every 4 hours.

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. Weaning of oxygen (i.e. when to wean oxygen and by how much) is at the discretion of the attending physicians and nurses and will occur at the 4-hourly time interval. Weaning oxygen more frequently than at the 4-hour usual spot check is permitted. Nurses can perform an additional spot check following the oxygen wean.

Continuous oxygen saturation monitoring group
Oxygen saturation will be measured continuously through the child's hospital stay until discharge. Weaning of oxygen will be as usual practice and will be left to the discretion of the attending physicians and nurses.

Criteria and Procedures for discontinuing or 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, and 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.

Strategies to improve adherence

A multi-faceted approach will be taken to support implementation of the trial and adherence to the allocated arms. Leadership support for the trial will be obtained from nursing and physician leaders and communicated to the clinical staff. Tailored education for nurses and physicians, including resident 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 were engaged in the trial concept and design and will provide support at sessions. Research assistants and nurse educators will provide one-on-one support for nurses and physicians participating in the trial.

Concomitant care

In keeping with a pragmatic trial design, all infants will receive standard care for bronchiolitis. A care map has been adapted from the site clinical practice guidelines (CPG) and order sets which were based on the AAP guidelines and recent systematic reviews.

Outcomes

Study outcomes include measures of effectiveness, acceptability of the interventions, safety, and cost.

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.[2] It is important to hospital administrators and the health care system as hospital stay accounts for a major portion of the large costs associated with bronchiolitis.[25] It has also been used as the primary outcome in other trials in inpatient management of bronchiolitis.[16,26,27]

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) Number of blood samples drawn and blood tests (c) Nasopharyngeal tests for viruses (yes/no) (d) Blood culture (yes/no) (e) Number of bronchodilator treatments used (f) steroid administration (yes/no) (g) Number of times the nasal passage (or deeper)

was suctioned (h) IV fluids initiated (yes/no) and duration (i) 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 triage in the emergency department: This will be defined as the length of time (measured in hours) from triage in the emergency department to discharge from hospital. This has been chosen as a secondary outcome and not a primary outcome as the length of time from triage to transfer to the GPIU will not be influenced by the intervention.

Parent anxiety: Parents will be asked to rate their level of anxiety at the current time (state anxiety) and generally (trait anxiety) every 24 hours, using two questions abstracted from the adult State Trait Anxiety Inventory[28]: "I feel at ease" (state, right now); "I am a steady person (trait, generally). Response options are: not at all (1); somewhat (2); moderately so (3); very much so (4).

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: Parents will be phoned after discharge to record the number of unscheduled visits to an emergency department, physician's office, or admission to hospital 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.[29] The electronic medical record will also be reviewed to determine any emergency department visits and any admissions to hospital and the reasons for the visit.

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.[29] All costs, parameter estimates and ranges will be derived from study data. Standardized methods for the conduct of health economic evaluations will be followed.

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

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.

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.[30,31]

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 caregivers. 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

The Ontario Child Health Support Unit at SickKids and CHEO (oschu.ca) will serve as the trials and data management centre. REDCap software will be used for data management.

Data Monitoring

A Data Monitoring Committee was deemed not to be necessary by research ethics board (REB). There will be no interim analysis or plans for early trial termination.

Statistical Methods

Sample size

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-hour 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 to recruit the 210 subjects. This seasonal definition of November to May will capture the peak months of respiratory viral infections responsible for bronchiolitis.[32]

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 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 (≥ 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.

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: For the cost-effective analysis costs will be adjusted for inflation and reported in 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.[33,34] 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.

Patient and Public Involvement

Patients and the public were not directly involved in the development of the study (i.e. research question, outcomes choice, study design, recruitment, assessment of burden of interventions). Outcomes chosen include those reported as a priority to patients as noted in the literature.[2,35] Furthermore, we conducted a pilot study to ensure that trial processes were feasible and acceptable from a patient perspective. Study results will be disseminated to the public through social media.

Ethical and dissemination

We received approval from the Research Ethics Board at all sites. Written informed consent will be obtained from each participant by the site research staff. Identifiable personal health information will not be uploaded to the REDCap database. Protocol amendments will be approved by Research Ethics Boards prior to implementation of protocol changes. All study investigators will have access to the final trial dataset. The International Committee of Medical Journal Editors authorship eligibility guidelines will be used for publications. End of study dissemination activities will be conducted locally to clinical groups and incorporated into site CPGs; findings will be presented through webinars and society meetings (e.g. the Paediatric Academic Society, AAP Paediatric Hospital Medicine meetings, Canadian Paediatric Society), and through social media. We anticipate publication of findings in a general medical or paediatric journal. We will work with knowledge users to incorporate the study findings into professional society practice guidelines.

DISCUSSION

Bronchiolitis is one of the most common reasons for hospitalization in infants in the developed world and accounts for significant health care costs. The use of pulse oximetry has become common practice in hospitalized infants, however there is no RCT evidence on how to best use this technology in this practice context. The overall goal of our pragmatic RCT is to determine whether intermittent vs. continuous pulse oximetry results in a shorter length of hospital stay in infants with a stable clinical status hospitalized with bronchiolitis. Secondary outcomes include nursing satisfaction with monitoring, parental anxiety and days missed from work, and outcomes related to safety (intensive care unit consultation and admission, revisits after discharge, and mortality).

Several aspects of this trial are important to highlight. First, our inclusion criteria were specifically designed to include infants who are in the stable phase of their illness during hospitalization and exclude infants at higher risk of deterioration. We took this conservative approach to maximize safety and promote acceptance of clinicians to the intermittent monitoring intervention. Second, infants who are on supplemental oxygen and have a stable clinical status are eligible for randomization. Third, we are using the same target oxygen saturation in both groups. Fourth, it is important to take a multi-faceted approach to supporting this practice change to ensure adherence to the allocated arm and success of the trial. We have obtained support from clinical leadership including nursing, physicians, respiratory therapists and hospital administrators. We will also target groups using opinion leaders using small group sessions and support front line clinicians.

We took the approach of not blinding clinicians and parents to the allocated monitoring strategy in this trial for several reasons. First, it is important to simulate the monitoring strategy intended with fidelity. The act of continuous or intermittent monitoring of oxygen saturation may alter the clinical assessments of treating nurses and physicians and their decisions regarding oxygen use and need for additional days of hospitalization as well as parental perceptions of their child's health. For example, previous researchers have suggested that continuous oxygen saturation monitoring results in overreliance in technology and under reliance of clinical assessment, which leads to over use of oxygen and longer hospital stay. Thus, we are interested in understanding if knowledge of treatment arm affects clinician behavior and decisions around oxygen use and length of stay, assuming the same target oxygen saturation of 90% in both groups. By taking this approach, our estimates of effectiveness will be more applicable to usual care settings. In pragmatic trials, it has been suggested that unblinded treatment and assessment of clinical outcomes may be important for the preservation of the 'ecology of care', since blinding may have a significant effect on patients' experience.[30, 31] Further, the inclusion of objective outcome measures may reduce the potential for bias resulting from patients' expectations about the effectiveness of each treatment. Our primary outcome measure is an objective measure of length of hospital stay. Second, although methods are available to blind group assignment in monitoring trials (e.g. providing a non-true continuous reading in between intermittent oximetry spot checks), this would ostensibly result in comparing two continuous monitoring arms. Third, as we are also measuring discharge readiness as a secondary outcome (defined by the child's clinical status) we will be able to assess differences between both arms in discharge readiness and total length of stay.

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Authors' contributions

SM conceived and designed the study and drafted the first version of the manuscript. GW conceived the study and participated in the design and manuscript revisions. PP conceived and designed the study and revised the manuscript. LG, CP, RK, AB, MR, MS, NK, KBR, ML, LP, MEM, AW, and SS participated in the design of the study and manuscript revisions. All authors read and revised the manuscript critically for important intellectual content and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Figure Legends

Figure 1. Trial Schematic

Figure 2. Schedule of enrolment, interventions, and assessments

*ED=emergency department
Patients who are eligible are approached once they meet clinical stability criteria during the hospitalization. This maybe on the first day of hospitalization or subsequent days. The intervention is applied until discharge and follow-up occurs after 15 days post discharge.

Figure 1. Trial Schematic

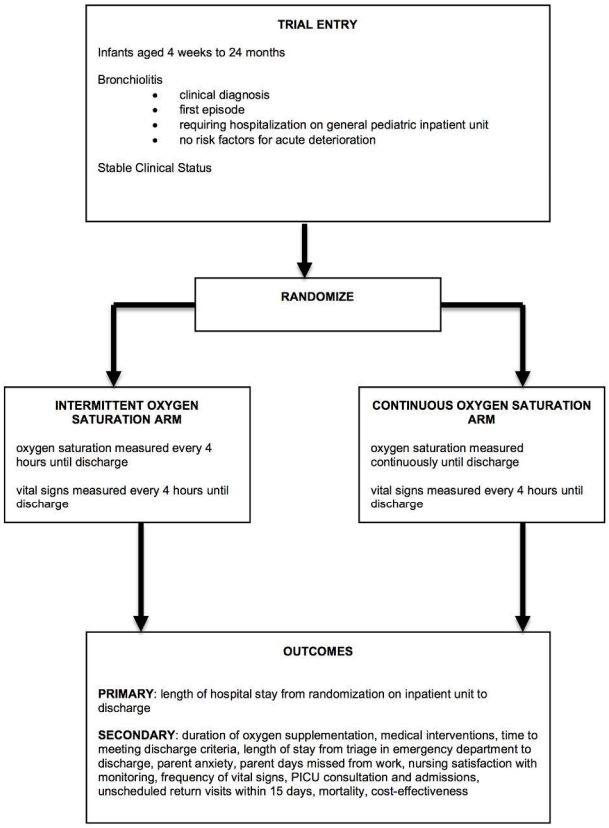

Figure 1. Trial Schematic

215x279mm (300 x 300 DPI)

Figure 2. Schedule of enrolment, interventions, and assessments

	Enrolment	Allocation	Post-allocation					Close out
TIMEPOINT**	***Hospital Admission***	**Hospital day$_x$**	***Hospital day$_{x+1}$***	***Hospital day$_{x+2}$***	***Hospital day$_{x+y}$***	***Discharge from hospital***	***15 days post discharge***	***Recruitment completed***
ENROLMENT:								
Eligibility screen	X	X						
Informed consent		X						
Allocation		X						
INTERVENTIONS:								
Intermittent Oxygen Saturation Monitoring		X	X	X	X	X		
Continuous Oxygen Saturation Monitoring		X	X	X	X	X		
ASSESSMENTS:								
Baseline clinical and demographic data	X	X						
Primary outcome: Time (hours) from randomization to discharge from hospital						X		
Secondary outcomes: duration of oxygen supplementation, medical interventions, time to						X		

meeting discharge criteria, length of hospital stay from ED, parent anxiety, PICU admission/consultation								
Nursing satisfaction		X	X	X	X	X		
Parent days missed from work, unscheduled return to care within 15 days of discharge, mortality							X	
Cost-effectiveness								X

*ED=emergency department

Patients who are eligible are approached once they meet clinical stability criteria during the hospitalization. This maybe on the first day of hospitalization or subsequent days. The intervention is applied until discharge and follow-up occurs after 15 days post discharge.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	Table 1
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3,18
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__6,7_____
	6b	Explanation for choice of comparators	__6,_____
Objectives	7	Specific objectives or hypotheses	___7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___7_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_8_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___8,9_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__10_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_10_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___10_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_10,11_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__11,12_____

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__13,14_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_10_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__12_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_12_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__12_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_13_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_13_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_13_____

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__10_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__13_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__13,14_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__13,14_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__14_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__13_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_13_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_11,12_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_NA_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__15_____

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__15_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___15_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__NA_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_15_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__15_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_NA_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__15_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__15_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___NA_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__available on request_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__NA_____ _

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Intermittent vs. continuous oxygen saturation monitoring for infants hospitalized with bronchiolitis: study protocol for a pragmatic randomized controlled trial

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Secondary Subject Heading:	Evidence based practice, Paediatrics, Medical management
Keywords:	bronchiolitis, pulse oximetry, randomized controlled trial

Intermittent vs. continuous oxygen saturation monitoring for infants hospitalized with bronchiolitis: study protocol for a pragmatic randomized controlled trial

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Keywords: bronchiolitis; pulse oximetry; randomized controlled trial; pragmatic trial; length of stay; safety; cost

Protocol Version date: March 7, 2017

Word Count: 4,257

ABSTRACT

Introduction: Bronchiolitis is the most common reason for hospitalization in infants in developed countries. The main focus of hospital care is on supportive care, such as monitoring for hypoxia and supplemental oxygen administration, as active therapies lack effectiveness. Pulse oximetry is used to monitor hypoxia in hospitalized infants and is used either intermittently or continuously. Observational studies have suggested that continuous pulse oximetry use leads to a longer length of hospital stay in stable infants. The use of continuous pulse oximetry may lead to unnecessary clinical intervention due to readings that are of little clinical significance, false positive readings and less reliance on the clinical status. There is a lack of high quality evidence to guide which pulse oximetry monitoring strategy, intermittent or continuous, is superior in infants hospitalized with bronchiolitis with respect to patient and policy-relevant outcomes.

Methods and analysis: This is a multi-centre, pragmatic randomized controlled trial comparing two strategies for pulse oximetry monitoring in infants hospitalized for bronchiolitis. Infants aged 1 month to 2 years presenting to Canadian tertiary and community hospitals will be randomized after stabilization to receive either intermittent or continuous oxygen saturation monitoring on the inpatient unit until discharge. The primary outcome is length of hospital stay. Secondary outcomes include additional measures of effectiveness, acceptability, safety and cost. We will need to enroll 210 infants in order to detect a 12-hour difference in length of stay with a type 1 error rate of 5% and a power of 90%.

Ethics and dissemination: Research ethics approval has been obtained for this trial. This trial will provide data to guide hospitals and clinicians on the optimal pulse oximetry monitoring strategy in infants hospitalized with bronchiolitis. We will disseminate the findings of this study through peer reviewed publication, professional societies and meetings.

Trial Registration
Clinicaltrials.gov: NCT02947204

Keywords
Bronchiolitis, pulse oximetry, randomized controlled trial

Strengths and limitations of this study

- This pragmatic trial is addressing how to best use pulse oximetry for bronchiolitis, a common hospital condition in children
- The trial is recruiting patients in both community and specialized children's hospitals and measuring outcomes relevant to patients, clinicians and the health system so that the finds are meaningful to the real-world setting
- Clinicians and patients are not blinded to the interventions as we are interested in knowing if knowledge of the treatment arm affects behavior and management decisions.

List of Abbreviations

RCT: randomized controlled trial
GPIU: general paediatric inpatient unit
PICU: paediatric intensive care unit
ED: emergency department
AAP: American Academy of Paediatrics
CPG: clinical practice guideline
VAS: visual analogue scale
CCRT: critical care response team
RA: research assistant

INTRODUCTION

Bronchiolitis is the most common acute lower respiratory tract infection that affects infants and young children less than 2 years of age.[1,2] It presents with a viral upper respiratory prodrome followed by tachypnea, chest retractions, and diffuse crackles, wheeze, or both. It is a leading cause of infant hospitalization and is cumulatively expensive for the health care system.[3,4] Although the illness is self-limited, some infants require hospitalization for fast and labored breathing, hypoxia, and feeding difficulties. Systematic reviews of a large body of evidence have shown minimal effectiveness for a range of active medical treatments, specifically drug therapies including steroids and inhaled bronchodilators.[5-9] Thus, the focus of inpatient management is on supportive care, which includes monitoring vital signs, oxygen supplementation for hypoxia, and nutritional and/or fluid supplementation.

Over the past two decades noninvasive oxygen saturation (S_pO_2) monitoring, or pulse oximetry, has been widely available for identifying hypoxia.[10] Pulse oximetry can be used intermittently, such as every 4 hours, or continuously in hospitalized infants with bronchiolitis. Although pulse oximetry was introduced into bronchiolitis hospital management without health technology assessment, it has become common clinical practice to utilize continuous oxygen saturation monitoring at many centres.

Observational studies have suggested that the use of continuous oxygen saturation monitoring in stable hospitalized infants with bronchiolitis may actually unnecessarily prolong hospital stay.[11-13] It has been proposed that continuous monitoring leads to "over monitoring" in stable infants. This leads to greater false positive readings, clinicians reacting to low readings that are not clinically important and less reliance on the clinical status of the infant in decision-making around management and disposition. This then results in a longer duration of oxygen supplementation and/or prolonged observation in hospital. A randomized controlled trial conducted in the emergency department demonstrated clinician overreliance on oxygen saturation monitoring in the management of infants with bronchiolitis.[14] Experts concluded, "the art of medicine and clinical assessment should not be trumped by overreliance on a single physiologic parameter".[15]

Current clinical practice guidelines from the American Academy of Paediatrics (AAP) have recommended that clinicians "may not choose to use continuous pulse oximetry or administer supplemental oxygen if the saturation exceeds 90%".[1] Their recommendations are graded as evidence level D (expert opinion, case reports, reasoning from first principles). Subsequent to the guideline publication, the first trial comparing intermittent vs. continuous pulse oximetry monitoring was reported.[16] All infants were randomized upon admission to hospital. Infants randomized to intermittent monitoring were switched after the infants were non-hypoxemic. 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). Some limitations of this trial include: only inclusion of non-hypoxemic infants for intermittent monitoring;

powered to detect only an 18-hour difference in LOS (i.e. underpowered); and initiating measurement of the primary and some secondary outcomes before implementation of the monitoring intervention. An expert commentary highlighted the need for further trials.[17]

Two broad concerns around health care delivery have emerged that make this trial especially relevant. 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.[18, 19, 20] Second is a concern around overdiagnosis, the detection of an abnormality that does not benefit the patient, and how it may be harming children.[21] 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.[21] Given these broad concerns around overuse of physiologic monitoring and the evidence gap around the most effective oxygen monitoring strategy for such a common condition as bronchiolitis, high quality evidence is needed to guide best practices and healthy policy.

METHODS

Trial design

This is 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 (each season from November to May) (see Figure 1 for trial schemata). Trial recruitment commenced November 2016. This protocol follows SPIRIT guidelines (see Figure 2 for schedule of enrollment, interventions, and assessment).[22]

Rationale for choice of methods

Pragmatic randomized trials seek to answer the question "Does this intervention work under usual conditions?" and guides trial design decisions in 10 domains.[23] A pragmatic design will strengthen the generalizability and relevance of the study findings to the practice setting for which it is intended. We will include patients from both tertiary and community hospital settings; medical management will be consistent with usual clinical care; and we will be measuring outcomes that are important to patients and health care decision makers including cost. This study is embedded within the environment of the knowledge users who will promote uptake of the intervention and study findings; a study conducted in several settings of different types (community regional hospital as well as free-standing children's hospital) over more than one bronchiolitis season will also enhance generalizability and knowledge transfer.

A pilot study was conducted at one site (The Hospital for Sick Children, Toronto; clinicaltrials.gov NCT01646606). The pilot study demonstrated feasibility of the trial processes (i.e. number of eligible subjects, recruitment rate, inclusion/exclusion procedures, the acceptability of the intervention and willingness to randomize for clinicians, adherence to interventions, rates of completion of follow-up data) and provided data for sample size determination for this multi-centre trial.

Study Setting

This study will occur at three Ontario children's hospitals [The Hospital for Sick Children, Toronto (SickKids), McMaster Children's Hospital, Hamilton, and Children's Hospital of Eastern Ontario (CHEO)] and three Ontario community paediatric centre (Trillium Health Partners, Mississauga, North York General Hospital, Toronto, and Lakeridge Health) on the General Paediatric Inpatient Units (GPIU). Children with bronchiolitis are admitted to the GPIU following initial stabilization and will be eligible for the study. Children with severe bronchiolitis are admitted to the Paediatric Intensive Care Unit (PICU) and will not be eligible for the study.

Eligibility criteria

Our eligibility criteria reflects our intention of only including infants who are in a stable phase of their hospitalization and not at higher risk of deterioration.

Inclusion criteria

- Age: 4 weeks to 24 months old. Infants less than 4 weeks are at high risk for requiring care in the PICU; infants greater than 24 months do not meet the standard definitions for bronchiolitis.
- First episode of acute bronchiolitis. Infants with recurrent episodes may have an alternate diagnosis such as asthma.
- Clinical diagnosis of bronchiolitis by the attending physician as a constellation of clinical findings on history and physical exam; clinical findings include: a preceding viral upper respiratory infection, presence of wheeze on chest auscultation, and increased respiratory rate.[1]
- 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.

Exclusion criteria

The exclusion criteria are based on known risk factors for acute clinical deterioration:

- 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

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

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, society guidelines and a trial.[1,24] Nurses will measure vital signs every 4 hours.

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. Weaning of oxygen (i.e. when to wean oxygen and by how much) is at the discretion of the attending physicians and nurses and will occur at the 4-hourly time interval. Weaning oxygen more frequently than at the 4-hour usual spot check is permitted. Nurses can perform an additional spot check following the oxygen wean.

Continuous oxygen saturation monitoring group
Oxygen saturation will be measured continuously through the child's hospital stay until discharge. Weaning of oxygen will be as usual practice and will be left to the discretion of the attending physicians and nurses.

Criteria and Procedures for discontinuing or 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, and 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.

Strategies to improve adherence

A multi-faceted approach will be taken to support implementation of the trial and adherence to the allocated arms. Leadership support for the trial will be obtained from nursing and physician leaders and communicated to the clinical staff. Tailored education for nurses and physicians, including resident 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 were engaged in the trial concept and design and will provide support at sessions. Research assistants and nurse educators will provide one-on-one support for nurses and physicians participating in the trial.

Concomitant care

In keeping with a pragmatic trial design, all infants will receive standard care for bronchiolitis. A care map has been adapted from the site clinical practice guidelines (CPG) and order sets which were based on the AAP guidelines and recent systematic reviews.

Outcomes

Study outcomes include measures of effectiveness, acceptability of the interventions, safety, and cost.

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.[2] It is important to hospital administrators and the health care system as hospital stay accounts for a major portion of the large costs associated with bronchiolitis.[25] It has also been used as the primary outcome in other trials in inpatient management of bronchiolitis.[16,26,27]

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) Number of blood samples drawn and blood tests (c) Nasopharyngeal tests for viruses (yes/no) (d) Blood culture (yes/no) (e) Number of bronchodilator treatments used (f) steroid administration (yes/no) (g) Number of times the nasal passage (or deeper)

was suctioned (h) IV fluids initiated (yes/no) and duration (i) 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 triage in the emergency department: This will be defined as the length of time (measured in hours) from triage in the emergency department to discharge from hospital. This has been chosen as a secondary outcome and not a primary outcome as the length of time from triage to transfer to the GPIU will not be influenced by the intervention.

Parent anxiety: Parents will be asked to rate their level of anxiety at the current time (state anxiety) and generally (trait anxiety) every 24 hours, using two questions abstracted from the adult State Trait Anxiety Inventory[28]: "I feel at ease" (state, right now); "I am a steady person (trait, generally). Response options are: not at all (1); somewhat (2); moderately so (3); very much so (4).

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: Parents will be phoned after discharge to record the number of unscheduled visits to an emergency department, physician's office, or admission to hospital 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.[29] The electronic medical record will also be reviewed to determine any emergency department visits and any admissions to hospital and the reasons for the visit.

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.[29] All costs, parameter estimates and ranges will be derived from study data. Standardized methods for the conduct of health economic evaluations will be followed.

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

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.

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.[30,31]

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 caregivers. 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

The Ontario Child Health Support Unit at SickKids and CHEO (oschu.ca) will serve as the trials and data management centre. REDCap software will be used for data management.

Data Monitoring

A Data Monitoring Committee was deemed not to be necessary by research ethics board (REB). There will be no interim analysis or plans for early trial termination.

Statistical Methods

Sample size

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-hour 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 to recruit the 210 subjects. This seasonal definition of November to May will capture the peak months of respiratory viral infections responsible for bronchiolitis.[32]

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 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 (≥ 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.

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: For the cost-effective analysis costs will be adjusted for inflation and reported in 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.[33,34] 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.

Patient and Public Involvement

Patients and the public were not directly involved in the development of the study (i.e. research question, outcomes choice, study design, recruitment, assessment of burden of interventions). Outcomes chosen include those reported as a priority to patients as noted in the literature.[2,35] Furthermore, we conducted a pilot study to ensure that trial processes were feasible and acceptable from a patient perspective. Study results will be disseminated to the public through social media.

Ethical and dissemination

We received approval from the Research Ethics Board at all sites. Written informed consent will be obtained from each participant by the site research staff. Identifiable personal health information will not be uploaded to the REDCap database. Protocol amendments will be approved by Research Ethics Boards prior to implementation of protocol changes. All study investigators will have access to the final trial dataset. The International Committee of Medical Journal Editors authorship eligibility guidelines will be used for publications. End of study dissemination activities will be conducted locally to clinical groups and incorporated into site CPGs; findings will be presented through webinars and society meetings (e.g. the Paediatric Academic Society, AAP Paediatric Hospital Medicine meetings, Canadian Paediatric Society), and through social media. We anticipate publication of findings in a general medical or paediatric journal. We will work with knowledge users to incorporate the study findings into professional society practice guidelines.

DISCUSSION

Bronchiolitis is one of the most common reasons for hospitalization in infants in the developed world and accounts for significant health care costs. The use of pulse oximetry has become common practice in hospitalized infants, however there is no RCT evidence on how to best use this technology in this practice context. The overall goal of our pragmatic RCT is to determine whether intermittent vs. continuous pulse oximetry results in a shorter length of hospital stay in infants with a stable clinical status hospitalized with bronchiolitis. Secondary outcomes include nursing satisfaction with monitoring, parental anxiety and days missed from work, and outcomes related to safety (intensive care unit consultation and admission, revisits after discharge, and mortality).

Several aspects of this trial are important to highlight. First, our inclusion criteria were specifically designed to include infants who are in the stable phase of their illness during hospitalization and exclude infants at higher risk of deterioration. We took this conservative approach to maximize safety and promote acceptance of clinicians to the intermittent monitoring intervention. Second, infants who are on supplemental oxygen and have a stable clinical status are eligible for randomization. Third, we are using the same target oxygen saturation in both groups. Fourth, it is important to take a multi-faceted approach to supporting this practice change to ensure adherence to the allocated arm and success of the trial. We have obtained support from clinical leadership including nursing, physicians, respiratory therapists and hospital administrators. We will also target groups using opinion leaders using small group sessions and support front line clinicians.

We took the approach of not blinding clinicians and parents to the allocated monitoring strategy in this trial for several reasons. First, it is important to simulate the monitoring strategy intended with fidelity. The act of continuous or intermittent monitoring of oxygen saturation may alter the clinical assessments of treating nurses and physicians and their decisions regarding oxygen use and need for additional days of hospitalization as well as parental perceptions of their child's health. For example, previous researchers have suggested that continuous oxygen saturation monitoring results in overreliance in technology and under reliance of clinical assessment, which leads to over use of oxygen and longer hospital stay. Thus, we are interested in understanding if knowledge of treatment arm affects clinician behavior and decisions around oxygen use and length of stay, assuming the same target oxygen saturation of 90% in both groups. By taking this approach, our estimates of effectiveness will be more applicable to usual care settings. In pragmatic trials, it has been suggested that unblinded treatment and assessment of clinical outcomes may be important for the preservation of the 'ecology of care', since blinding may have a significant effect on patients' experience.[30, 31] Further, the inclusion of objective outcome measures may reduce the potential for bias resulting from patients' expectations about the effectiveness of each treatment. Our primary outcome measure is an objective measure of length of hospital stay. Second, although methods are available to blind group assignment in monitoring trials (e.g. providing a non-true continuous reading in between intermittent oximetry spot checks), this would ostensibly result in comparing two continuous monitoring arms. Third, as we are also measuring discharge readiness as a secondary outcome (defined by the child's clinical status) we will be able to assess differences between both arms in discharge readiness and total length of stay.

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Authors' contributions

SM conceived and designed the study and drafted the first version of the manuscript. GW conceived the study and participated in the design and manuscript revisions. PP conceived and designed the study and revised the manuscript. LG, CP, RK, AB, MR, MS, NK, KBR, ML, LP, MEM, AW, and SS participated in the design of the study and manuscript revisions. All authors read and revised the manuscript critically for important intellectual content and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Figure Legends

Figure 1. Trial Schematic

Figure 2. Schedule of enrolment, interventions, and assessments

*ED=emergency department
Patients who are eligible are approached once they meet clinical stability criteria during the hospitalization. This maybe on the first day of hospitalization or subsequent days. The intervention is applied until discharge and follow-up occurs after 15 days post discharge.

Figure 1. Trial Schematic

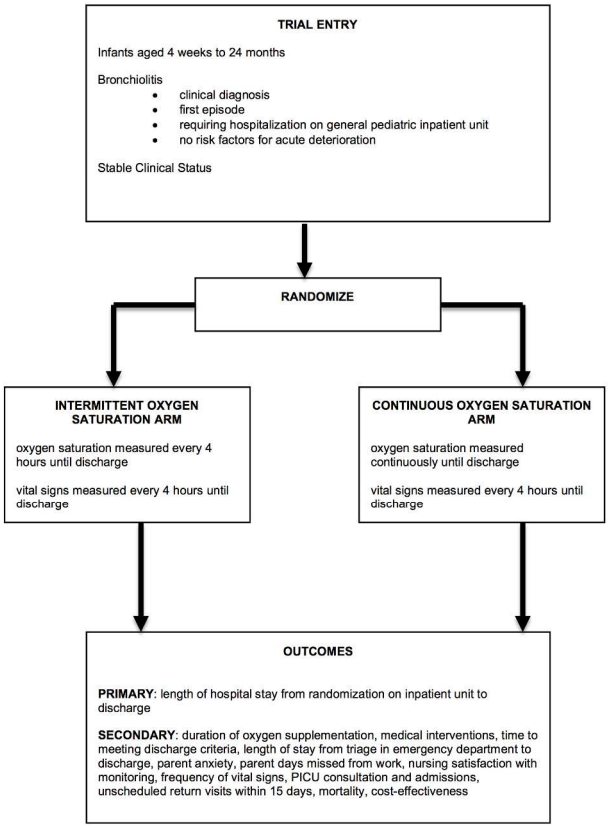

Figure 1. Trial Schematic

215x279mm (300 x 300 DPI)

Figure 2. Schedule of enrolment, interventions, and assessments

	Enrolment	Allocation	Post-allocation					Close out
TIMEPOINT**	*Hospital Admission*	Hospital day$_x$	*Hospital day$_{x+1}$*	*Hospital day$_{x+2}$*	*Hospital day$_{x+y}$*	*Discharge from hospital*	*15 days post discharge*	*Recruitment completed*
ENROLMENT:								
Eligibility screen	X	X						
Informed consent		X						
Allocation		X						
INTERVENTIONS:								
Intermittent Oxygen Saturation Monitoring		X	X	X	X	X		
Continuous Oxygen Saturation Monitoring		X	X	X	X	X		
ASSESSMENTS:								
Baseline clinical and demographic data	X	X						
Primary outcome: Time (hours) from randomization to discharge from hospital						X		
Secondary outcomes: duration of oxygen supplementation, medical interventions, time to meeting discharge criteria, length of hospital stay from ED, parent anxiety, PICU admission/consultation						X		
Nursing satisfaction		X	X	X	X	X		
Parent days missed from work, unscheduled return to care within 15 days of discharge. mortality							X	
Cost-effectiveness								X

*ED=emergency department
Patients who are eligible are approached once they meet clinical stability criteria during the hospitalization. This maybe on the first day of hospitalization or subsequent days. The intervention is applied until discharge and follow-up occurs after 15 days post discharge.

Figure 2. Schedule of enrolment, interventions, and assessments‼ ┼ ‼

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279x215mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	Table 1
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3,18
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__6,7_____
	6b	Explanation for choice of comparators	__6,_____
Objectives	7	Specific objectives or hypotheses	___7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___7_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_8_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	___8,9_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__10_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_10_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___10_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_10,11_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__11,12_____

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__13,14_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_10_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__12_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_12_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__12_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_13_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_13_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_13_____

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__10_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__13_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__13,14_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__13,14_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__14_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__13_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_13_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_11,12_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_NA_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__15_____

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__15_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___15_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__NA_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_15_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__15_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_NA_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__15_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__15_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___NA_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__available on request_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__NA_____ _

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.