FORM-STAT-04A-01	Statistical Analysis Plan
Version 1.0	

Randomised controlled trial of a combination of Dexamethasone and Adrenaline for Bronchiolitis: DAB Trial

September 2018 version 14

Document Version History

Version Date	Version	Author	Signature	Change Description	Reason/Comment
27th April 2020	1.0	Rachel Schembri		Initial release.	Not applicable.

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LIST OF ABBREVIATIONS

AE	Adverse Event
BP	Blood Pressure
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
DSMC	Data Safety Monitoring Committee
ED	Emergency Department
GCP	Good Clinical Practice
ICU	Intensive Care Unit
IM	Intramuscular
IPPV	Intermittent Positive Pressure Ventilation (mechanical ventilation)
IV	Intravenous
ITT	Intent-To-Treat
LOCF	Last Observation Carry Forward
LOS	Length of Stay
MedDRA	Medical Dictionary for Regulatory Activities
NICU	Neonatal Intensive Care Unit
PICU	Paediatric Intensive Care Unit
PPS	Positive Pressure Support (high-flow oxygen or CPAP or IPPV)
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SpO2	Arterial Oxygen Saturation
WHO DD	World Health Organization Drug Dictionary

1. STUDY OBJECTIVES

1.1. PRIMARY OBJECTIVE

To determine whether the addition of parenteral dexamethasone and nebulised adrenaline to standard care reduces the duration of positive pressure support (PPS) in children admitted to the intensive care unit with bronchiolitis who receive PPS. Positive pressure support includes therapies such as high-flow nasal prong oxygen of 1 L/kg/min, nasopharyngeal continuous positive airway pressure (CPAP) or invasive positive pressure ventilation (IPPV).

1.2. SECONDARY OBJECTIVES

To determine whether the addition of parenteral dexamethasone and nebulised adrenaline to standard care affects the rate of PPS, and the rate and duration of CPAP and/or mechanical ventilation (IPPV) (but not high-flow nasal prong oxygen) as well as length of hospital and intensive care unit (ICU) stay compared with standard care alone.

2. BACKGROUND/INTRODUCTION

A previous large multicentre trial demonstrated a significant benefit of the combined intervention of dexamethasone and nebulised adrenaline compared with placebo (before adjustment for multiple comparisons) for children presenting to the emergency department (ED) with bronchiolitis. The trial was conducted by the Canadian Pediatric Emergency Research Group, and showed evidence of a reduction in hospital admissions among children who presented to ED with bronchiolitis if they were treated with the combined intervention compared to placebo over a 6 day period (Plint 2009). The sickest patients, and those at high risk of severe illness, such as those <37 weeks gestation and those with chronic cardiopulmonary disease, were excluded from the study. Consequently, it is difficult to extrapolate this result to the treatment of bronchiolitis patients who are admitted to intensive care. Therefore, a further randomised trial is necessary to determine whether treatment with steroids and adrenaline in addition to standard care benefits children with severe bronchiolitis compared with standard care alone.

2.1. STUDY DESIGN

The study is an open labelled randomised controlled trial in children less than 18 months of age diagnosed with bronchiolitis who require admission to intensive care. Standard treatment plus parenteral dexamethasone plus nebulised adrenaline will be compared to standard treatment alone, with the duration of PPS being the primary endpoint. Patients not yet requiring PPS can also be recruited in this study but will not be included in any analyses if they do not receive any PPS whilst in the ICU. The trial will be undertaken in 4 sites: the paediatric ICU (PICU) at the Royal Children's Hospital Melbourne, the PICU at Princess Margaret Hospital Perth, the PICU at Starship Hospital, and the PICU at Middlemore Hospital Auckland.

Participants will be randomised to the intervention (in which case they will receive standard treatment plus parenteral dexamethasone plus nebulised adrenaline) or the control (in which case they will receive standard care only) groups in a 1:1 ratio. Randomisation will be stratified by (i) unit, (ii) level of respiratory support (none, non-invasive positive pressure, endotracheal intubation plus mechanical ventilation) at the time of randomisation, and (iii) the presence of either cyanotic congenital heart disease or the presence of chronic lung disease requiring oxygen therapy for more than 14 days in the last 6 months) i.e. 4x3x2x2 = 48 strata.

Block randomisation will be used within each stratum, with a fixed block size. To maintain allocation concealment, the block size will be known only by the person generating the randomisation. After approximately the first 50 participants had been recruited, the large number of strata meant that there was an unequal number of participants in the two treatment groups. In order to reduce this imbalance, the randomisation procedure was modified so that the first participant in any new block was randomised to the intervention or control group with a probability inversely related to the overall proportion of participants in the groups.

Both treatment and control subjects will receive the standard care that is normally provided for children with bronchiolitis in intensive care. Standard care involves the provision of respiratory support including oxygen therapy, nutritional support and general intensive care and is detailed in the Royal Children's Hospital Paediatric Intensive Care Guideline Handbook (Shann 2003). Standard care will not include the use of bronchodilators such as salbutamol.

If the child is becoming exhausted or has SpO2 <92% despite receiving oxygen at any time during the study in either group, non-invasive positive pressure support will be given using either high-flow oxygen therapy or nasopharyngeal CPAP (NCPAP) of 6-12 cm H2O (Beasley, BMJ 1981;283:1506-8). If the child is becoming tired or has SpO2 <92% despite CPAP, endotracheal intubation and mechanical ventilation (IPPV) will be provided. An increase in work of breathing determined by respiratory rate or chest excursion or both will also result in escalation of respiratory support.

2.2. TREATMENT GROUPS

Standard therapy for bronchiolitis usually comprises oxygen therapy, positive pressure respiratory support administered by a gas flow device or mechanical ventilator, nutritional support and sedation. Both arms will receive these therapies. Once recruited and randomised, patients randomised to the intervention group will be given a combination of corticosteroids plus nebulised adrenaline in addition to standard therapy, and those in the control group will receive standard therapy alone as determined by their random allocation. Dexamethasone and adrenaline are medications that are commonly used in this age group for the treatment of other respiratory infections.

2.3. STUDY POPULATION

Patients will be enrolled if they meet all the following criteria:

- a clinical diagnosis of bronchiolitis, defined as a first or second episode of wheezing or respiratory distress associated with a respiratory tract infection plus either radiological evidence of chest hyperinflation or clinical evidence of prolonged expiration
- less than 18 months of age
- no previous enrolment to this study
- admission to intensive care for respiratory distress (not apnoea alone)
- recruitment and initiation of the study therapy within 4 hours of admission to intensive care

Note, participants who do not require PPS at enrolment could be recruited and randomized into this trial but will not be included in any of the analyses, including the primary outcome if no PPS was administered during the admission.

Patients with the following will be excluded

- Corrected gestational age of less than 37 weeks at time of admission to the intensive care.
- Clinical evidence of croup (laryngotracheobronchitis)

- Received immunosuppressive treatment, including any dose of corticosteroids, in the last 7 days.
- On ECMO or HFOV at the time of enrolment
- Previously enrolled in the study

2.4. INTERVENTION

While in intensive care, patients in the intervention group will receive 0.6 mg/kg dexamethasone IM or IV. If there is no intravenous cannula sited at the time of enrolment oral prednisolone 4mg/kg will be an alternative to dexamethasone. This dose is based on the equivalent anti-inflammatory dose of dexamethasone. After the initial loading dose, then 1 mg/kg of methylprednisolone IV or prednisolone NG or orally 8 hourly for 9 doses (days 1-3 of the study), then daily for three days (days 4-6). Starting at the same time as the loading dose of dexamethasone/ prednisolone, patients will be given nebulised adrenaline providing the resting heart rate is <180 beats per minute: If eligible 5 doses of 0.05ml/kg of 1% adrenaline (or 0.5ml/kg of 1/1000 adrenaline) to a maximum of 6 ml or if less, made up to total maximal volume of 6ml using 0.9% saline and nebulised using 12L/min of 02 and repeated every 30 minutes to a total of 5 doses, then given 1-4 hourly (but at least 4 hourly)for 72 hours. The decision to prescribe adrenaline nebulisations will be determined by the subject's degree of respiratory compromise assessed on an hourly basis. This means that nebulised adrenaline may be given hourly, second hourly, third hourly and at the least and no less than fourth hourly. Beyond 72 hours, nebulised adrenaline can be administered on a prn basis rather than a minimum of every 4 hours and may continue for a further 3 days while in intensive care. At discharge from the intensive care all study medications will cease. Participants in the standard care arm will not receive dexamethasone or nebulised adrenaline as described above but these drugs can be used in both groups for post endotracheal tube extubation stridor which is considered part of standard therapy. Doses of these drugs for post endotracheal tube extubation stridor are usually single doses.

2.5. SAMPLE SIZE

From an audit of 1,723 children with bronchiolitis admitted to PICUs in Australia and New Zealand in the four years 2001-2004; 1,096 children (64%) received respiratory support, and the mean of the natural log of the hours of respiratory support was 4.08 (geometric mean 59.4 hours), with a SD of 1.10. Assuming the geometric mean duration of support in the control group is 59 hours, to detect a ratio of 0.60 or less in the duration of respiratory support for intervention/control (corresponding to a reduction of at least 24 hours of support in the intervention group) with a power of 90% and a p-value of 0.05, 98 patients receiving PPS will be needed in the intervention group and 98 in the control group (based on an SD in both groups of 1.10 on the log scale). As approximately 64% of the children admitted to ICU receive respiratory support, 153 children will need to be randomised to the intervention group and 153 to the control group to provide 98 ventilated participants in each group. Therefore we aim to recruit a total of 306 participants.

2.6. STUDY PROCEDURE

1. Child admitted to the intensive care unit with bronchiolitis
2. Inclusion criteria and exclusion assessed
3. Informed consent obtained or declined
4. Randomisation performed online

    Allocation to intervention arm

    a. CRF assigned to patient
    b. Dexamethasone, prednisolone and adrenaline prescribed
    c. Pressure rate product assessed once within 24 hours of respiratory support

d. CRF completed within 2 weeks of study completion

OR

Allocation to control arm

a. CRF assigned to patient
b. Pressure rate product assessed once within 24 hours of respiratory support
c. CRF completed within 2 weeks of study completion

5. Data collection, local site de-identification are entered into database.
6. Interim DSMC assessments will occur annually to assess safety.
7. At the conclusion of the trial the data will be analysed for manuscript preparation and submission for publication.

3. POPULATIONS FOR ANALYSIS

Analysis will be via intention-to-treat where outcome data are available including all participants as randomised, with the exception of participants whose parents have withdrawn consent for their child's data to be used as part of this study who will be excluded from analysis. Only children who received some PPS will be included in the analyses.

4. OUTCOME VARIABLES

4.1. PRIMARY OUTCOME

The study's primary outcome is the duration of non-invasive or invasive PPS (in children who receive such support) required from the time of randomisation until discharge from intensive care.

This will be captured as hours of PPS calculated by summing hours of high-flow nasal prong oxygen, CPAP and IPPV for each participant.

4.2. SECONDARY OUTCOMES

- Intensive care length of stay defined as a) required length of stay from randomization to 'ready to discharge', and b) actual length of stay from randomization to actual discharge
- Hospital length of stay (time from randomization to hospital discharge)
- Whether or not the child received any high-flow during their ICU admission
- Whether or not the child received CPAP during their ICU admission
- Whether or not the child received mechanical ventilation (IPPV) during their ICU admission
- Whether or not the child received nasal CPAP and/or mechanical ventilation during their ICU admission
- The number of hours of high-flow while in ICU
- The number of hours of CPAP while in ICU
- The number of hours of mechanical ventilation (IPPV) while in ICU
- The number of hours of nasal CPAP and mechanical ventilation (IPPV) while in ICU
- The number of children who escalated from high-flow (at randomization) to CPAP while in ICU
- The number of children who escalated from high-flow (at randomization) to mechanical ventilation (IPPV) while in ICU
- The number of children who escalated from CPAP (at randomization) to mechanical ventilation (IPPV) while in ICU
- Pressure-rate product (if a nasogastric tube is already in situ.
  Note: The pressure-rate product is a way of measuring the strain on the lung. The pressure can be estimated by measuring the transmitted pressure through an existing routinely placed nasogastric

tube and then multiplied by the patient's respiratory rate. The pressure-rate product was to be measured within the first 24 hours of respiratory support. This was included in the protocol as a listed outcome, however, it was hoped that a research student would be available to make these measures. This did not transpire, and as such, no pressure rate product data exists to be analysed, which will need to be explained in the publication.

4.3. OTHER VARIABLES

DEMOGRAPHY AND BASELINE

- Age (at randomisation) (months)
- Weight – kgs
- Premature (less than 37weeks gestation or greater than or equal to 37 weeks gestation)
- Cyanotic heart disease (Y/N)
- Chronic lung disease (Y/N)
- Viral aetiology (RSV or HMPV positive)
- Respiratory support at enrolment (Y/N and type of support)
- Unit (4 levels)

SAFETY

The following adverse events were recorded as part of the study from the time of randomisation to hospital discharge:

- Arrhythmia
- Hypertension (not caused by discomfort)
- Tachycardia
- Adrenaline related adverse events
- Hyperglycaemia
- All 'other' Adverse Events
- Serious Adverse Events (SAE)

5. STATISTICAL METHODOLOGY

5.1. GENERAL METHODOLOGY

HANDLING OF MISSING DATA

If there is <5% missing data in the primary outcome and the majority of secondary outcomes, then a complete case analysis will be conducted. If the rate of missing data is >5% and there is evidence that the data are missing at random, then multiple imputation will be conducted.

SENSITIVITY ANALYSES

The primary analyses investigate PPS from the time of randomisation until actual discharge from ICU. Six children continued to receive PPS after their discharge from ICU. A sensitivity analysis will be conducted to include all of the hours of PPS (ICU and beyond).

After the commencement of the trial a protocol amendment was made to include high-flow in addition to CPAP and mechanical ventilation (IPPV). However, the randomisation was stratified by high-flow and CPAP (combined) versus IPPV. A sensitivity analysis will be conducted on the primary outcome to adjust for respiratory support type as three separate categories (high-flow, CPAP or IPPV) than two categories. Low cases of heart and lung disease were observed in the trial and as such a sensitivity analysis will also be conducted on the primary outcome with no adjustment for this stratification factor.

SUBGROUP ANALYSIS

The duration of PPS will also be compared between treatment groups in the following subgroups:

1. Participants with cyanotic congenital heart disease
2. Participants born prematurely (defined as <37 weeks gestation)
3. Participants with RSV positive bronchiolitis
4. Participants with human metapneumovirus bronchiolitis
5. Participants with chronic lung disease

Given that the study is powered to compare the intervention and control groups for the trial as a whole, the results from these subgroup analyses will be exploratory only as the study will be underpowered to determine any effect within these subgroups.

CLASSIFICATION OF PROTOCOL VIOLATION

The following will be classified as protocol violations and will be summarised as the number and proportion of participants with each of these violations:

1. Study drug (missed or extra dose administered)
    a. Failed to discontinue study drug at discharge from ICU
    b. Missed dose of study drug in the intervention group
        i. Steroid
        ii. Adrenaline
    c. Study drug administered to control group
    d. Delayed commencement of study drugs in the intervention group (> 4 hours from admission)
2. Enrolment
    a. Exclusion or inclusion criteria breach
3. Misrandomisation
    a. Administration of the incorrect allocated arm
4. Drugs administered that are not permitted
    a. Salbutamol
    b. Other bronchodilators
    c. Adrenaline or dexamethasone in the standard care group (unless for post extubation stridor)

5.2. PRIMARY DATA ANALYSES

The primary outcome of duration of non-invasive and invasive PPS will be summarised as a geometric mean, along with a mean and SD on the natural log scale resented by treatment group in those who receive at least some PPS. Duration of support will compared between groups using linear regression carried out on the natural log scale, adjusted for stratification factors used at randomisation, again just including those who receive at least some PPS.

5.3. SECONDARY DATA ANALYSES

The secondary outcome of duration (from randomisation) of mechanical ventilation (IPPV) plus CPAP will be presented using medians and interquartile ranges and analysed using a zero-inflated Poisson regression adjusted for stratification factors used at randomisation. The Poisson regression will analyse whole

numbers, and so this outcome will be analysed in minutes rather than hours. Additional non-parametric analyses will be performed as a sensitivity analysis using the Wilcoxon rank sum test.

The secondary outcomes of duration (from randomisation) of high-flow, CPAP, mechanical ventilation (IPPV), CPAP plus mechanical ventilation, length of stay in ICU, and stay in hospital will be summarised as a geometric mean, along with a mean and SD on the natural log scale, by treatment group. These outcomes will be compared between groups using linear regression carried out on the natural log scale adjusted for stratification factors used at randomisation. As with the primary outcome, the analysis of these outcomes will only be conducted on those where the duration is >0. Arithmetic means of the duration of high-flow, nasopharyngeal CPAP, IPPV, ICU stay and hospital stay will also be calculated.

Outcomes regarding the receipt of PPS, high-flow, CPAP, mechanical ventilation (IPPV) will be summarised as the number and proportion of participants requiring each type of support in each group from randomisation to discharge from ICU. A comparison of these outcomes between the groups will be made using logistic regression adjusted for stratification factors used at randomisation.

If there are deaths during the study period, a secondary analysis will be carried out using survival analysis. In initial analysis participants who die will be censored at the time of death. A competing risks analysis will also be carried out treating death as a competing risk. Again analyses will be adjusted for stratification factors used at randomisation.

6. SIGNATURES

Signature of Principal Investigator:  Date 18/7/2020

Print Name Dr Ben Gelbart

Signature of Trial Statistician:  Date 20/7/2020

Print Name Dr Rachel Schembri