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Statistical Analysis Plan

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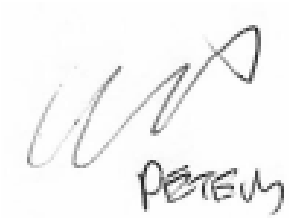
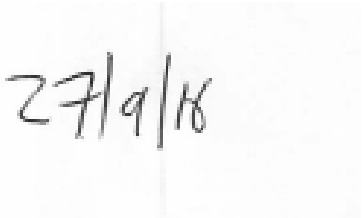
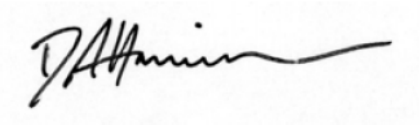
Role, Name and Position	**Signature**	**Date**
Chief investigator: Prof Mark Peters (Professor of Paediatric Intensive Care, University College London)		
Senior Statistician: Dr David Harrison (Senior Statistician, ICNARC)		27/09/2016

Version history

Version number	Date	Summary of main changes from previous versions
1.0	22/09/2016	N/A

Contents

Abbreviations

AE	adverse event
BiPAP	bilevel positive airway pressure
CPAP	continuous positive airways pressure
FiO_2	fraction of inspired oxygen
GOSH	Great Ormond Street Hospital for Children
HFHO	High Flow Humidified Oxygen
ICNARC	Intensive Care National Audit & Research Centre
ICU	intensive care unit
PELOD	Paediatric Logistic Organ Dysfunction score
PICU	paediatric intensive care unit
PICANet	Paediatric Intensive Care Audit Network
PIM2	Paediatric Index of Mortality version 2
SAE	serious adverse event
$ScvO_2$	central venous oxygen saturation
SpO_2	oxygen saturation

1. Background

The randomised study of early continuous positive airways pressure in acute respiratory failure in children with impaired immunity (SCARF) is a pragmatic, open, randomised controlled trial in infants and children with severely impaired immunity and acute respiratory failure.

This document describes the proposed statistical analyses for the Trial. It is important to set these out and agree on them in advance of analysing the outcome data for the Trial, so that data-derived decisions in the analyses are avoided.

2. Objective and hypotheses

The primary objective of the Trial is to determine if admission to the paediatric intensive care unit (PICU) for early delivery of continuous positive airways pressure (CPAP) – i.e. before it is required to maintain gas exchange – reduces the requirement for invasive mechanical ventilation and improves survival in infants and children with severely impaired immunity and acute respiratory failure compared to standard care. The secondary objectives include comparing mortality at 30 days, 90 days and one year between the two treatment groups.

The hypothesis of the Trial is that early admission to the (PICU) for early delivery of CPAP will reduce the need for intubation and invasive mechanical ventilation within 30 days and improve survival from both acute and acute on chronic respiratory failure in children with impaired immunity.

3. Study design

3.1 Inclusion/exclusion criteria

The Trial population will consist of infants and children receiving treatment at a participating site who fulfil all of the inclusion criteria and none of the exclusion criteria below.

3.1.1 Inclusion criteria

- Age less than 18 years
- Expected to have impaired immunity for at least three months as a result of a primary diagnosis, therapy or a combination of both
- Acute respiratory failure or acute on chronic respiratory failure

3.1.2 Exclusion criteria

- Already receiving invasive mechanical ventilation for non-respiratory indications
- Other acute indication for emergency PICU admission and invasive mechanical ventilation, independent of the degree of respiratory failure (e.g. shock, reduced level of consciousness, seizures), as assessed by the PICU team
- Recent oesophageal/gastric surgery
- End-of-life care plan in place with limitation of resuscitation
- Life expectancy less than 12 months

- Already receiving treatment on PICU

3.2 Study Treatment

The treatments used in the Trial are described below.

3.2.1 Intervention group

Participants allocated to the intervention group (early CPAP) will be admitted to the PICU and receive CPAP of at least 6cm H_2O with supplemental oxygen for a minimum of 12 hours per day for at least four consecutive days (Level 2 respiratory support). The interface for delivering CPAP (i.e. via face mask, helmet or infant flow-driver) will be at the discretion of the clinical team responsible for the participant's care. All other care will be determined by the clinical team primarily responsible for the participant's care.

3.2.2 Control group

Participants allocated to the control group (usual treatment) will remain on the ward and receive supplemental oxygen to maintain oxygen saturation in accordance with standard local practice (Level 1 respiratory support). All other care (including antimicrobial therapy, fluid therapy, analgesia and sedative agents, bronchodilator therapy) will be determined by the clinical team primarily responsible for the child's care. Participants in the control group will be admitted to the PICU in accordance with standard acutely ill child protocols and as deemed necessary by the ICU outreach/Medical Rapid response teams and the clinical team responsible for the child's care.

3.2.3 Levels of respiratory support

The four levels of respiratory support are as follows:

i. Level 1: inspired oxygen therapy on the ward (control group only);
ii. Level 2: CPAP at 6-10cm H_2O;
iii. Level 3: non-invasive bilevel positive airway pressure (BiPAP) via facemask or helmet;
iv. Level 4: intubation and mechanical ventilation.

3.3 Outcome measures

3.3.1 Primary

The primary outcome measure is the requirement for intubation and invasive mechanical ventilation (Level 4 respiratory support) within 30 days post-randomisation

3.3.2 Secondary

The secondary outcome measures are:

- maximum and aggregate paediatric logistic organ dysfunction score (PELOD) at 30 days post-randomisation;
- mortality at 30 days post-randomisation;
- requirement for Level 2 or Level 3 respiratory support within 30 days post-randomisation;
- days free from any ventilator support (Level 2, 3 or 4 respiratory support) at 30 days post-randomisation;

- days free from supplemental oxygen (i.e. above pre-acute respiratory failure requirement) at 30 days post-randomisation;
- hospital mortality;
- mortality at 90 days post-randomisation; and
- mortality at one year post-randomisation.

4. Sample size calculation

Data submissions to the Paediatric Intensive Care Audit Network (PICANet), the national clinical audit for PICUs in the UK, reported a mean of 3.3 patients per month with severely impaired immunity admitted to GOSH PICU over an eight-year period (2003-10). Two thirds were admitted with respiratory failure as the primary reason for admission and 75% of these received mechanical ventilation. We estimated that a similar number experience acute respiratory distress on the ward fitting our inclusion criteria that do not require ICU admission. Therefore we expected to randomise around 4-5 participants per month and anticipated an intubation rate of around 35-40% in the control group. Assuming the same relative risk reduction (~60%) as observed in adult studies, a sample of 148 children (74 in each treatment group) was required to detect a reduction in intubation rate from 35% to 14% with 80% power and a type 1 error rate of 5% (two-sided).

At the Trial Steering Committee meeting in November 2014, the decision was taken, due to poor recruitment, to continue the study to the current planned end of patient recruitment (January 2016) but not to seek additional funding to extend recruitment beyond this date.

5. End of trial

The end of the trial will be when the last participant has completed their one year follow-up.

6. Analysis principles

All analyses will be conducted by intention to treat. The patients will be analysed according to the treatment group they were randomised to, irrespective of whether the treatment allocated was received i.e. all patients will be included in the analysis, regardless of whether they have, or have not, adhered to the protocol. A two-sided p value of <0.05 will be taken to indicate a statistically significant result.

7. Handling of missing data

As the amount of missing data is anticipated to be minimal, a sensitivity approach will be taken when the primary outcome variable is missing. The primary analysis will be repeated once assuming that all patients allocated to early CPAP with missing outcomes did not receive invasive mechanical ventilation (Level 4 respiratory support), and all patients allocated to standard treatment with missing outcomes did receive invasive mechanical ventilation (Level 4 respiratory support). The analysis will then be repeated again with the opposite assumptions. This will then give the absolute range of how much the results could change if the primary outcome variable were complete.

In adjusted analyses missing baseline data will be handled by multiple imputation using chained equations.

8. Initial descriptive analyses

8.1 Recruitment, treatment allocation and follow-up

Recruitment to the Trial, treatment allocation and completeness of follow-up will be illustrated by a CONSORT flow diagram. All participating sites have maintained a Screening Log of infants and children who are eligible (fulfil all of the inclusion criteria and none of the exclusion criteria) but not randomised, or who fulfil all of the inclusion criteria but meet one or more of the exclusion criteria. Reasons for non-recruitment will be categorised and summarised.

8.2 Baseline characteristics

The following baseline (pre-randomisation) demographic and clinical factors will be summarised by treatment group but not subjected to statistical testing:

- Age group (<12 months; ≥12 months)
- Age in months
- Gender
- Weight
- Acute respiratory failure or acute on chronic respiratory failure
- Bone marrow transplant
- Cause(s) of impaired immunity
- Suspected cause of acute respiratory failure (at the time of randomisation)
- PIM2r score[1]
- Supplemental O_2 requirement (pre-acute respiratory failure)

Numbers and percentages within each treatment group will be reported for categorical factors; means (with SD) and medians (with IQR) within each treatment group will be reported for continuous factors. P values will not be calculated or quoted.

8.3 Clinical management

Clinical management will be summarised by treatment group but not subjected to statistical testing.

The treatment groups will be compared for the following:

- Admitted to PICU
- Length of stay in PICU
- CPAP (Level 2 respiratory support) received
- Length of stay in acute hospital (from randomisation)

Numbers (%) or means (SD) and medians (IQR), as appropriate, will be given in each treatment group. P values will not be calculated or quoted.

8.4 Protocol adherence

Numbers and percentages of protocol deviations will be reported. The following protocol deviations will be reported for the intervention (early CPAP) group:

- Did not start CPAP within 24 hours
- CPAP not received for specified time period (other than due to escalation of respiratory support)
- Higher level of respiratory support received without clear clinical criteria documented for escalation
- High Flow Humidified Oxygen (HFHO) received

The following protocol deviations will be reported for the control (usual treatment) group:

- Higher level of respiratory support received without clear clinical criteria documented for escalation
- High Flow Humidified Oxygen (HFHO) received

Overall adherence will be reported as the number and percentage of patients in each treatment group not meeting any of the above criteria.

9. Primary analysis

The number and percentage of patients requiring invasive mechanical ventilation 30 days following randomisation will be reported. Invasive mechanical ventilation by 30 days following randomisation will be compared between the treatment groups, unadjusted, using Fisher's exact test and reported as a relative risk with 95% confidence interval and as an absolute risk reduction with 95% confidence interval.

As a secondary analysis, the primary outcome will also be analysed using logistic regression adjusted for the following baseline covariates: age, weight, bone marrow transplantation and PIM2 score[1]. Other covariates originally planned for inclusion in the adjusted analysis (cause of impaired immunity, suspected main cause of acute respiratory failure) will not be included in the model due to the smaller sample size. The results of the logistic regression model will be reported as an adjusted odds ratio with a 95% confidence interval. The unadjusted odds ratio will be presented for comparison.

10. Secondary analyses

The subsequent secondary analyses will be adjusted using the following baseline covariates: age, weight, bone marrow transplantation and PIM2 score[1]. The baseline covariates have been selected *a priori* for their anticipated strong association with the outcome. No further selection of covariates will be performed based on imbalance at baseline or significance in univariable analyses.

10.1 Mortality at acute hospital discharge, 30-days, 90-days and one year post-randomisation

The number and percentage of deaths at acute hospital discharge at 30 days, 90 days and one year following randomisation will be reported for the treatment groups. Differences in mortality will be

compared, unadjusted, using Fisher's exact test and relative risk with a 95% confidence interval. They will also be compared adjusted, using logistic regression - adjusted for the same *a priori* baseline variables reported above.

Kaplan Meier curves comparing the treatment groups will be plotted up to 90 days and one year following randomisation.

10.2 Requirement for Level 2 or Level 3 respiratory support within 30 days post-randomisation

The number and percentage of children and infants requiring level 2 or level 3 respiratory support within 30 days following randomisation will be reported for the treatment groups. Differences in requirement of level 2 or level 3 respiratory support will be compared, unadjusted, using Fisher's exact test and relative risk with a 95% confidence interval. They will also be compared adjusted, using logistic regression - adjusted for the same *a priori* baseline variables reported above. The results of the logistic regression model will be reported as an adjusted odds ratio with 95% confidence interval. The unadjusted odds ratio will be presented for comparison.

10.3 Paediatric logistic organ dysfunction score (PELOD score^2) at 30 days post-randomisation

The maximum and aggregate paediatric logistic organ dysfunction score (PELOD score^2) at 30 days following randomisation will be summarised, within each treatment group. Patients that die within 30 days post randomisation will be considered to have the maximum possible PELOD score (71 points) from the day of death onwards. Differences between the treatment groups will be compared using linear regression - adjusted for the same *a priori* baseline variables reported above. The results of the linear regression model will be reported adjusted, and unadjusted for comparison, with 95% confidence interval for the coefficients.

10.4 Days free from any ventilator support at 30 days post-randomisation

The mean number of days free from any ventilator support up to 30 days following randomisation, within each treatment group will be reported. Patients that die within 30 days post-randomisation will be considered to have zero days free from any ventilator support. Differences between the treatment groups will be compared using linear regression - adjusted for the same *a priori* baseline variables reported above. The results of the linear regression model will be reported adjusted, and unadjusted for comparison, with 95% confidence interval for the coefficients.

10.5 Days free from supplemental oxygen at 30 days post-randomisation

The mean number of days free from any supplemental oxygen ventilator support up to 30 days following randomisation, within each treatment group will be reported. Patients that die within 30 days post-randomisation will be considered to have zero days free from supplemental oxygen. Differences between the treatment groups will be compared using multilevel linear regression - adjusted for the same *a priori* baseline variables reported above. The results of the multilevel linear regression model will be reported adjusted, and unadjusted for comparison, with 95% confidence interval for the coefficients.

11. Subgroup analyses

Due to the small sample size, no subgroup analyses are planned.

12. Interim analyses

A single interim analysis was planned to be conducted at 50% recruitment. The results of the interim analysis were to be reviewed by the DMEC, using a Peto-Haybittle stopping rule ($P<0.001$) to recommend early termination of the trial due to harm. However, as the required number of patients was not fulfilled, the interim analysis could not be carried out.

13. Safety

The number and percentage of Serious Adverse Events (SAEs) within 30 days (either from admission to PICU for early delivery of CPAP or from randomisation for children and infants randomised to standard care) will be reported. SAEs will be compared between treatment groups using Fisher's exact test.

References

1. Slater A, Shann F, Pearson G, Paediatric Index of Mortality (PIM) Study Group. PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med. 2003 Feb; 29(2): 278-85.
2. Leteurtre S, Duhamel A, Grandbastien B, Proulx F, Cotting J, et al. Daily estimation of the severity of multiple organ dysfunction syndrome in critically ill children. CMAJ 2010 Aug10; 182(11): 1181-7.

Appendix 1: Dummy tables and figures

Proposed tables

i. Table 1: Comparison of baseline characteristics by treatment group

Variables		Early CPAP	Usual treatment
		N=XX	N=XX
Age group	0-11 months, n (%)	XX (XX.X)	XX (XX.X)
	12 months or older, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Age (months)	mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	median (IQR)	XX (XX, XX)	XX (XX, XX)
	[N]	[XX]	[XX]
Gender	Male, n (%)	XX (XX.X)	XX (XX.X)
	Female, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Weight (kg)	mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	median (IQR)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
	[N]	[XX]	[XX]
Acute respiratory failure criteria met	Acute respiratory failure, n (%)	XX (XX.X)	XX (XX.X)
	Acute on chronic respiratory failure, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Bone marrow transplant	Yes, n (%)	XX (XX.X)	XX (XX.X)
	No, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Cause of impaired immunity*	High risk of severe neutropenia, n (%)	XX (XX.X)	XX (XX.X)
	Severe immunodeficiency, n (%)	XX (XX.X)	XX (XX.X)
	Haemophagocytic lymphohistiocytosis, n (%)	XX (XX.X)	XX (XX.X)
	Undergoing bone marrow transplantation, n (%)	XX (XX.X)	XX (XX.X)
	Other condition/therapy, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Suspected main cause of acute respiratory failure	Viral pneumonitis, n (%)	XX (XX.X)	XX (XX.X)
	Bacterial chest infection, n (%)	XX (XX.X)	XX (XX.X)
	Graft-versus-host disease, n (%)	XX (XX.X)	XX (XX.X)
	Fluid overload, n (%)	XX (XX.X)	XX (XX.X)
	Veno-occlusive disease, n (%)	XX (XX.X)	XX (XX.X)
	Other condition/therapy*, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
PIM2r score	mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	median (IQR)	XX (XX, XX)	XX (XX, XX)
	[N]	[XX]	[XX]
Supplemental O_2 requirement (pre-acute respiratory failure)	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]

* patients may have more than one cause of impaired immunity; n: number of patients; %: percentage of patients; N: total number of patients; SD: standard deviation; IQR: interquartile range

ii. Table 2: Comparison of clinical management by treatment group

Variables		Early CPAP	Usual treatment
		N=XX	N=XX
PICU admission	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Length of stay in PICU (days)	mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	median (IQR)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
	[N]	[XX]	[XX]
CPAP (Level 2 respiratory support) received	No, n (%)	XX (XX.X)	XX (XX.X)
	Yes, n (%)	XX (XX.X)	XX (XX.X)
	[N]	[XX]	[XX]
Length of stay in acute hospital (days)	mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	median (IQR)	XX (XX, XX)	XX (XX, XX)
	[N]	[XX]	[XX]

n: number of patients; %: percentage of patients; N: total number of patients; SD: standard deviation; IQR: interquartile range

iii. Table 3: Protocol adherence by treatment group

	Early CPAP	Usual treatment
	N=XX	N=XX
Protocol deviations		
Did not start CPAP within 24 hours	XX (XX.X)	N/A
CPAP not received for specified time period*	XX (XX.X)	N/A
Higher level of respiratory support received without clear clinical criteria documented for escalation	XX (XX.X)	XX (XX.X)
High Flow Humidified Oxygen (HFHO) received	XX (XX.X)	XX (XX.X)
Overall adherence, n (%)	**XX (XX.X)**	**XX (XX.X)**

*other than due to escalation of respiratory support; n: number of patients; %: percentage of patients; N: total number of patients; SD: standard deviation; IQR: interquartile range

iv. Table 4: Comparison of outcomes by treatment group

Outcomes	Early CPAP N=XX	Usual treatment N=XX	Effect estimate (95% CI)	P value
Primary outcome				
Requirement for intubation and invasive mechanical ventilation (Level 4 respiratory support) within 30 days*, n (%)	XX (XX.X)	XX (XX.X)	Relative risk: X.XX (X.XX, X.XX) Absolute risk reduction: X.X (X.X, X.X) Odds ratio: X.XX (X.XX, X.XX) Adjusted odds ratio: X.XX (X.XX, X.XX)	0.XXX 0.XXX
Secondary outcomes				
Maximum PELOD score[2] at 30 days*, mean (SD)	XX.X (XX.X)	XX.X (XX.X)	Mean difference: X.X (X.X, X.X) Adjusted mean difference: X.X (X.X, X.X)	0.XXX 0.XXX
Aggregate PELOD score[2] at 30 days*, mean (SD)	XX.X (XX.X)	XX.X (XX.X)	Mean difference: X.X (X.X, X.X) Adjusted mean difference: X.X (X.X, X.X)	0.XXX 0.XXX
Mortality at 30 days*, n (%)	XX (XX.X)	XX (XX.X)	Odds ratio: X.XX (X.XX, X.XX) Adjusted odds ratio: X.XX (X.XX, X.XX)	0.XXX 0.XXX
Requirement for Level 2 or Level 3 respiratory support within 30 days*, n (%)	XX (XX.X)	XX (XX.X)	Odds ratio: X.XX (X.XX, X.XX) Adjusted odds ratio: X.XX (X.XX, X.XX)	0.XXX 0.XXX
Days free from any ventilator support at 30 days*, mean (SD)	XX.X (XX.X)	XX.X (XX.X)	Mean difference: X.X (X.X, X.X) Adjusted mean difference: X.X (X.X, X.X)	0.XXX 0.XXX
Days free from supplemental oxygen at 30 days*, mean (SD)	XX.X (XX.X)	XX.X (XX.X)	Mean difference: X.X (X.X, X.X) Adjusted mean difference: X.X (X.X, X.X)	0.XXX 0.XXX
Hospital mortality, n (%)	XX (XX.X)	XX (XX.X)	Odds ratio: X.XX (X.XX, X.XX) Adjusted odds ratio: X.XX (X.XX, X.XX)	0.XXX 0.XXX
Mortality at 90 days*, n (%)	XX (XX.X)	XX (XX.X)	Odds ratio: X.XX (X.XX, X.XX) Adjusted odds ratio: X.XX (X.XX, X.XX)	0.XXX 0.XXX
Mortality at one year*, n (%)	XX (XX.X)	XX (XX.X)	Odds ratio: X.XX (X.XX, X.XX) Adjusted odds ratio: X.XX (X.XX, X.XX)	0.XXX 0.XXX

*post-randomisation; n: number of patients; %: percentage of patients; SD: standard deviation

v. Table 5a: Logistic regression model for requirement of invasive mechanical ventilation at 30 days post-randomisation

Variables	Odds ratio	95% CI	P-value
Treatment			
Usual treatment	1		
Early CPAP	X.XX	X.XX, X.XX	0.XXX
Age (per year)	X.XX	X.XX, X.XX	0.XXX
Weight (per 5kg)	X.XX	X.XX, X.XX	0.XXX
Bone marrow transplantation			
No	1		
Yes	X.XX	X.XX, X.XX	0.XXX
PIM2r score (per point)	X.XX	X.XX, X.XX	0.XXX

vi. Table 5b: Linear regression model for maximum PELOD score at 30 days post-randomisation

Variables	Coefficient	95% CI	P-value
Constant	X.XX	X.XX, X.XX	0.XXX
Treatment			
Usual treatment	0		
Early CPAP	X.XX	X.XX, X.XX	0.XXX
Age (per year)	X.XX	X.XX, X.XX	0.XXX
Weight (per 5kg)	X.XX	X.XX, X.XX	0.XXX
Bone marrow transplantation			
No	0		
Yes	X.XX	X.XX, X.XX	0.XXX
PIM2r score (per point)	X.XX	X.XX, X.XX	0.XXX

vii. Table 5c: Linear regression model for aggregate PELOD score at 30 days post-randomisation

Variables	Coefficient	95% CI	P-value
Constant	X.XX	X.XX, X.XX	0.XXX
Treatment			
Usual treatment	0		
Early CPAP	X.XX	X.XX, X.XX	0.XXX
Age (per year)	X.XX	X.XX, X.XX	0.XXX
Weight (per 5kg)	X.XX	X.XX, X.XX	0.XXX
Bone marrow transplantation			
No	0		
Yes	X.XX	X.XX, X.XX	0.XXX
PIM2r score (per point)	X.XX	X.XX, X.XX	0.XXX

viii. Table 5d: Logistic regression model for mortality at 30 days post-randomisation

Variables	Odds ratio	95% CI	P-value
Treatment			
Usual treatment	1		
Early CPAP	X.XX	X.XX, X.XX	0.XXX
Age (per year)	X.XX	X.XX, X.XX	0.XXX
Weight (per 5kg)	X.XX	X.XX, X.XX	0.XXX
Bone marrow transplantation			
No	1		
Yes	X.XX	X.XX, X.XX	0.XXX
PIM2r score (per point)	X.XX	X.XX, X.XX	0.XXX

ix. Table 5e: Logistic regression model for requirement for Level 2 or Level 3 respiratory support within 30 days post-randomisation

Variables	Odds ratio	95% CI	P-value
Treatment			
Usual treatment	1		
Early CPAP	X.XX	X.XX, X.XX	0.XXX
Age (per year)	X.XX	X.XX, X.XX	0.XXX
Weight (per 5kg)	X.XX	X.XX, X.XX	0.XXX
Bone marrow transplantation			
No	1		
Yes	X.XX	X.XX, X.XX	0.XXX
PIM2r score (per point)	X.XX	X.XX, X.XX	0.XXX

x. Table 5f: Linear regression model for days free from any ventilator support at 30 days post-randomisation

Variables	Coefficient	95% CI	P-value
Constant	X.XX	X.XX, X.XX	0.XXX
Treatment			
Usual treatment	0		
Early CPAP	X.XX	X.XX, X.XX	0.XXX
Age (per year)	X.XX	X.XX, X.XX	0.XXX
Weight (per 5kg)	X.XX	X.XX, X.XX	0.XXX
Bone marrow transplantation			
No	0		
Yes	X.XX	X.XX, X.XX	0.XXX
PIM2r score (per point)	X.XX	X.XX, X.XX	0.XXX

xi. Table 5g: Linear regression model for days free from supplemental oxygen at 30 days post-randomisation

Variables	Coefficient	95% CI	P-value
Constant	X.XX	X.XX, X.XX	0.XXX
Treatment			
Usual treatment	0		
Early CPAP	X.XX	X.XX, X.XX	0.XXX
Age (per year)	X.XX	X.XX, X.XX	0.XXX
Weight (per 5kg)	X.XX	X.XX, X.XX	0.XXX
Bone marrow transplantation			
No	0		
Yes	X.XX	X.XX, X.XX	0.XXX
PIM2r score (per point)	X.XX	X.XX, X.XX	0.XXX

xii. Table 5h: Logistic regression model for hospital mortality

Variables	Odds ratio	95% CI	P-value
Treatment			
Usual treatment	1		
Early CPAP	X.XX	X.XX, X.XX	0.XXX
Age (per year)	X.XX	X.XX, X.XX	0.XXX
Weight (per 5kg)	X.XX	X.XX, X.XX	0.XXX
Bone marrow transplantation			
No	1		
Yes	X.XX	X.XX, X.XX	0.XXX
PIM2r score (per point)	X.XX	X.XX, X.XX	0.XXX

xiii. Table 5i: Logistic regression model for mortality at 90 days post-randomisation

Variables	Odds ratio	95% CI	P-value
Treatment			
Usual treatment	1		
Early CPAP	X.XX	X.XX, X.XX	0.XXX
Age (per year)	X.XX	X.XX, X.XX	0.XXX
Weight (per 5kg)	X.XX	X.XX, X.XX	0.XXX
Bone marrow transplantation			
No	1		
Yes	X.XX	X.XX, X.XX	0.XXX
PIM2r score (per point)	X.XX	X.XX, X.XX	0.XXX

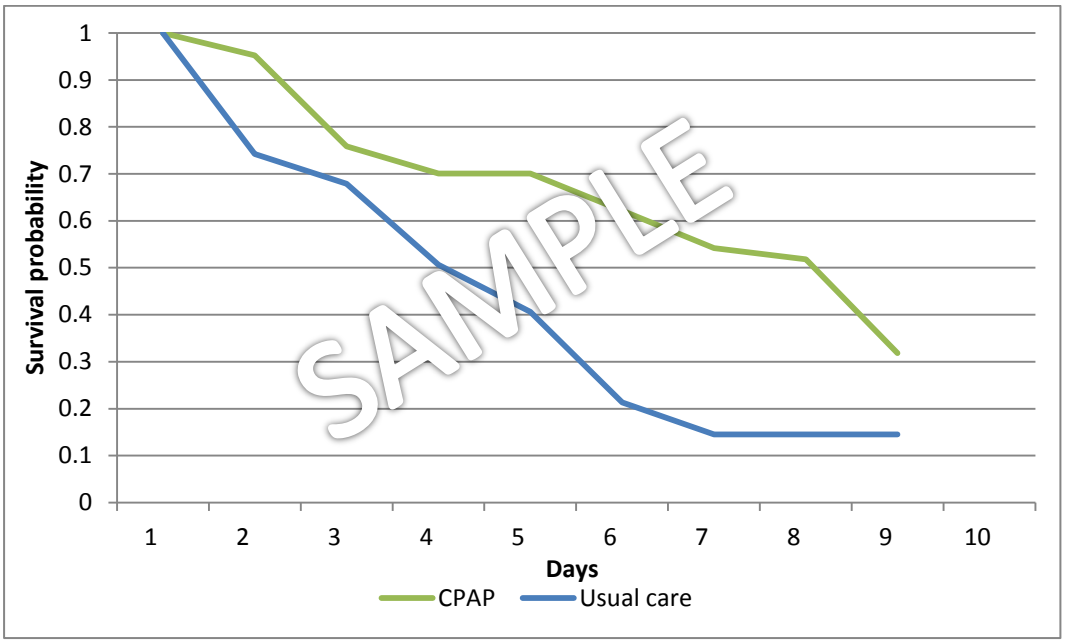
xiv. Table 5j: Logistic regression model for mortality at one year post-randomisation

Variables	Odds ratio	95% CI	P-value
Treatment			
Usual treatment	1		
Early CPAP	X.XX	X.XX, X.XX	0.XXX
Age (per year)	X.XX	X.XX, X.XX	0.XXX
Weight (per 5kg)	X.XX	X.XX, X.XX	0.XXX
Bone marrow transplantation			
No	1		
Yes	X.XX	X.XX, X.XX	0.XXX
PIM2r score (per point)	X.XX	X.XX, X.XX	0.XXX

Proposed graphs

i. Figure 1: CONSORT flow diagram

ii. Figure 2a: Kaplan-Meier plot comparing survival to 90 days post-randomisation between treatment groups



iii. Figure 2b: Kaplan-Meier plot comparing survival to one year post-randomisation between treatment groups