Title Page:

Multi-centre, Randomised Trial to Investigate Early Nasal High-Flow Therapy in Paediatric Acute Hypoxaemic Respiratory Failure: A Statistical Analysis Plan for a randomised controlled trial – a Paediatric Acute Respiratory Intervention Studies (PARIS II)

Authors Details

On behalf of the **PCCRG, PARIS Group and PREDICT**

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DECLARATIONS

Ethics approval and consent to participate:

The study protocol has been reviewed and approved by ethics committees in Australia (Children's Health Queensland Human Research Ethics Committee [HREC/15/QRCH/159] and The University of Queensland Human Research Ethics Committee [2016001491]) and New Zealand (Health and Disability Ethics Committee [HDEC 17/NTA/135]). The study was carried out in compliance with national and state legal and regulatory requirements and according to the International Principles of Good Clinical Practice (ICH-GCP). Written, informed consent was obtained from the legal guardian of all trial participants.

Consent for publication:

Not applicable.

Availability of data and material:

Not applicable.

Competing interests:

D. Franklin, A. Schibler and S.R. Dalziel have received travel support from Fisher and Paykel Healthcare. All other authors have no conflicts to disclose. Fisher and Paykel have provided equipment and consumables for the study but have had no input in the study design.

Author contributions:

The statistical analysis plan first draft was designed by K. Gibbons, A. Schibler and D. Franklin with final agreement including M. Jones. K. Gibbons, A. Schibler and D. Franklin were responsible for drafting this manuscript, with comments and feedback from all other authors.

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Abstract:

BACKGROUND: Paediatric Acute Respiratory Intervention Studies (PARIS) 2 is a multicentre, randomised controlled trial aiming to recruit 1,512 patients, investigating if nasal high-flow in children aged 1-4 years plus 364 days with acute hypoxaemic respiratory failure reduces the hospital length of stay.

OBJECTIVE: To provide a statistical analysis plan (SAP) before completion of data monitoring and locking of the study database. Final analyses for this study will adhere to this SAP which details all pre-planned analyses. Statistical code for analyses have been prepared alongside this SAP and are accessible online.

METHODS: This SAP is designed collaboratively by the chief investigators and trial statistician and builds on the previously published study protocol. This SAP provides detail on pre-planned statistical analyses including cohort description and analysis of primary and secondary outcomes. Statistical methods to compare outcomes are planned in detail to ensure methods are verifiable and reproducible.

RESULTS: This SAP provides the trial outline, list of mock tables, and analysis code describing the statistical analyses on cohort baseline description, primary and secondary outcome analyses and adverse event reporting. We detail the pre-specified subgroup and sensitivity analyses and the respective statistical tests.

CONCLUSION: This SAP for the PARIS 2 trial establishes detailed pre-planned analyses alongside Stata scripts to analyse the largest trial in the field of paediatric respiratory diseases and nasal high-flow therapy. This SAP provides state-of-the art standards for trial analysis validity aiming to minimise bias of analyses.

TRIAL REGISTRATION: ACTRN12618000210279.

Formal approval by Australian New Zealand Clinical Trials Registry on 9 February 2018

http://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374240

Key Words:
Paediatric, Children, Respiratory Disease, Respiratory Support, Oxygen Therapy, Statistical Analysis, Randomised Controlled Trial

List of Abbreviations:

ABBREVIATION	TERM
AHRF	Acute Hypoxaemic Respiratory Failure
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
ED	Emergency Department
EWT	Early Warning Tool
FiO_2	Fraction of Inspired Oxygen
HREC	Human Research Ethics Committee
ICU	Intensive Care Unit
NHF	Nasal High-Flow
PARIS	Paediatric Acute Respiratory Intervention Studies
PCCRG	Paediatric Critical Care Research Group
SAP	Statistical analysis plan
SOT	Standard oxygen-therapy
SpO_2	Transcutaneous Oxygen saturation

Introduction

Approximately 15-20% of children with acute hypoxaemic respiratory failure (AHRF) can rapidly deteriorate and require assisted breathing with positive pressure support in an intensive care unit (ICU). Nasal high-flow (NHF) therapy is a commonly used mode of respiratory support which may reduce the work of breathing. Observational studies have suggested that NHF reduces the need for intubation and mechanical ventilation (1-6). Large randomised trials have shown that NHF therapy is as effective as non-invasive ventilation in newborns, and improves outcomes for adults with AHRF (7). Because of its ease of application and non-invasive nature, NHF therapy in children presenting to emergency departments (EDs) has become increasingly popular (8, 9). Due to a lack of high-grade evidence we have designed the PARIS 2 study, a randomised multi-centre randomised controlled trial (RCT) to test the hypothesis that children with AHRF on NHF therapy as a first line oxygen therapy have a reduced hospital length of stay compared with children on standard-oxygen therapy (SOT). Secondary hypotheses are that early use of NHF reduces the requirement to escalate therapy, reduces transfers to higher level of care such as intensive care, reduces the proportion of adverse events, reduces length of oxygen therapy and improves comfort levels of children on NHF. A final secondary objective is to determine the ex post within-trial and ex ante longer term cost-effectiveness of NHF.

Study design and participants

The PARIS 2 trial is a binational, multicentre, RCT in children aged one to four years with AHRF. A total of 1,512 patients are anticipated to be recruited from EDs and general paediatric wards of regional and metropolitan hospitals and tertiary children's hospitals across 14 sites in Australia and New Zealand. The primary objective of the trial is to demonstrate if early use of NHF therapy in children presenting with AHRF will reduce the hospital length of stay, when

compared with SOT. The secondary objectives are to demonstrate if early use of NHF therapy reduces the requirement to escalate therapy, reduces transfers to higher level of care such as intensive care, reduces the proportion of adverse events, and reduces length of oxygen therapy. Additional secondary outcomes are to demonstrate ex post within-trial and ex ante longer term cost-effectiveness of NHF therapy, and to ascertain comfort levels for children on NHF therapy (10). Eligibility for inclusion is determined prior to randomisation with the following criteria: 1) children aged 1–4 years plus 364 days presenting with AHRF, and 2) require hospital admission despite initial assessment and therapy, and 3) an ongoing oxygen requirement (SpO_2 <90/92% in room air, dependent on hospital policy threshold), and 4) have a persistent tachypnoea of ≥35 breaths/min for ≥10 mins at the time of randomisation. Exclusion criteria are: 1) oxygen requirement and therapy in the ED existed for longer than four hours prior to inclusion, 2) previous use of NHF during this illness episode, 3) upper airway obstruction, 4) craniofacial malformation, 5) critically ill (requiring immediate non-invasive or invasive ventilation, decreased level of consciousness) with the need of closer observation in ICU, 6) basal skull fracture, 7) trauma, 8) cyanotic heart disease, 9) home oxygen therapy, 10) palliative care, 11) cystic fibrosis, 12) oncology, and/or 13) child protection patients (10).

The study protocol has been approved by the Children's Health Queensland Human Research Ethics Committee (HREC) (HREC/15/QRCH/159; original submission approved 30/09/2015). Minor modifications to the original study protocol were reviewed and approved by the HREC and are provided in Supplementary Appendix (Section S1). This SAP is based on version 13.0.4 of the study protocol.

Sample size

The sample size calculation was based on the primary outcome of hospital length of stay with survival analysis as the primary analysis method. A difference in length of hospital stay of at least half a day was considered clinically meaningful; for the sample size calculation this was reduced to 0.4 day to increase the sample size to adjust for the effect of clustering. Assuming a median length of hospital stay in the SOT arm of two days (based on pilot data), compared with a median length of hospital stay in the NHF therapy arm of 1.6 days, 5% level of significance and 90% power we require 1,209 children. Allowing for up to 20% non-compliance 1,512 children are required in total; 756 in each treatment group.

Randomisation

Eligible patients are randomly assigned to NHF therapy or SOT in a 1:1 ratio with stratification by site and then by obstructive (or reactive airway disease) and non-obstructive (or parenchymal lung disease) as defined by the admitting clinician at the time of randomisation (10). A computer-based randomisation tool (hosted by Griffith University) is used with a block size of ten integrated into the randomisation schedule. Once eligibility is determined and appropriate consent processes followed (either prospective consent or consent-to-continue), the clinician logs in to the program and obtains the next allocation for the relative strata. All sites except one are using the computer-based randomisation tool. This one participating site (which does not have the capacity to use the online randomisation tool) is using opaque and sealed envelopes in block sizes of ten containing the randomised study arm allocation and study number in sequential order.

Intervention

Children allocated to NHF therapy are receiving high-flow at weight specific flows and oxygen fraction titrated to achieve target saturations. Children allocated to SOT are receiving oxygen using standard sub-nasal cannula or face-mask oxygen to achieve target saturations. All other medical therapies are directed by the attending clinician. The study intervention cannot be blinded.

Outcome measures

The definition and detail of calculation of outcome measures can be found in the Supplementary Appendix (Section S2), along with the Stata scripts written to calculate these outcomes (available on GitHub (11)). Briefly, the outcome measures are (10):

- Primary outcome: hospital length of stay
- Secondary outcomes:
    - length of oxygen therapy since randomisation;
    - receiving a change in oxygen therapy in general ward settings from NHF therapy to SOT or from SOT to NHF therapy;
    - intensive care/high dependency care admission;
    - transfer to a tertiary hospital;
    - escalation of therapy such as non-invasive or invasive ventilation;
    - tolerance level of NHF therapy;
    - clinical triggers that result in a change of therapy;
    - complications and serious adverse events; and
    - health care cost-effectiveness.

Health care cost-effectiveness will be addressed in a separate manuscript and not further discussed in this SAP.

Data monitoring

All study data obtained from the hospital medical records is being entered into a case report form (CRF) locally and then transferred into an online database (WebSpirit, Paediatric Trials Network Australia, Melbourne). Data monitoring is being undertaken throughout the trial, based on a data monitoring and auditing plan (DMAP) devised by the study team. The DMAP was developed in accordance with the ICH E6 (R2) Good Clinical Practice Guideline (12). Briefly, the DMAP includes the following components:

- source data verification on all screening, randomisation, consent data items and data items related to the primary outcome and key secondary outcomes for every enrolled patient; and
- source data verification on all remaining data items for 15% of enrolled patients from each site.

Each site is being monitored independently by a research co-ordinator from a different trial site. This is being undertaken through a combination of on-site monitoring and remote monitoring (due to the coronavirus disease [COVID-19] pandemic). Each relevant data item is being verified individually by comparing the entered value with the value in the source documentation. Where discrepancies are found, the site research co-ordinator and monitor meet to discuss and resolve the discrepancies by review of the original source document. Once data monitoring is finalised, the patient's WebSpirit data entry record is locked in preparation for analysis.

Statistical analysis

Statistical analysis principles

- The primary analysis will be conducted based on the intention-to-treat principle. Specifically, patients who were randomised and provided informed consent will be

analysed based on the treatment group they were allocated to, independent of compliance with the treatment delivered. A per-protocol analysis including all patients who commenced on a study therapy (regardless of whether it was the one they were randomised to) will also be undertaken and reported in supplementary material.

- Statistical tests will be two-sided applying a statistical significance level of 0.05. We will not apply formal correction for multiple testing to any of the subgroup analyses, sensitivity analyses, or to the secondary outcomes. We will ensure conclusions drawn as a result of analyses are interpreted with deference to multiple comparisons.
- If there is missing data for the primary outcome, multiple imputation will be used.
- Continuous variables will be assessed for normality; this will be undertaken using visual inspection of histograms and Q-Q plots.
- Standard descriptive statistics will be used when summarising variables; frequencies (percentages) for discrete variables, mean and standard deviation (SD) for continuous variables, or, if continuous variables are non-normally distributed, median with interquartile range (IQR).
- Subgroup analyses will be executed regardless of any potential treatment effect on the primary or secondary outcomes in the main cohort.
- To ensure transparency and reproducibility, the Stata code that will be used to analyse the final study data will be made available on GitHub (11).
- Changes in the analysis plan by the investigators effective after publication of this SAP will be declared as such.
- The statistical analysis will be undertaken using StataSE version 16 (StataCorp Pty Ltd, College Station, Texas).

Interim analysis

One pre-planned interim analysis was undertaken after the primary outcome measure was finalised for 100 patients for evaluation of safety only. At that time, the Data and Safety Monitoring Board recommended continuation of the trial.

Datasets analysed

The planned Consolidated Standards of Reporting Trials (CONSORT) (13) flow diagram will include all patients being screened for the study (Figure 1). All other analyses will be performed on patients who underwent randomisation and provided informed consent. If consent is not obtained or is withdrawn, data will be excluded from the analyses, unless the withdrawn patient/s permitted the use of data up to the point of withdrawal. The primary dataset for analysis will include baseline variables (demographics, comorbidities, diagnosis), outcomes (primary and secondary), adverse events and details on changes of therapy. Following completion of the data monitoring process, data will be extracted from the study WebSpirit database and imported into StataSE version 16 (StataCorp Pty Ltd, College Station, Texas) for analysis.

Trial profile and overview

Recruitment of patients into the trial will be represented using a flow chart based on the CONSORT guideline (13) (Figure 1). This will describe screened patients, those meeting exclusion criteria, eligible patients, consent process, those randomised into each of the study arms, with the documentation of the primary outcome. We will report on the start and stop date of the trial and provide the recruitment graph by month including division into the contributing sites as a supplementary figure.

Patient baseline characteristics

Baseline characteristics (including demographic data, comorbidities) at time of randomisation will be reported for each of the two treatment groups (statistical comparison between groups will not be undertaken and analyses of outcome measures will not be adjusted for differences noted in baseline characteristics) (Table 1).

Intervention characteristics

We will report on the allocated study intervention versus the received intervention.

Outcome measures analysis

Primary outcome measure

The primary outcome measure (hospital length of stay) will be visually presented using a Kaplan-Meier plot. A Cox proportional hazards model will be used to assess differences between treatment groups with treatment group and stratification variable (obstructive versus non-obstructive airway disease) as fixed effects and site as a random effect (i.e. utilising a shared frailty model). The hazard ratio and 95% confidence interval (CI) will be presented as an estimate of treatment effect (Table 2). Assumptions of the models will be tested and reported on. Additionally, the Hodges–Lehmann method will be used to estimate the median (unadjusted) difference and associated 95% CI.

Secondary outcome measures

For binary outcome measures (e.g. intensive care admission), logistic regression analyses adjusting for treatment group and the stratification variable (obstructive versus non-obstructive airway disease) as fixed effects and site as a random effect will be used, with unadjusted and adjusted odds ratios (ORs) and 95% CIs reported (Table 3). Similar analyses will be

undertaken for continuous outcomes; regression analyses with adjustment for treatment group and stratification variable as fixed effects and site (random effect), with reporting of mean difference (unadjusted and adjusted) and 95% CIs. Survival outcomes (such as length of oxygen therapy) will be treated in the same manner as the primary outcome, however no p-value will be reported.

Safety outcomes

All adverse outcomes defined in the study protocol will be reported as per Table 3 and compared between the two study groups using logistic regression as described above for secondary outcomes.

Subgroup analyses

We will undertake the following pre-planned subgroup analyses:

1) obstructive versus non-obstructive diagnosis at time of randomisation (stratification variable; primary outcome only) (Table 2);
2) obstructive versus non-obstructive diagnosis on discharge using diagnosis related group (DRG) codes (primary outcome only) (Table 2);
3) age in one-year steps (i.e. one-year-olds, two-year-olds, three-year-olds, four-year-olds) (primary outcome only) (Table 2);
4) comparison of length of ICU stay between treatment groups for those patients who were admitted to ICU (reported in-text).

Analyses 1, 3 and 4 were pre-planned. Analysis 2 was not pre-planned, however during the study it has become apparent that the discharge diagnosis can often be quite different to the diagnosis on admission. The DRG codes will be categorised into obstructive versus non-

obstructive airway disease as per the entry strata, and the results of this analysis will be compared to the entry strata and reported in the supplementary material.

Subgroup analyses will be undertaken using the same analysis methods described for the primary outcome measure, with the addition of the subgroup variable and its related interaction term into the main regression model; the interaction effect (and 95% CI and p-value) will be reported, alongside the descriptive statistics for the outcome under investigation.

Additionally, two pre-planned sensitivity analyses that address outcomes that may be partially subjective will be undertaken. The outcome for the first sensitivity analysis will be a composite outcome defined as intensive care/high dependency care admission and three or more of the following clinical criteria present:

a) heart rate remains >160/min for longer than two hours prior to admission to intensive care/high dependency care;
b) respiratory rate remains >45/min for longer than two hours prior to admission to intensive care/high dependency care;
c) oxygen requirement in NHF therapy arm exceeds FiO2 > 40/50% (dependant on hospital standard policy) to maintain SpO2 ≥90/92% or oxygen requirement in control oxygen arm exceeds SOT (2L/min by nasal prong, or 8L/min by face-mask) to maintain SpO2 ≥90/92% (dependant on hospital standard policy threshold) prior to admission to intensive care/high dependency care; and
d) the hospital internal Early Warning Tool (EWT) calls for medical review prior to escalation.

The outcome for the second sensitivity analysis will be a composite outcome defined as transfer to a tertiary hospital and three or more of the following clinical criteria present:

a) heart rate remains >160/min for longer than two hours prior to request for transfer;
b) respiratory rate remains >45/min for longer than two hours prior to to request for transfer;
c) oxygen requirement in NHF therapy arm exceeds FiO2 > 40/50% (dependant on hospital standard policy) to maintain SpO2 ≥90/92% or oxygen requirement in control oxygen arm exceeds SOT (2L/min by nasal prong, or 8L/min by face mask) to maintain SpO2 ≥90/92% (dependant on hospital standard policy threshold) prior to request for transfer; and
d) the hospital internal Early Warning Tool (EWT) calls for medical review prior to escalation.

Results will be presented in the same manner as primary analyses and included in supplementary material.

Treatment of missing data

Missing data will be imputed for the primary outcome measure if hospital length of stay is not available. Fully conditional specification will be used for imputation; the imputation model will include randomised treatment arm, study site and the stratification variable. Ten sets of imputed data will be created using the methods described for the primary outcome. A pooled common effect estimate and 95% confidence interval will be generated from the imputed datasets.

Conclusion

The PARIS 2 trial will be analysed according to the analysis principles outlined in this publication. Transparency and accountability is being ensured through publicly accessible analysis code.

Trial status

Protocol version: 13.0

Date of first recruitment: 15 December 2017

Date of last recruitment: 27 March 2020

Currently cleaning the data and has not been unlocked or viewed as of 27 July 2020.

List of planned figures

Figure 1. CONSORT participant flow diagram

Figure 2. Kaplan-Meier survival curve of primary outcome (all patients, and the pre-specified subgroups)

List of planned Supplementary Appendix material

- Funding sources
- Trial steering committee and PARIS trial investigators
- Data Monitoring Plan
- Enrolment statistics by month, site and country
- Diagnosis at discharge
- List of protocol violations
- Results of interim analysis
- Consent details
- List of adverse events
- Results of per-protocol analysis
- Results of sensitivity analyses
- Figures detailing physiological parameters over time
- Table of diagnosis at discharge

Data and Safety Monitoring Board:

Phil Sargent, Scott Burgess.

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Figure 1. Proposed CONSORT participant flow diagram

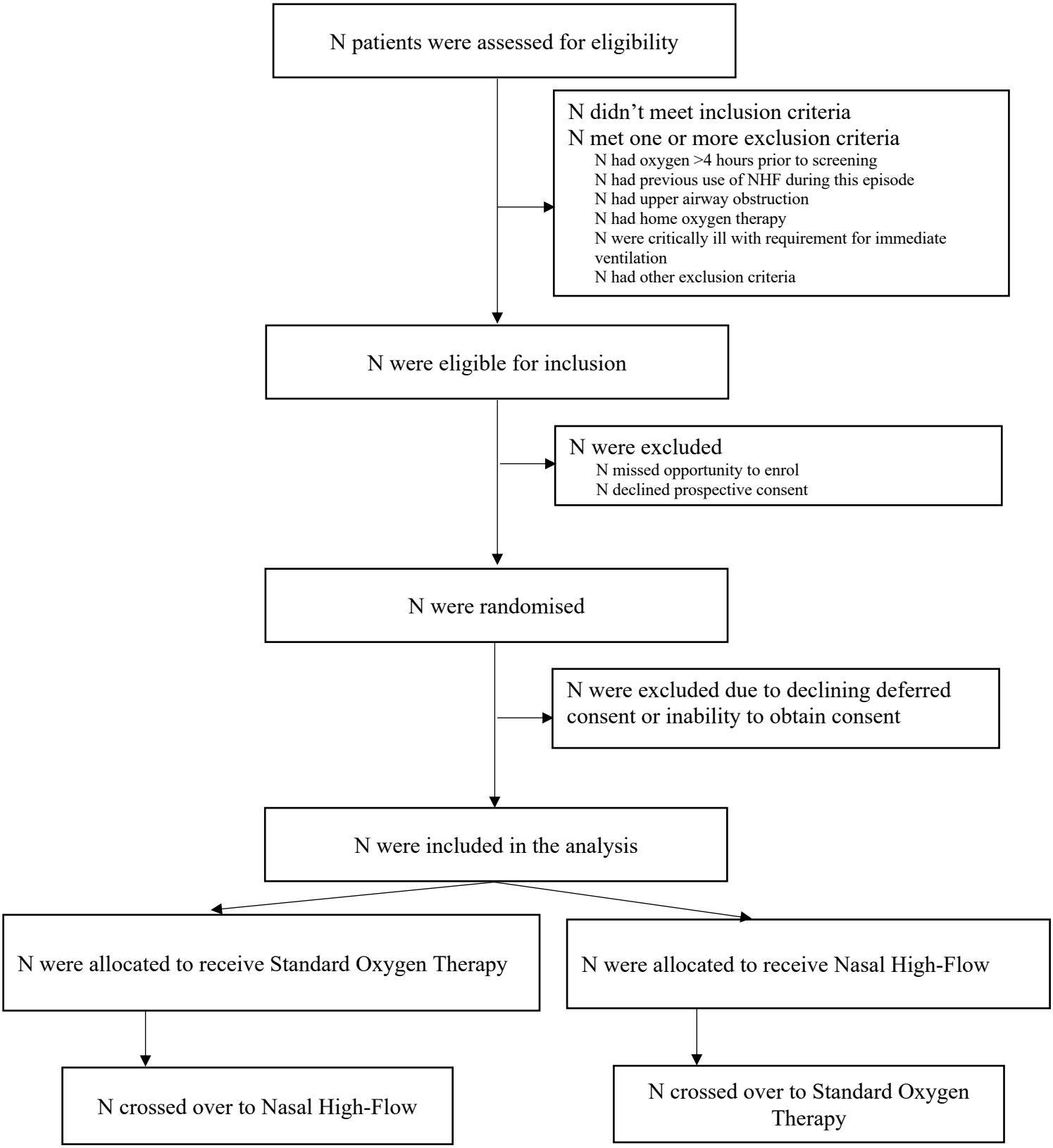

Table 1. Characteristics of infants enrolled in PARIS 2 trial

Characteristic	**Standard Oxygen Therapy N=**	**Nasal High-Flow N=**
Age at randomisation (years) *mean (SD)/median (IQR)*		
Weight (kg) *mean (SD)/median (IQR)*		
Female sex *n (%)*		
Ethnicity *n (%)*		
Caucasian		
Aboriginal/Torres Strait Islander		
Asian		
Maori		
Pacific Islander		
Other		
Unknown		
Premature birth[&] *n (%)*		
Neonatal respiratory support[#] *n (%)*		
Oxygen only *n (%)*		
Non-invasive ventilation *n (%)*		
Invasive ventilation *n (%)*		
Previous hospital admission for respiratory disease *n (%)*		
Previous ICU admission for respiratory support *n (%)*		
Invasive ventilation *n (%)*		
Non-invasive ventilation *n (%)*		
Nasal high-flow *n (%)*		
Chronic lung disease *n (%)*		
Congenital heart disease *n (%)*		
Patient history of wheeze *n (%)*		
Family history of asthma[$] *n (%)*		
Family history of allergy *n (%)*		
Currently attending child care *n (%)*		
Viral aetiology^		
Viral testing performed *n (%)*		
Adenovirus *n (%)*		
Influenza *n (%)*		
Metapneumovirus *n (%)*		
Respiratory syncytial virus (RSV) *n (%)*		
Multiple viruses *n (%)*		
No virus detected on nasopharyngeal aspirate *n (%)*		
Diagnosis at admission		
Obstructive* *n (%)*		
Asthma *n (%)*		

Bronchiolitis *n (%)*		
Viral induced wheeze *n (%)*		
Reactive airways disease *n (%)*		
Pneumonitis *n (%)*		
Other obstructive airway disease *n (%)*		
Non-obstructive* *n (%)*		
Pneumonia bacterial/viral *n (%)*		
Acute LRTI *n (%)*		
Acute respiratory distress disorder *n (%)*		
Pneumonitis *n (%)*		
Bronchopneumonia *n (%)*		
Bronchiectasis *n (%)*		
Aspiration *n (%)*		
Other non-obstructive airway disease *n (%)*		
Severity pre-enrolment		
Heart rate beats/min *mean (SD)*		
Respiratory rate breaths/min *mean (SD)*		
SpO_2 *median (IQR)*		
Time from presentation to randomisation (hours) *mean (SD)*		
Time of onset of illness to presentation (days) *median (IQR)*		
Hospital has on-site intensive care unit *n (%)*		
Country of hospital		
Australia *n (%)*		
New Zealand *n (%)*		

[&] denominator excludes children where it was unknown whether they were premature (standard group N=xx; nasal high flow group N=xx)**;** [#] denominator excludes children where it was unknown whether they received respiratory support post-birth (standard group N=xx; nasal high flow group N=xx)**;** [$] denominator excludes children where it was unknown if there is a family history of asthma (standard group N=xx; nasal high flow group N=xx)**;** [^] denominator is the number of children with a nasopharyngeal aspirate taken (standard group N=xx; nasal high flow group N=xx); [*]used for stratification

SD standard deviation; IQR interquartile range; ICU intensive care unit; LRTI lower respiratory tract infection

Table 2. Primary outcome in the total trial cohort and subgroups

Outcome	**Standard Oxygen Therapy N=**	**Nasal High-Flow N=**	**Estimate of Difference (95% CI)**	**Adjusted Estimate of Difference (95% CI)[#]**	**p-value**
Total trial cohort					
Hospital length of stay *median (IQR)* [#&]					
Subgroup: presence or absence of obstructive airway disease at randomisation^					
Obstructive disease hospital length of stay *median (IQR)*					
Non-obstructive disease hospital length of stay *median (IQR)*					
Subgroup: presence or absence of obstructive airway disease at discharge^					
Obstructive disease hospital length of stay *median (IQR)*					
Non-obstructive disease hospital length of stay *median (IQR)*					
Subgroup: age at randomisation^					
1 year olds hospital length of stay *median (IQR)*					
2 year olds hospital length of stay *median (IQR)*					
3 year olds hospital length of stay *median (IQR)*					
4 year olds hospital length of stay *median (IQR)*					

IQR interquartile range; CI confidence interval

[#] adjusted for presence or absence of obstructive airway disease at randomisation and study site

[&] unadjusted p-value = xxx

^ p-value represents interaction term determined by logistic regression

Table 3. Secondary outcomes in the total trial cohort

Outcome	**Standard Oxygen Therapy N=**	**Nasal High-Flow N=**	**Unadjusted Estimate of Difference (95% CI)[#]**	**Adjusted Estimate of Difference (95% CI)[#]**
Total hospital length of stay *median (IQR)*				
Length of oxygen therapy since randomisation *median (IQR)*				
Change in oxygen therapy in general ward *n (%)*				
Intensive care/high dependency care admission *n (%)*				
Transfer to a tertiary hospital *n (%)*				
Escalation of therapy *n (%)*				
Tolerance level at four hours				
Parental rating *mean (SD)/median (IQR)*				
Staff rating *mean (SD)/median (IQR)*				
Tolerance level between four and 48 hours^				
Parental rating *mean (SD)/median (IQR)*				
Staff rating *mean (SD)/median (IQR)*				
Clinical trigger/s for first change in randomised therapy*				
Change in heart rate *n (%)*				
Change in respiratory rate *n (%)*				
Increasing oxygen requirement *n (%)*				
EWT trigger *n (%)*				
Increased work of breathing *n (%)*				
Decreased level of consciousness *n (%)*				
Deterioration of cardiovascular function with impaired peripheral perfusion *n (%)*				
Clinician directed *n (%)*				
Intensive care unit review *n (%)*				
Other *n (%)*				

Complications and adverse events				
Death *n (%)*				
Air leak syndrome *n (%)*				
Emergency intubation *n (%)*				
Cardiac arrest *n (%)*				
Respiratory arrest *n (%)*				
Other *n (%)*				

SD standard deviation; IQR interquartile range; CI confidence interval; EWT early warning tool

^ Median (IQR) hours post-commencement of oxygen therapy that VAS scale administered was xx (xx) in the standard oxygen group and yy (yy) in the nasal high-flow group

adjusted for presence or absence of obstructive airway disease at randomisation and study site

* multiple clinical triggers per change in therapy may be recorded

Supplementary Appendix

S1. List of approved protocol modifications

Version Number	Approval Date	List of Modifications
1 (Original)	30.09.2015	Original pilot protocol
2.0	26.11.2015	• Study duration changed • Additional exclusion criteria included • Additional screening components included
3.0	01.02.2016	• Added Lady Cilento Children's Hospital Principal Investigator • Changed SpO_2 threshold to 92% • Included feeding whilst on NHF therapy • Modified inclusion criteria with requiring hospital admission despite initial assessment and therapy including inhalation/burst therapy
4.0	08.03.2016	• Additions to background, hypotheses and recruitment process • Added definition of AHRF and diagnostic groups • Modification to inclusion/exclusion criteria
5.0	26.05.2016	• Additional exclusion criteria included
6.0 (Full study protocol)	28.03.2017	• Pilot to full study protocol changes: o Pilot data included o Additional sites and investigators o Sample size based on latest pilot data o Limited age group to 1 to 4 years plus 364 days o Changes in primary outcome from pilot to fully powered trial with specific criteria post pilot data o Changes to aim, hypothesis, primary objective, secondary objectives, serious adverse events o Changes to definition of AHRF with obstructive versus non-obstructive randomisation o Changes to escalation of care or change in therapy o Changes to inclusion/exclusion criteria, data analysis plan and health economic evaluation post pilot trial o Introduced tolerance component with a COMFORT Score using a VAS measurement tool

Version Number	Approval Date	List of Modifications
		○ Included prototype nasal cannula trial validation (HREC/15/QPAH/273)
7.0	28.04.2017	• Changes to inclusion criteria pre-roll out to PREDICT sites, New Zealand consent and formatting document
8.0	31.05.2017	• Changes to data collection, inclusion criteria, definition of obstructive and non-obstructive groups
9.0	28.06.2017	• Changes outlining two different ways of randomisation – computer generated and envelope based dependent on institution
10.0	28.09.2017	• Clarification to primary objective of study, exclusion criteria and interim analysis
11.0	11.12.2017	• Minor changes to wording of primary outcome for clarity and responder vs non-responder and inclusion/exclusion criteria and sample size.
12.0	31.05.2018	• Changes to incorporate Western Australia and New South Wales as prospective consent only and inclusion of 50% saturation threshold for John Hunter Children's Hospital
13.0	06.02.2019	• Adjusted sample size for non-normal distribution of length of stay • Changed Lady Cilento Children's Hospital to new hospital name (Queensland Children's Hospital)

Section S2. Definition of outcomes

Primary outcome

Hospital length of stay is defined as the time from randomisation to discharge from hospital.

Secondary outcomes

- Total hospital length of stay defined as the time from presentation to discharge from hospital.
- Length of oxygen therapy since randomisation is defined as the time from randomisation to the time that the patient is off any oxygen therapy (NHF or standard oxygen therapy).
- Receiving a change in oxygen therapy in general ward settings is defined as:
    - changing from standard oxygen therapy to NHF therapy;
    - changing from standard oxygen therapy to fly-by/blow-by oxygen;
    - changing from NHF to standard oxygen therapy;
    - changing from NHF to fly-by/blow-by oxygen;
    - changing from NHF at weight-specific flow rates as per protocol to higher rates; or
    - changing from NHF at weight-specific flow rates as per protocol to lower rates.
- Intensive care/high dependency care admission is the admission of the child to an intensive care unit or high dependency care unit within the admission hospital or transfer to one of these units within another hospital.
- Transfer to a tertiary hospital is defined as transfer from a non-tertiary hospital to a tertiary hospital for escalation of care (for this study, the following hospitals are considered non-tertiary hospitals: Caboolture Hospital, Ipswich Hospital, Redcliffe, The Prince Charles Hospital). If the site where the patient is originally randomised is a tertiary site, they will not be included in the denominator for this outcome.
- Escalation of therapy includes:

- admission to intensive care unit/high dependency unit; or
- transfer to a tertiary hospital; or
- commencement of non-invasive or invasive ventilation (NIV, CPAP, intubation and mechanical ventilation).

- Tolerance level of therapy is measured using a 100mm unmarked visual analogue scale (VAS) (one end of scale is labelled 'no discomfort' and the other end of the scale is labelled 'maximal imaginable discomfort') completed separately by the parent/carer and the nurse at the following times:
  - one hour post commencement of oxygen therapy; and
  - between four and 48 hours post commencement of oxygen therapy.
- Clinical triggers that result in a first change of randomised therapy include any of the following (the denominator for this outcome is the number of children who had a change of therapy; only the clinical trigger for the first change of therapy, in the situation where multiple change of therapy occur, is reported):
  - elevated heart rate (beats/min), reported as change from pre-randomisation observations to observations taken at time of change in therapy;
  - elevated respiratory rate (breaths/min), reported as change from pre-randomisation observations to observations taken at time of change in therapy;
  - increasing oxygen requirement (FiO_2 or O_2 in L/min), reported as change from first observations post commencement of therapy to observations taken at time of change in therapy;
  - Early warning tool trigger;
  - increased work of breathing;
  - decreased level of consciousness;
  - deterioration of cardiovascular function with impaired peripheral perfusion;

    - clinician decision;
    - ICU review involved; or
    - other relevant reason.
- Complications and serious adverse events reported are:
    - death before hospital discharge;
    - air leak syndrome, including pneumothorax;
    - emergency and unexplained intubation;
    - cardiac arrest;
    - unexplained respiratory arrest requiring mechanical ventilation; or
    - other.