Automated Oxygen Control for Preterm Infants on Continuous Positive Airway Pressure (CPAP): Phase 1/2 Trial in Southwest Nigeria.

Statistical Analysis Plan

Version 1
10 March 2023

HREC 84704

Based on protocol version 1.5, dated 6/08/2022

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List of Abbreviations

AE   adverse event
ADE   adverse device effect
bpm   beats per minute
CI   confidence interval
CPAP   Continuous Positive Airway Pressure; bCPAP is 'bubble' CPAP
FiO_2 Fraction of Inspired Oxygen
s   second
SAE   serious adverse event
SADE   serious adverse device event
SpO_2 Oxygen saturation measured by transcutaneous pulse oximetry
SSI   significant safety issue
USADE   unanticipated serious adverse device event
USM   urgent safety measure
VDL1.1   Van Diemen's Land 1.1 algorithm

1.   ADMINISTRATIVE INFORMATION

Protocol: v1.5; 6/8/2022
ClinicalTrials.gov register Identifier: NCT05508308
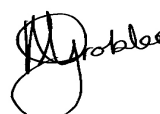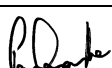
1.1   Document Version History

Version Date	Version	Author	Signature	Change Description	Reason/Comment
	1.0			Initial release.	Not applicable.

1.2   Approvals

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and confirm that this analysis plan was developed in a completely blinded manner (i.e. without knowledge of the effect of the intervention being assessed)

Name	Role on Study	Affiliation	Signature	Date
Rami Subhi	Associate investigator/Author	Murdoch Childrens Research Institute		10/03/2023
Anneke Grobler	Statistician/Author	Murdoch Childrens Research Institute		10/3/2023
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Hamish Graham	Principial investigator	Murdoch Childrens Research Institute		10/03/2023

2.   STUDY SYNOPSIS

A randomised cross-over trial of manual versus automated control of oxygen (OxyMate) for preterm infants on Continuous Positive Airway Pressure (CPAP). This trial will use an established technology (automated

oxygen titration algorithm, VDL1.1) partnered with a low-cost CPAP device in a low-resource setting. It will involve preterm infants requiring CPAP respiratory support with allocation to OxyMate or manual oxygen control for consecutive 24 h periods in random sequence.

The trial will be conducted at two study sites University College Hospital Ibadan (UCH) and Sacred Heart Hospital Lantoro (SHHL) in Southwest Nigeria. The planned sample size is to collect 40 complete studies. The trial is expected to have a duration of 20 weeks. Each child will be enrolled for approximately 2 days.

The aim of this study is to investigate the safety and potential efficacy of OxyMate automated oxygen control compared to manual control for preterm babies (<34 weeks or <2kg if gestation unknown) on CPAP, and explore feasibility and appropriateness of this technology in Nigeria.
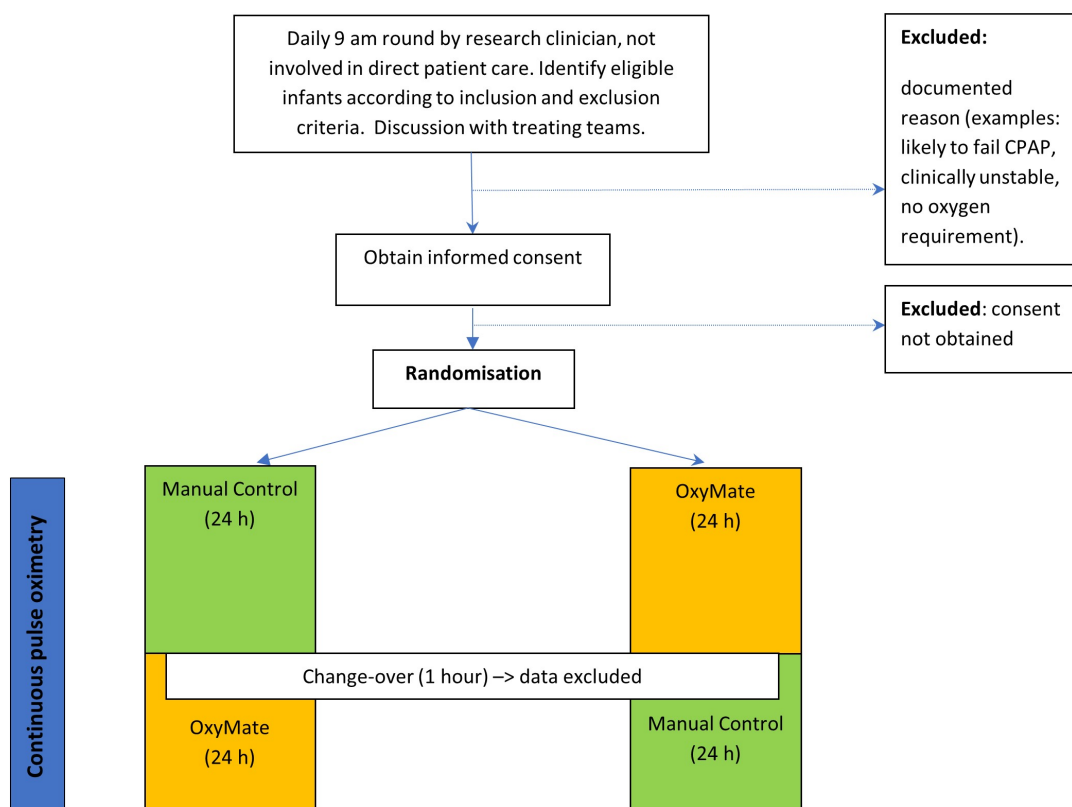
Figure 1: Trial design

2.1.   Primary Objective and Outcome

The primary objective of this trial is to evaluate the impact of OxyMate on safe oxygen saturation targeting compared to manual control of oxygen for preterm infants in Nigeria.

The primary outcome is: Proportion of time (over total recorded time) in the target SpO_2 range (91-95%, or 91-100% when in room air). This will be measured as percent time, where the denominator is usable time, excluding all periods during which the SpO_2 values are missing.

Secondary outcome for the primary objective: Proportion of time (over total usable time) in SpO_2 target range (91-95%) when receiving supplemental oxygen. This will be measured as percent time when in oxygen.

2.2.   Secondary Objectives and Outcomes

OBJECTIVE	OUTCOME & OUTCOME MEASURE
To evaluate whether OxyMate prevents time in, and episodes of, hypoxaemia compared to manual control of oxygen.	Proportion of time (over total usable time) with SpO_2<90% (hypoxaemia). This will be measured as percent time.
	Proportion of time (over total usable time) with SpO_2 <80% (severe hypoxaemia). This will be measured as percent time.
	Frequency of 30s episodes with SpO_2 continuously <80% (severe hypoxaemic episodes). Measured as mean number of episodes per hour.
	Duration of episodes with SpO_2 continuously <80% for manual and automated control epochs. Measured in seconds.
To evaluate whether OxyMate prevents time in, and episodes of, hyperoxaemia compared to manual control of oxygen.	Proportion of time (over total usable time) with SpO_2 >96% when receiving supplemental oxygen (hyperoxaemia). Measured as percent time when in oxygen.
	Proportion of time (over total usable time) with SpO_2 >98% when receiving supplemental oxygen (severe hyperoxaemia). Measured as percent time when in oxygen.
	Frequency of 30s episodes with SpO_2 continuously >96% (hyperoxaemic episodes). Measured as mean number of episodes per hour.
	Dduration of episodes with SpO_2 continuously >96% for manual and automated control epochs. Measured in seconds.
To evaluate whether OxyMate reduces nursing workload compared to manual control of oxygen.	Frequency of manual FiO_2 adjustments in both manual and automated arms. This is measured as mean number of FiO_2 adjustments/hour.
To evaluate whether OxyMate is safe compared to manual control of oxygen.	Number and duration of periods of no FiO_2 increment for ≥30s with SpO_2 <80% (i.e. failure to respond to severe hypoxaemia). Measured as mean number of episodes per hour, and mean duration per episode.
	Number and duration of periods with SpO_2 <80% for ≥30s with any bradycardia (heart rate <100 bpm). Measured as mean number of episodes per hour, and mean duration per episode.
	Number of OxyMate malfunction events
To evaluate whether OxyMate is acceptable and feasible to healthcare workers.	Score on User Survey questions using Likert scale.
To evaluate the cost of OxyMate.	Total costs of prototype system (Diamedica +/- oxygen automation)
To evaluate participants duration of CPAP and oxygen therapy.	Duration of time on CPAP with supplemental oxygen. Measured in hours.
	Duration of time on CPAP in room air. Measured in hours.
	Duration of time on low-flow oxygen therapy. Measured in hours.
To evaluate participant clinical outcomes	Final discharge outcome. Measured as categorical outcome (died in hospital, discharged well, discharged against medical advice, ongoing admission, other).
	Length of stay. Measured in days.

2.3.   Study Population

Preterm infants <34 weeks or <2 kg birthweight if gestation unknown, on CPAP and supplemental oxygen.

Inclusion criteria:
- ≥12 hours old

- Receiving CPAP support and supplemental oxygen (FiO$_2$ >0.21) for respiratory insufficiency
- Projected requirement for CPAP and oxygen therapy for >48 hours

Exclusion criteria:
- Deemed likely to fail CPAP in the next 48 hours, and would otherwise qualify for surfactant therapy and/or mechanical ventilation at initial assessment were it available: SpO$_2$ <85% with FiO$_2$ >0.50 on CPAP 8 cmH$_2$O, clinical features of hypercapnic respiratory failure (hypoventilation, reduced level of alertness)
- Deemed clinically unstable or recommended for palliation by treating team
- Cause of hypoxaemia likely to be non-respiratory – e.g. cyanotic heart disease
- Informed consent from parent/guardians not obtained

2.4.   Intervention

Automated oxygen control arm (OxyMate): Automated control of oxygen therapy partnered with CPAP delivered as per standard practice. The automated oxygen control set-up (OxyMate) will consist of: continuous pulse oximetry input, a computer algorithm (VDL1.1) that calculates changes to delivered FiO$_2$ based on the input SpO$_2$, and a mechanism to automatically effect changes to delivered FiO$_2$. The system will target an SpO$_2$ of 93% (mid-point of the target range). There will be several embedded safety mechanisms, including the ability to manually over-ride OxyMate at any stage. Pulse oximeter alarms will be as for the manual control arm, with additional automated system alarms in place.

Manual oxygen control arm: Oxygen therapy delivered with CPAP as per standard practice, except for the addition of continuous pulse oximetry. Nursing staff will make manual adjustments to FiO$_2$ provided to infants on CPAP. Oxygen saturations (SpO$_2$) will be monitored by continuous pulse oximetry, and nurses asked to target the range of SpO$_2$ 91-95%. Pulse oximeter alarms will be set to alert nurses to periods of hypoxaemia (SpO$_2$<88%) and hyperoxaemia (SpO$_2$>96%).

2.5.   Randomisation and Blinding

An independent statistician will prepare the randomisation schedule using a computer generated algorithm, with stratification by health facility. Infants will be randomised in a 1:1 ratio, using blocked randomisation.

Given the nature of the intervention blinding is not possible and this will be an open label trial.

2.6.   Sample Size

To detect a difference in the proportion of time spent in target range between treatment groups of at least 10%, and assuming a similar (~10%) standard deviation of the paired difference to the previous studies conducted using the automated algorithms, with a power of 0.9 and α of 0.05 would require a sample of 13 infants. To adequately test the equipment with a range of infants and staff members and obtain meaningful feedback on acceptability, we will aim to recruit 40 infants (15-30 per site).

No infants will be excluded post-randomisation. However, infants no longer requiring CPAP during the crossover study period, or having SpO$_2$ consistently>95% for 4 hours when receiving room air, will contribute 'incomplete' data (i.e. only contributing data up until the point they ceased CPAP, or until the point at which SpO$_2$ goes above and remains above 95% consistently for 4 hours without supplemental oxygen), and another infant enrolled to reach a total of 40 complete studies.

2.7.   Study Procedures

Infants will be managed with each mode of control for 24 hours, prior to crossing over to the other mode of control. Change over will simply involve flicking the computer switch from manual to automated control (or vice versa) and will be enacted immediately. It will not require any adjustment or interruption of the CPAP and it will not involve additional action from clinical staff. While FiO$_2$ adjustments have their effect relatively

rapidly, we will drop the first hour of data after switching modes from analysis (washout) to avoid contamination between arms.

For infants in manual control, nursing staff are asked to target SpO_2 91-95%, with pulse oximeter alarms set at SpO_2<88% and SpO_2>96%. Treating teams will have access to continuous pulse oximetry display of SpO_2 and pulse rate.

For infants on OxyMate, nursing staff will be asked to manage babies as per routine care, including SpO_2 targeting. They will be instructed that manual override of OxyMate is possible at any time by manually turning one of the flow meters. Continuous pulse oximetry display will be available, in addition to a laptop screen displaying pulse rate, SpO_2 and alarm messages. Disabling OxyMate indefinitely will be possible by pressing a large button on the laptop touch screen (and will be automatically recorded in the computer log).

During routine cares (e.g. nappy changes or nasogastric tube reinsertion), nursing staff will be provided the option to manually override OxyMate, but it is not prescribed to do so, and the Van Diemen's Land (VDL1.1) algorithm has been found to be effective during care times.

Full details of the background to the trial and its design are presented in the protocol.

3.   GENERAL STATISTICAL METHODOLOGY

3.1.   Objectives of Analysis Plan

This analysis plan covers the analysis of the primary and secondary objectives.

3.2.   Analysis Software

All analyses will be done in Stata (version 17 or higher).

3.3.   Definition of analysis populations

All participants who are randomised will be included in the analysis, even if they did not complete the study. Data will be analysed according to the intention to treat principle which will include all participants who were randomised in the treatment arm they were randomised to.

3.4.   Definitions related to Adverse Events (AEs)

	Definition	Effect	Mechanism linking device to effect
Adverse Device Effect (ADE)	Any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device.	• Death and serious adverse event (SAE) • Prolonged hypoxaemia • Prolonged hyperoxaemia	In OxyMate automated mode: • Failure to respond to SpO_2 deviation, resulting in prolonged hypoxaemia or hyperoxaemia • Failure of alarms to alert health workers to rising oxygen requirement
Device deficiencies	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include	• Prolonged (>30 s) episode of severe hypoxaemia (SpO_2 <80%) without an increase in FiO_2 • Prolonged (>30 s)	Errors in: • Algorithm – failure to respond correctly to SpO_2 data • Servomotor controller – failure to correctly adjust oxygen/air flow

	Definition	Effect	Mechanism linking device to effect
	malfunctions, use errors and inadequate labelling.	episode of severe hyperoxaemia (SpO_2 >98% when receiving oxygen) without a decrease in FiO_2	• Alarms – failure to detect/alert to errors
Adverse Event (AE)	Any untoward medical occurrence in a participant administered a medicinal product and that does not necessarily have a causal relationship with this treatment.	• Death • Other clinical deterioration, new illness, or new injury	

Serious Adverse Event (SAE)	Any AE that led to:
	
	• Death
	
	• Serious deterioration in the health of the participant, resulting in:
	  o a life-threatening illness or injury
	  o a permanent impairment of a body structure or a body function, or
	  o prolonged hospitalisation, or
	  o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function		

Serious Adverse Device Event (SADE)	-	An adverse device effect that has resulted in any of the consequences of a SAE.	
Unanticipated Serious Adverse Device Effect (USADE)	-	A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.	
Significant Safety Issue (SSI)	-	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.	
Urgent Safety Measure (USM)	-	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. Note: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.	

3.5.   Adjustment for Multiplicity

No adjustment for multiplicity will be made.

3.6.   Interim Analyses

There will be no interim analysis.

3.7.   Handling of Missing Data

The greatest risk of missing data will be from missing pulse oximetry reading due to disconnection or poor perfusion. Previous studies suggest that the proportion of SpO_2 readings missing will be 2-4%, and very likely evenly balanced in the two study arms.

No imputation of missing data will be done. The proportions of time in each SpO_2 range will be calculated using the denominator of usable time, i.e. without inclusion of time with missing SpO_2 readings. For incomplete studies (i.e. infants who do not complete both phases) we will include all data of continuous pulse oximetry up to the point of cessation or ineligibility but exclude data obtained after the infant discontinued or was no longer eligible (e.g. infants who cease CPAP or who have SpO_2>95% for 4 hours while in room air). We will record other clinical data (e.g. clinical outcomes and complications) for all infants irrespective of whether or not they completed one or both treatment phases.

4.   DESCRIPTIVE STATISTICS

4.1.   Recruitment and Follow-up

We will include a flowchart reporting:
- Number screened
- Number excluded and reasons for exclusion
- Number randomised, and treatment allocation
- Number discontinuing study prior to complete 49 hours and timing and reasons for discontinuation
- Number with complete studies
- Number analysed

4.2.   Baseline Characteristics

The following variables will be summarised at enrolment into the study:
- Gestation
- Birth weight
- Age in hours
- Diagnosis

Baseline characteristics will be summarised by mean and standard deviations (SDs) for continuous variables, and counts and percentages for categorical variables.

4.3.   Protocol Deviations

Protocol deviations will be listed. Some infants will cease CPAP or no longer require oxygen. These studies will be considered incomplete. The number of participants with and reasons for incomplete studies will be summarised.

4.4.   Compliance

The primary and some of the secondary outcomes assess whether health workers comply with the recommendation to titrate FiO_2 such that SpO_2 is maintained within a safe range.

We will report how many of the infants in each of the time periods were receiving the CPAP method they were assigned to for the majority of the time while receiving oxygen. The percentage of time in manual or automated control in each of the periods will be given.

5.   ANALYSIS OF THE PRIMARY OUTCOME(S)

5.1.   Main Analysis

Primary outcome: Percent of time (over total recorded time) in the target SpO_2 range (91-95%, or 91-100% when in room air).

Cross-over studies introduce risks of carry-over and period effects, and we have attempted to account for these in the study design. We consider carry-over effects to be small given that change from one mode of control to the other is instantaneous. We have allowed for a 1-hour change over period where data are not

included in the analysis. Period effects are possible with changes in practice over the study period for each infant but large changes in care over the 48 hour study period are unlikely. The clinical condition of infants will be dynamic and may change over the study period, but the primary outcome of time in target SpO_2 range will be comparable irrespective of the clinical course of an infant as long as they remain on oxygen.

We will compare mean percentage time in target SpO_2 range (y in code below) between the two 24 h arms of manual and automated control using weighted repeated measures mixed model linear regression adjusting for randomised group, treatment (manual vs automated), period, repeated measure in the same participant and facility (site). All infants will be included in this analysis, even those who do not provide complete studies. The weights will be calculated as the reciprocal of the total time in manual and automated control divided by 24 hours for each period separately. Infants who provide complete studies will have a weight of 1.

The following Stata code will be used:

```
xtmixed y treatment randomised_group period site [pw = weight] || participant: period
```

We will plot the primary outcome across the treatments for individual participants using spaghetti (line) plots. The x-axis will represent manual and automated, while the y-axis will be the percent of time in target range. The colours of the lines will represent the randomisation (which treatment was received first) and complete studies will be indicated with solid lines and incomplete studies with dashed lines.

Secondary outcome for the primary objective: "Proportion of time (over total usable time) in SpO_2 target range (91-95%) when receiving supplemental oxygen", measured as percent time when in oxygen, will be analysed in the same way as described for the primary outcome.

In order to understand whether incomplete studies are related to the order in which the treatments were received we will summarise the following:
- The number of infants who were randomised to start on the automated treatment (in Period 1) vs the manual treatment who come off oxygen during the study period
- The number of hours of oxygen treatment received by infants who were randomised to start on the automated treatment (in Period 1) vs the manual treatment

5.2.   Sensitivity Analyses

No sensitivity analysis is planned.

5.3.   Subgroup Analyses

In subgroup analysis we will extend this model to test whether the following variables modify the effect of the intervention, by adding an interaction term between the treatment and the subgroup indicator. Each of these subgroups will be assessed separately.

The prespecified subgroups are:
- Gestation (<32 weeks; $\geq$ 32 weeks)
- Birthweight (<1.5 kg, $\geq$ 1.5 kg)
- Post-natal age at enrolment ($\leq$ 24 hours; > 24 hours)
- Baseline FiO_2 requirement at enrolment FiO_2 <0.3, FiO_2 0.3-0.4; FiO_2 > 0.4

The following Stata code will be used:

```
xtmixed y treatment##subgroup randomised_group period site [pw = weight] || participant: period
```

Subgroup analyses not be done unless specifically specified. It will be done for the primary outcome and for the secondary outcome of the primary objective.

6. SECONDARY OUTCOMES

6.1 Proportion of time (over total usable time) with SpO_2<90% (hypoxaemia)

This will be measured as percent time. This will be analysed in the same way as the primary outcome.

6.2 Proportion of time (over total usable time) with SpO_2 <80% (severe hypoxaemia)

This will be measured as percent time. This will be analysed in the same way as the primary outcome. The same subgroup analysis as specified for the primary outcome will be done.

6.3 Frequency of 30s episodes with SpO_2 continuously <80% (severe hypoxaemic episodes)

This will be measured as the number of episodes per hour, calculated by taking the total number of episodes each infant had, divided by the duration of the period (in hours) for that infant. This variable is expected to be left-skewed. We will report the median, with 95% confidence interval (CI), in each treatment. The two treatments will be compared using a Poisson regression model to calculate the incidence rate ratio, which will provide the percentage increase in frequency of episodes for the manual arm compared to the automated arm. The same variables will be included in a repeated measures mixed model as described for the primary outcome.

The Stata code will be:
mepoisson y treatment randomised_group period site [pw = weight] || participant: period, covariance (unstructured) irr

6.4 Duration of episodes with SpO_2 continuously <80% for manual and automated control epochs

This will be summarised as the median and range within each treatment.

6.5 Proportion of time (over total usable time) with SpO_2 >96% when receiving supplemental oxygen (hyperoxaemia)

This will be measured as percent time when in oxygen. This will be analysed in the same way as the primary outcome. The same subgroup analyses as specified for the primary outcome will be done.

6.6 Proportion of time (over total usable time) with SpO_2 >98% when receiving supplemental oxygen (severe hyperoxaemia)

This will be measured as percent time when in oxygen. This will be analysed in the same way as the primary outcome.

6.7 Frequency of 30s episodes with SpO_2 continuously >96% (hyperoxaemic episodes)

This will be measured as number of episodes per hour and analysed in the same way as Secondary objective 6.3.

6.8 Duration of episodes with SpO_2 continuously >96% for manual and automated control epochs

This will be summarised as the median and range within each treatment.

6.9 Frequency of manual FiO_2 adjustments

This is measured as number of FiO_2 adjustments/hour. This will be analysed in the same way as Secondary objective 6.3.

6.10 Number and duration of periods of no FiO₂ increment for ≥30s with SpO₂ <80% (i.e. failure to respond to severe hypoxaemia)

This is measured as number of episodes per hour and mean duration per episode. The number of episodes will be analysed in the same way as Secondary objective 6.3. For each infant the mean duration of all periods of failure to respond to severe hypoxaemia will be calculated. These means will be described and compared between the treatment arms using the same method as for the primary outcome.

6.11 Number and duration of periods of with SpO₂ <80% for ≥30s with any bradycardia (heart rate <100 bpm)

This will be measured as number of episodes per hour and mean duration per episode. The number of episodes will be analysed in the same way as Secondary objective 6.3. For each infant the mean duration of all periods with bradycardia will be calculated. These means will be described and compared between the treatment arms using the same method as for the primary outcome.

6.12 Number of OxyMate malfunction events

The number of OxyMate malfunction events will be given. We will describe the timing and nature of the events in a listing.

6.13 Acceptability and feasibility of OxyMate to healthcare workers

Eight Likert scale questions will be asked to assess the healthcare workers perception of acceptability, trust, advantage, feasibility and usefulness of OxyMate. These questions will be summarised using means and standard deviations, for each question separately.

6.14 Cost of OxyMate

We will collect and report the total cost of the OxyMate system, including equipment, installation, maintenance and repair cost, and estimate running costs.

6.15 Duration of CPAP and oxygen therapy

This will be measured as:
- Duration of time on CPAP with supplemental oxygen, measured in hours (from randomization until hospital discharge)
- Duration of time on CPAP in room air, measured in hours (from randomization until until hospital discharge)
- Duration of time on low-flow oxygen therapy, measured in hours (from randomization until until hospital discharge)

These will be summarised for all infants enrolled as the mean duration for each of these, with 95% confidence intervals.

6.16 Discharge outcome

The discharge outcome for each infant will be summarised as the number and proportion in each of the following categories: died in hospital, discharged well, discharged against medical advice, ongoing admission, other.

6.17 Length of stay

Length of hospital stay will be measured in days. If all the children had been discharged, this will be summarised as mean and standard deviation. If some of the children had not been discharged, this will be summarised as median and interquartile range.

7.   SAFETY OUTCOMES

We will evaluate safety by summarising all CPAP complications and all safety events reported. This will include algorithm malfunctions and staff concerns. Summaries will be created for ADEs, device deficiencies, AEs, SAEs, SADEs, USADEs, SSIs and USMs. No laboratory variables will be analysed.

8.   LISTINGS, TABLES AND FIGURES

Table 1: Summary of screening failures

Screening failures	University College Hospital Ibadan (UCH)	Sacred Heart Hospital Lantoro (SHHL)	All
Reason for screening failure xxx			

Table 2: Participant disposition
Summary of section 4.1

Table 3: Baseline characteristics

Variable	Mean (95% CI)	Number (Proportion)
All variables listed in Section 4.2		

Table 4: Compliance to randomisation: Number of patients who received each of the interventions when assigned to the intervention

	Period 1	Period 2
Received manual	x/x	x/x
Received automated	x/x	x/x

Table 5: Primary outcome: Percentage of time in the target SpO$_2$ range (91-95%, or 91-100% when in room air)

	Automated Mean (95% CI)	Manual Mean (95% CI)	Difference (Automated – manual) Mean (95% CI)	p-value

Table 6: Secondary outcome for the primary objective: Proportion of time (over total usable time) in SpO$_2$ target range (91-95%) when receiving supplemental oxygen.
Same as Table 4

Table 7: Duration of oxygen treatment

Treatment assigned to in first period	Number (%) who come off oxygen early	p-value	Mean (95% CI) hours on oxygen during the study	p-value
Manual (then automated)				
Automated (then manual)				

Figure 1: Number of infants receiving oxygen at various time points in the study

Period 1	Assigned to manual intervention N =		Assigned to automated intervention N =	
		N off O^2 = Reasons: N(%)		N off O^2 = Reasons: N(%)
		N off CPAP = Reasons N (%)		N off CPAP = Reasons N (%)
Period 2	Assigned to automated intervention N =		Assigned to manual intervention N =	
		N off O^2 = Reasons: N(%)		N off O^2 = Reasons: N(%)
		N off CPAP = Reasons N (%)		N off CPAP = Reasons N (%)
	Still on O_2 at end of study (n = x)		Still on O_2 at end of study (n = x)	

Table 8: Secondary outcomes

Variable	Automated Mean (95% CI)	Manual Mean (95% CI)	Difference (Automated – manual) Mean (95% CI)	p-value
Proportion of time (over total usable time) with SpO_2<90% (hypoxaemia)				
Proportion of time (over total usable time) with SpO_2 <80% (severe hypoxaemia)				
Proportion of time (over total usable time) with SpO_2 >96% when receiving supplemental oxygen (hyperoxaemia)				
Proportion of time (over total usable time) with SpO_2 >98% when receiving supplemental oxygen (severe hyperoxaemia)				
Duration of periods of no FiO_2 increment for ≥30s with SpO_2 <80% (i.e. failure to respond to severe hypoxaemia)				
Duration of periods of with SpO_2 <80% for ≥30s with any bradycardia (heart rate <100 bpm)				

Figure 2: Line diagram for primary outcome
Described in Section 5.1

Figure 3: Histogram of proportion of time in different SpO$_2$ ranges
Bars are presented by treatment

Table 9: Secondary outcomes analysed with Poisson regression

Variable	Automated Median (95% CI)	Manual Median (95% CI)	Incidence rate ratio (Manual/ Automated) (95% CI)	p-value
Frequency of 30s episodes with SpO$_2$ continuously <80% (severe hypoxaemic episodes)				
Frequency of 30s episodes with SpO$_2$ continuously >96% (hyperoxaemic episodes)				
Frequency of manual FiO$_2$ adjustments				
Number of periods of no FiO$_2$ increment for ≥30s with SpO$_2$ <80% (i.e. failure to respond to severe hypoxaemia).				
Number of periods of with SpO$_2$ <80% for ≥30s with any bradycardia (heart rate <100 bpm)				

Listing 1: Oxymate malfunction events
Listing of timing and nature of all OxyMate malfunction events.

Table 10: Acceptability and feasibility of OxyMate to healthcare workers

Question	Mean	Standard deviation
Acceptability: I like the automated oxygen …		
Trust: The automated oxygen control system for targeting …		
Trust: I am confident that the automated …		
Etc.		

Table 11: Duration of CPAP and oxygen therapy
Mean and 95% confidence interval for
Duration of time on CPAP with supplemental oxygen, measured in hours (until hospital discharge)
Duration of time on CPAP in room air, measured in hours (until hospital discharge)
Duration of time on low-flow oxygen therapy, measured in hours (until hospital discharge)

Table 12: Discharge outcome

Outcome	N (%)
Died in hospital	
Discharged well	
Discharged against medical advice	
Ongoing admission	
Other	

Table 13: Length of stay
Reported as either mean/standard deviation or median and interquartile range

Listing 2: Listing of Safety events
PID Treatment at time of event Randomised arm Description of event, Participant characteristics (gestation, birth weight, diagnosis), assessments and actions undertaken, clinical impact of infant, infant outcome