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# SANDWICH

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## Sedation AND Weaning In CHildren

Protocol Number and Version:	B17/13 Version 6.0
REC Number:	17/EM/0301
ISRCTN Number:	16998143

### STATISTICAL ANALYSIS PLAN

*Version 1.0*

*Final*

*25/02/2020*

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This document and all preceding versions will be stored in the Trial Master File for this trial

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## ABBREVIATIONS

AE	Adverse Event
CI	Confidence Interval
CRF	Case Report Form
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
eTMF	Electronic Trial Master File
FiO <sub>2</sub>	Fraction of Inspired Oxygen
HR	Hazard Ratio
HTA	Health Technology Assessment
ICH	International Conference of Harmonisation
ICC	Intracluster Correlation Coefficient
ICU	Intensive Care Unit
IMV	Invasive Mechanical Ventilation
ISRCTN	International Standard Randomised Controlled Trial Number
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute of Health Research
NHS	National Health Service
PEEP	Positive End Expiratory Pressure
PIP	Peak Inspiratory Pressure
PICANet	Paediatric Intensive Care Audit Network
PICU	Paediatric Intensive Care Unit
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SBT	Spontaneous Breathing Trial
SOP	Standard Operating Procedure
SW	Stepped Wedge
TMF	Trial Master File
TSC	Trial Steering Committee

## 1. BACKGROUND AND DESIGN

The aim of this study is to deliver a UK multi-centre, stepped wedge (SW), cluster, randomised control trial (RCT) to determine if a protocol-based intervention, incorporating co-ordinated care with greater nursing involvement to managing sedation and weaning ventilation, can reduce the duration of invasive mechanical ventilation (IMV) and is cost effective compared with usual care in children in PICUs.

The cluster design chosen is a stepped wedge cluster randomised trial. Cluster randomisation is essential, as the intervention is delivered at the level of the cluster (site) as the individual level components would be susceptible to contamination if patients were individually randomised. The stepped wedge design has been chosen over the conventional parallel cluster design for the following reasons: there are limited number of clusters available to allow detection of the important clinical effect at 90% power; units are more likely to participate in the trial if they are guaranteed their unit will at some point receive the intervention; it would be infeasible and more costly to deliver the intervention simultaneously to units randomised to the intervention in a parallel design; and if the intervention is found to be effective, knowledge translation will be easier as PICUs participating can potentially continue after the trial, maximising the benefits of any effects to the NHS and patients.

### 1.1 Study Objectives

#### Primary objective

To determine if the intervention reduces the duration of IMV in children expected to be ventilated for a prolonged period of time.

#### Secondary Objectives

To determine if the intervention:

- Reduces the duration of IMV in all eligible children irrespective of their expected ventilation duration (short or prolonged)
- Reduces length of PICU and hospital stay
- Does not cause additional harm as assessed through review of adverse events and respiratory complications
- Is cost effective in the NHS
- Is sustainable and acceptable to staff delivering care

### 1.2 Process Evaluation

A process evaluation will be conducted alongside the trial to explore the processes involved in delivering the intervention, in order to identify factors and the mechanisms of their interaction that are likely to impact on trial outcomes. The process evaluation is described in section 12 of the protocol. The following analysis will be completed and presented by site in order to determine an adherence score for sites:

- % comfort score measured
- % set a comfort score range
- % set ventilation targets

- % performed an a Spontaneous Breathing Trial (SBT) when criteria for SBT met
- % met criteria for SBT at least twice a day
- % reasons for non-progression to SBT
- % reasons for non-progression to extubation
- 

### 1.3 Internal Pilot

The SW design of this trial requires that all participating PICUs begin in the control phase of the trial when data collection begins. An internal pilot will be conducted in the first four sites randomised to the intervention.

Sites will be classified at the beginning of the study according to size (large/small) and the study will use a restricted randomisation process to ensure that the first four sites randomised to receive the intervention will include two large and two small sites.

Data collection will commence at all sites from month one, but the pilot will specifically evaluate and report on progress during the following time periods of each pilot site:

- Period from randomisation prior to the training period (to facilitate preparation of staff rotas)
- Training period
- Initial period after having implemented the intervention

Specifically, the following criteria will be considered:

- Monitoring if the actual patient numbers/month of eligible children matches predictions
- Feasibility of data collection procedures
- Monitoring the percentage of parents opting out from allowing their child's data collection
- Delivery of training (target >80% of staff/unit trained by the end of the pilot period)
- Adherence to elements of the intervention (review and feedback of compliance with COMFORT scoring and ward round sedation and ventilation planning; progression to SBT when readiness criteria are fulfilled. Target >75% by the end of the pilot period)

Formal progression criteria with cut off points will not be set; rather, it is proposed to consider all criteria simultaneously. Data collection will continue in all units until the formal decision to proceed is made by the Trial Steering Committee (TSC) in consultation with the NIHR Health Technology Assessment (HTA) secretariat based on available information.

### 1.4 Patient Eligibility Criteria

Within eligible clusters, patients will be eligible for inclusion in the data analysis if they fulfil the following criteria:

#### Inclusion Criteria

- All children (<16 years old) in participating PICUs receiving IMV.

## Exclusion Criteria

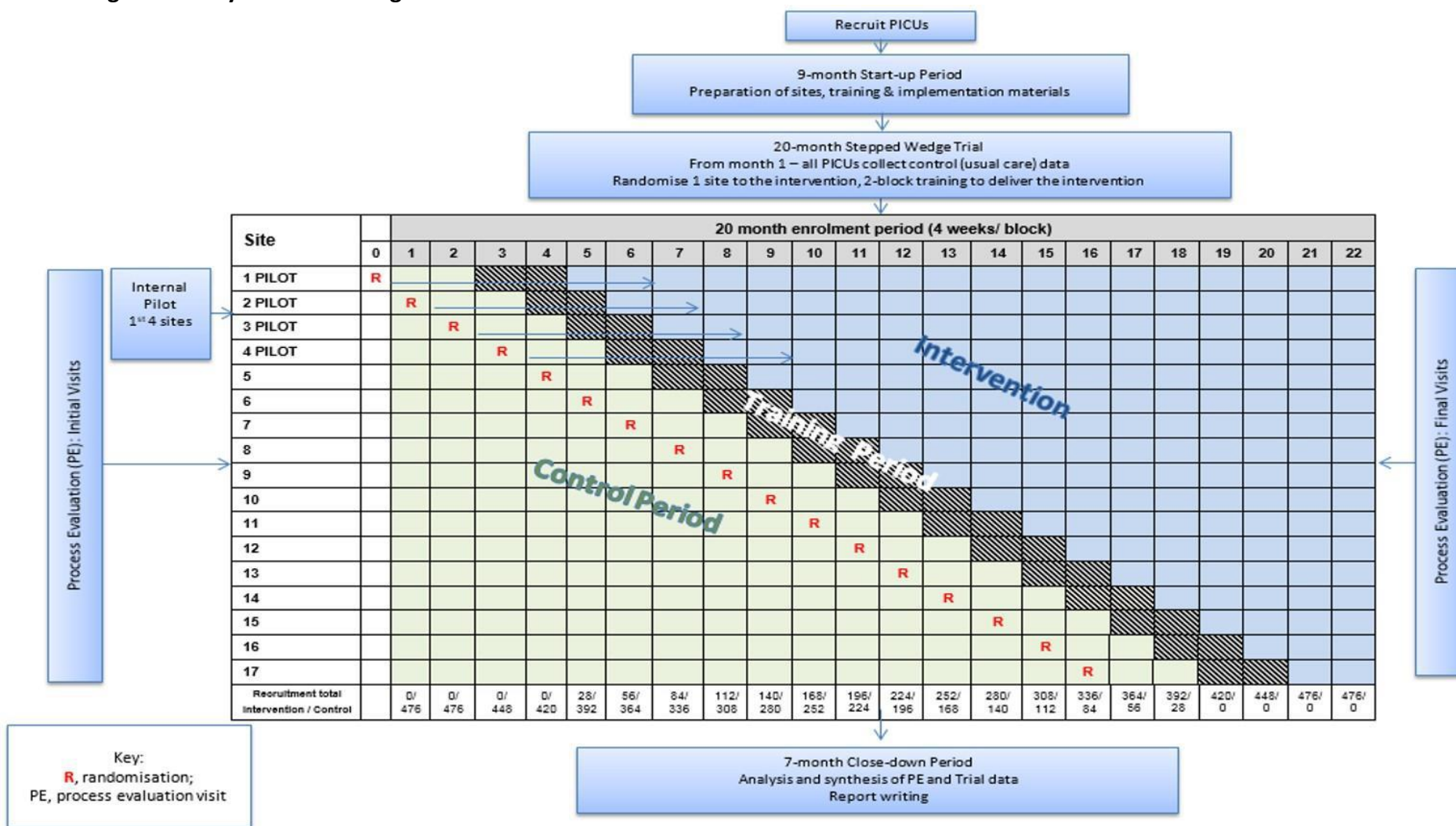
- Children who would not reach the primary endpoint (tracheostomy *in situ*; not expected to survive; treatment withdrawal).
- Children who are pregnant, as documented in their medical notes

### 1.5 Research Hypothesis

Children who are weaned from mechanical ventilation with a protocol-based approach will have a reduced duration of IMV than those weaned without a protocol-based approach.

Full details of the background to the trial and its design are presented in the protocol. The study schematic diagram (Figure 1) shows the stepped wedge, cluster, randomised design. The design involves sequential but random rollout of the intervention to clusters (hospital sites) over one month time periods. All participating sites begin the control phase of the trial when the data collection period begins. There will be an initial two-month period of baseline data collection during which no sites will be exposed to the intervention. Subsequently, every month, one site will be randomised to the intervention and start a two-month training period during which the intervention will be rolled out to that unit. Once each site has crossed over to the intervention it will remain exposed to the intervention for the remaining duration of the study. After the last site has fully transitioned to the intervention arm, there will be a final two-month period during which all sites will be fully exposed.

1.6 Figure 1 Study Schematic Diagram





## 2. OUTCOME MEASURES

Primary and secondary outcomes will be measured in all children, irrespective of their expected ventilation duration (short or prolonged).

### 2.1 Primary outcome measure(s)

The duration of IMV measured in hours from initiation of IMV until the first successful extubation (success is defined as still breathing spontaneously 48 hours following extubation). In cases where a child is admitted to a PICU already intubated, the duration of IMV will be measured in hours from admission until successful extubation. The duration of IMV will also be calculated for all patients who reach a censoring point. The time until extubation will not be known for those children who either die on ventilation, are transferred to another unit or are not weaned by 90 days. In order to minimise any potential within cluster contamination we censor patients when they move into the training period; and when the cluster moves into the intervention phase only new admissions are included. The censoring will be balanced across periods as data collection will continue to a maximum of 28 days at the end of the 20 month recruitment period. That means we will assume that children who were still intubated at the time their site moved into the training period, died on ventilation, were not weaned by 90 days or who were transferred to another unit on ventilation, will have an extubation time greater than the time until they died or were transferred.

### 2.2 Secondary outcome measures

- Incidence of successful extubation (defined as breathing spontaneously 48 hours following extubation)
- Number of unplanned extubations (defined as dislodgement of the endotracheal tube from the trachea, without the intention to extubate immediately and without the presence of airway competent clinical staff appropriately prepared for the procedure occurs)
- Number of reintubations
- Total duration of IMV
- Incidence and duration of post-extubation use of non-invasive ventilation
- Incidence of tracheostomy insertion
- Incidence of post-extubation stridor
- Any adverse events (e.g. unplanned removal of any invasive tube)
- PICU length of stay from admission to discharge measured in days
- Hospital length of stay from admission to discharge measured in days
- Mortality occurring within the ICU
- Mortality occurring within the hospital
- Cost per complication avoided at 28 days

Outcomes will be measured from patient admission up to 90 days or discharge (whichever is earlier). However, at the end of the 20-month enrolment period, data collection will continue for a maximum of 28 days only. Although, not pre specified as a secondary outcome in the protocol we will also include an analysis of total combined duration of IMV and NIV.

## 3. DATA

### 3.1 CRF Forms and variables

Full details of the data to be collected and the timing of data collection are described in the trial protocol.

A copy of the CRF is presented in the Trial Master File.

### 3.2 Management of datasets

At the time of analysis:

The Data Manager in collaboration with the Study Statistician will extract data from MACRO following procedures as detailed in the SOP DM09 Database Closure/Lock and the corresponding study Data Management Plan (DMP).

Trial data will be entered onto the electronic CRF on a Clinical Trial Database (MACRO) by delegated unit personnel and processed electronically as per NICTU Standard Operating Procedures (SOPs) and the study specific Data Management Plan (DMP).

Data queries will be ‘raised’ electronically (MACRO) where clarification from unit staff is required for data validations or missing data. Unit staff will ‘respond’ electronically to data queries ensuring that amendments, where applicable, are made to the Clinical Trial Database.

All essential documentation and trial records will be stored securely and access will be restricted to authorised personnel.

All study documentation, study data and patient medical records will be archived as per regulatory requirements and those responsible for archiving will be noted on the sponsor agreement.

Data will also be provided from each site via PICANet. NICTU staff will follow the steps outlined in the guideline on “SANDWICH How to manage PICANet Data” in relation to this data. The Trial Statistician will import the excel data files direct from the eTMF folder 13.8 “data management” into Stata and append the PICANet data from all sites to create a master file of the data. This master dataset can then be merged with the Macro data extracted into Stata for analysis purposes.

### 3.3 Data completion schedule

The total study duration will be 36 months. The first 9 months will constitute the start-up period and all participating sites will open and begin data collection in month 10. An internal pilot will run from months 10-18. The duration of the trial in participating sites will be 20 months. At the end of the 20-month trial period, no further patients will be enrolled into the trial. Children who have already been enrolled prior to this point will be followed up for 28 days only. There will be 7 months at the end of the trial for final data analysis, reporting and trial close down. The study timeline is shown in Table 1.

**Table 1. SANDWICH study timeline**

Year		1				2				3			
Quarter		1	2	3	4	1	2	3	4	1	2	3	4
Project - months		3	6	9	12	15	18	21	24	27	30	33	36
Trial Stage	Pre-grant start	Set up				Recruitment				Analysis & Reporting			
Recruit Staff	X	X											
Trial Set-up (Site Initiation and Training)	X	X	X	X									
Protocol Development	X	X											
Ethics Approval			X	X									
R&D Approvals			X	X									
Site Training (Ongoing Intervention training)					X	X	X	X	X	X			
Internal Pilot Study					X	X	X						
Main Study					X	X	X	X	X	X	X		
Number of Sites Open					15	15	15	15	15	15	15		
Patient Recruitment					952	2,240	3,500	4,760	6,020	7,280	9,520		
Patient Follow-up					X	X	X	X	X	X	X		
Data Collection & Validation					X	X	X	X	X	X	X	X	
Site Close Down											X	X	
Management Meetings		XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
DMEC Meetings			X		X		X		X		X		X
TSC Meetings			X		X		X		X		X		X
Data Analysis												X	X
Health Economics Analysis												X	X
Trial Report												X	X
Dissemination												X	X

### 3.4 Data verification

Study specific data validation checks will be implemented. The process of data validation ensuring the accuracy and quality of the data will be carried out according to SOP DM04 Data Validation and Discrepancy Management.

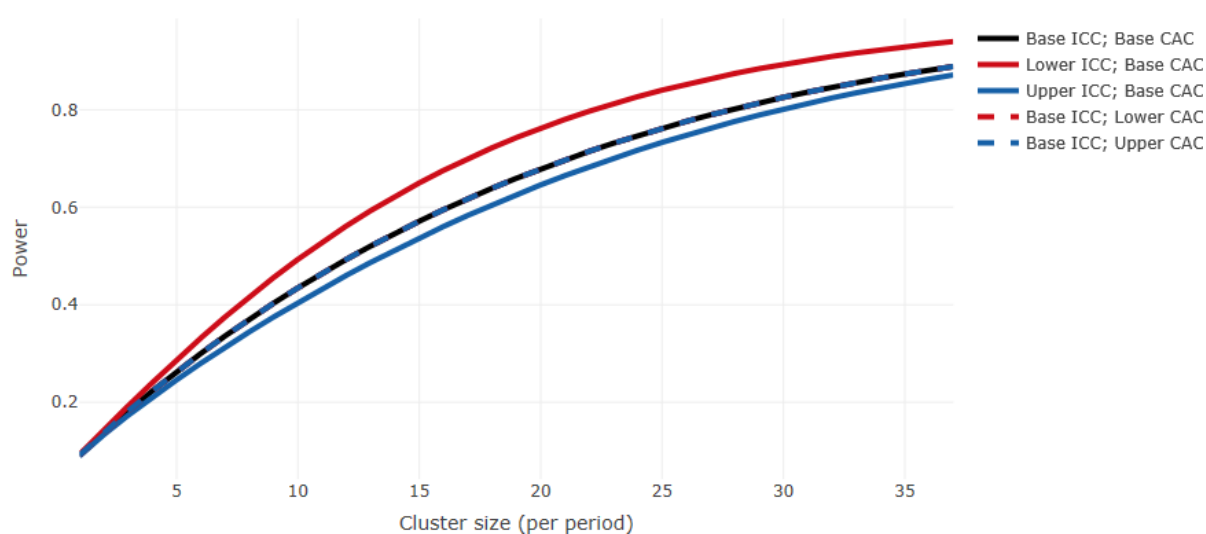
## 4. DEFINITION OF TERMS

Term	Definition
Successful Extubation	Success is defined as still breathing spontaneously 48 hours following extubation
Unplanned Extubation	Defined as dislodgement of the endotracheal tube from the trachea, without the intention to extubate immediately and without the presence of airway competent clinical staff appropriately prepared for the procedure occurs

## 5. SAMPLE SIZE CALCULATIONS

The primary aim of this study is to determine whether the intervention can reduce the average number of hours on invasive ventilation in eligible children. To inform the revised power calculation we used PICU admissions data for the years 2014-2016 from 18 units participating in the trial to determine parameters to inform the sample size calculation. In this trial, duration of ventilation is censored at the point of transitioning from the control to the training period, discharge to another hospital, at 90-days, death, and receiving a tracheostomy so applying censoring to this dataset provided us with a homogeneous population that more accurately reflected the trial population. The mean duration of mechanical ventilation was 5.8 (SD 9.6) days and an ICC (95% CI) of 0.005 (0.001 – 0.01). It is postulated that a reduction of one day on invasive ventilation is both clinically important and achievable.

The app <https://clusterrcts.shinyapps.io/rshinyapp/> was used to update the sample size calculation given this revised information. Using this app and for the actual design of the trial (using the actual information on the number of clusters and number of steps, rather than approximated values and using the following assumptions: no. clusters per sequence=1, ICC=0.005 (with consideration across the range 0.001-0.01), an exchangeable correlation structure, mean difference=1, SD=9.6, at 5% significance level, the power is approximately 80% for a cluster size of 28 (see power curve). The calculation is based on a standardised effect size (mean and SD) rather than the Hazard Ratio (which was used in the original calculation) because the Shinyapp does not yet accommodate survival outcomes. This is a conservative approach meaning that it should have slightly underestimated the power not having allowed for the time to event nature of the data. The expected sample size is 9520 based on an average cluster size of 28 patients per block (Figure 2).



**Figure 2. Power curve**

## 6. RANDOMISATION AND BLINDING

### 6.1 Randomisation

Each PICU will be allocated a unique ID. At the beginning of the study all sites will be classified according to size (large/small based on the number of children receiving IMV in participating PICU derived from PICANet 2017 annual report). Sites were ranked from smallest to largest and split at the median into two groups. A restricted

randomisation process will be used to ensure that the study is balanced with respect to site size across intervention and control phases of the trial. The trial statistician will generate the randomisation schedule before the trial commences and will hold in a restricted folder in the statistics section of the TMF. The trial statistician will inform trial management which site is next to crossover at set intervals throughout the trial. The randomisation will be completed in real time and will create a balance of large and small units in that each unit will be notified by trial management 12 weeks prior to moving into the training period according to the randomisation sequence.

The Stepped Wedge design of the study involves sequential but random rollout of the intervention over multiple time periods. The time period duration will depend on the number of clusters involved but will be approximately 4 weeks (hereafter referred to as one month). In this trial, the cluster is the hospital site, therefore randomisation will be conducted at the hospital site level. In general there is one PICU per site. One hospital (GOSH) has two PICU units. These two PICU units are separate but given they are within the same hospital they are not completely distinct entities (for example they share nursing staff). Due to the likely contamination between these two units for the purpose of randomisation they will be treated as one cluster.

This trial requires that all participating PICUs begin the control phase of the trial when the data collection period begins. There will be an initial two-month period of baseline data collection during which none of the PICUs will be exposed to the intervention. Subsequently, every month, one site will be randomised to the intervention and start a two-month training period during which the intervention will be rolled out to that unit. The two-month training periods during which the unit can neither be assumed to be exposed or not exposed, will not be included in the analysis (or power calculation). Once each PICU has crossed over to the intervention it will remain exposed to the intervention for the remaining duration of the study. After the last PICU has crossed over and has fully transitioned to the intervention arm, there will be a final two-month period during which all PICUs will be fully exposed.

## **6.2 Blinding and Allocation Concealment**

Due to the nature of the intervention and usual care sedation management and weaning processes the study will not be blinded. However, the randomisation process is designed to conceal allocation and details of the intervention until the point of randomisation, thus minimising potential attrition caused by advance knowledge of when a unit will receive the intervention.

Research nurses collecting data cannot be blinded to the allocated group because they will be involved in training staff in the intervention. However, patients do not need to be aware of whether they are receiving the intervention or usual care and any possible impact of loss of blinding will be explored in the process evaluation interviews with staff at the end of the trial.

# **7. ANALYSIS PRINCIPLES AND METHODS**

## **7.1 Baseline and Recruitment**

Baseline characteristics will be summarised by exposure and non-exposure to the intervention and summarised by their means and standard deviations, medians and inter-quartile ranges, or numbers and percentages as appropriate. Units will be classified as being exposed to the intervention on completion of their 8 week training period, and events occurring during this training period will not be included in the final analysis with the exception of hospital discharge. Recruitment will be presented as per the flow chart in section 8.2 detailing the no of clusters and observations at each step exposed or unexposed and if there were any withdrawals.

## **7.2 Censoring**

Some of the data observations will be censored i.e. children moving to other units (prior to extubation), children not weaned before the unit transitions to the training phase, those who are not weaned at the end of the 20-month trial period, children at the time they have a tracheostomy, those not weaned by 90 days, or children who die.

That means we will make the assumption that children who died on ventilation, not weaned before transitioning to the training phase/end of trial, were not weaned by 90 days, had a tracheostomy or who were transferred to another unit on ventilation, will have an extubation time (i.e. were removed from ventilation) greater than the time of these censoring events.

In order to minimise any potential within cluster contamination we censor patients when they move into the transition phase; and when the cluster moves into the intervention phase only new admissions are included.

### **7.3 Primary Outcome Analysis**

The primary aim of the study is to evaluate whether there is a difference in the duration of hours on invasive ventilation before and after exposure to the intervention: that is, does it improve clinical outcomes for the child. Therefore, we will use survival analysis and estimate a hazard ratio for the intervention effect. Our survival analysis will estimate the hazard of being extubated and removed from mechanical ventilation. This means that higher hazard ratios will signify success of the intervention.

We will explore various models in STATA, but anticipate fitting a Cox proportional hazards model, with a treatment by time interaction to incorporate any non-proportionality following tests for proportional hazards. Allowance will be made for clustering using a frailty term for each unit (this is similar to a random effect in a mixed effects model). We will also adjust for calendar time, since the intervention is sequentially rolled-out. It is possible that some children will be re-admitted or transferred: these patients will be treated as independent events and will be acknowledged within our analysis. Our primary estimate of the treatment effect will be a cluster and time adjusted hazard ratio (HR) along with 95% CIs in children expected to be ventilated for a prolonged period of time. Time adjustment is essential because this is a SW trial. An adjusted analysis will also be carried out where we will adjust for the following covariates: age, severity of illness (PIM3 score), respiratory vs other diagnostic grouping, type of admission (planned/unplanned), reason for admission (surgical / medical). We will also estimate the treatment effect in all eligible children as this is a secondary objective in the trial.

Null hypotheses and analyses for secondary outcomes take a similar form to that for the primary outcome, and where outcomes are not survival times, analysis will use the generalized linear mixed model, reporting risk differences (RD) and risk ratios (RR) for binary outcomes and mean differences for continuous outcomes (all adjusting for cluster and time effects) in children expected to be ventilated for a prolonged period of time. Analysis will be completed initially in STATA, however we will explore the impact of the use of SAS software on the precision of the estimates for the secondary outcomes as it can account for more complex correlation structures (see section 7.4). Additional sensitivity analyses will report the treatment effects in all eligible children.

### **7.4 Model based analysis proposal for secondary outcomes**

There are a number of requirements for the analysis model. Firstly, this is a clustered trial and all analysis will take clustering into account. Secondly, the trial has 17 clusters, and the model will allow for a correction due to the small number of clusters. Thirdly, the design is a stepped-wedge study and we will adjust for temporal confounding. Full details on how each of these will be undertaken, with justification is provided below.

#### **Binary outcomes**

A mixed effects binomial regression with a log-link will be used to estimate the relative risk; and a binomial model with identity link used to estimate the risk difference, with estimation using REML. In the case of non-convergence of the binomial model with a log-link, a Poisson model with robust standard errors will be fitted. If the binomial model with the identity link does not converge then only a relative risk will be reported. If neither the log or identity link converge we will use the logistic link and report odds ratios. We will include fixed effects for period and a fixed effect for intervention exposure. The primary analysis will allow for clustering as a random effect assuming an exchangeable correlation structure. To correct the potential inflation of the type I error rate due to small number of clusters, the Kenward and Roger small sample correction will be used [1]. In a sensitivity analysis we will explore if models with more complicated correlation structures are a better fit to the data. These models are not being used as our primary analysis models as there is limited understanding as to when such models will converge and how to choose between the various different correlation structures which might be plausible. To this end we will additionally fit generalised linear mixed models (with same link functions and fixed

effects as described above) to include the following correlation structures: a block exchangeable correlation structure to include a random cluster and random cluster by period effect; and a discrete time decay correlation structure including a random cluster effect with auto-regressive structure (AR(1)). We will report AIC and log-likelihoods from all models so we can make an informal comparison of goodness of fit. Although there are currently no recommended models to formally compare goodness of fit between different correlation structures, any large differences in goodness of fit between these models should be evident from conventional goodness of fit statistics. Should there be large differences and differences between results (point estimates of treatment effects and confidence intervals, results will be interpreted cautiously). These binary models will be fitted in SAS using proc glimmix because Stata both does not accommodate small sample corrections for binary outcomes and does not accommodate correlation structures other than the exchangeable one. However, binary outcomes will be analysed in Stata without the small sample correction and under the exchangeable correlation structure as a means of verification of results.

### **Additional sensitivity analyses**

To additionally explore if the categorical effect for time (i.e. fixed period effect) is both parsimonious and adequate to represent the extent of the secular trend, we will model the time effect using a spline function. The number of knots used here will be taken as the default. Again, for verification of results this model will also be fitted in Stata under the exchangeable correlation structure and without a small sample correction. Models will be extended to include random cluster by intervention effects (with a non-zero covariance term) to examine if results are sensitive to the assumption of no intervention by cluster interaction. Models will also be extended to include an interaction between treatment and number of periods since first treated, to examine if there is any indication of a relationship between duration of exposure to the intervention and outcomes.

### **Continuous outcomes**

For continuous outcomes we will report mean differences estimated from mixed effects linear regression with identity link. All continuous outcomes will be checked for normality and appropriate transformations used. All analysis other than choice of link function will take the same form above. In SAS this will be achieved using proc mixed (hpmixed for exponential decay to improve computational time); in Stata using mixed.

### **Estimation and reporting of within cluster correlations**

We will report time adjusted within-cluster correlations for all outcomes. We will report correlations from the different assumed correlation structures (so we will report intra-cluster correlations (ICC); within and between-period correlations; and within-period correlations and exponential decay). As well as reporting correlations we will additionally report all variance components. For all outcomes (continuous and binary) we will report correlations on the latent scale (i.e. proportions scale for binary outcomes) as is appropriate to inform future sample size calculations. To this end, to estimate the intra-cluster correlations, a linear mixed effects regression model with an identity-link will be fitted, with a random cluster effect and fixed period effect and fixed intervention effect. To report the estimated within-period ICC, between-period ICC assuming a block-exchangeable correlation structure we will fit a linear mixed effects regression model with an identity-link, with a random cluster and random cluster by period effect, and fixed period effect and fixed intervention effect. To report the within-period ICC and the rate of exponential decay under the discrete time decay correlation structure we will fit a linear mixed effects regression model with an identity-link, with a random cluster and auto-regressive structure (AR(1)), and fixed period effect and fixed intervention effect. No small sample corrections will be made when fitting models for intra-cluster correlation estimates as interest here is in the variance components and not the treatment effect. Again, these models will be fitted in SAS using mixed (or hpmixed) because Stata does not accommodate these more complex correlation structures. Again, for verification, these models will be additionally fitted in Stata under the exchangeable correlation structure as a means of verification of the results.

### **Missing Data**

Due to the nature of the trial and outcomes that will be collected, missing data will be kept to a minimum and therefore, there will be no requirement for the use of multiple imputation.

### **SubGroup Analysis**

Exploratory analysis for duration of IMV in the prolonged and pooled populations will be reported using interaction tests and 99% confidence intervals for the following subgroups:

1. Size of unit (2 groups - large; small)
2. Adherence (3 groups - tertiles of ranked averages)
3. Type of admission to unit (planned; unplanned)
4. Reason for admission (3 groups - surgical / medical - respiratory / medical- others)

The SW design will also allow us to investigate intervention effect heterogeneity across clusters and time.

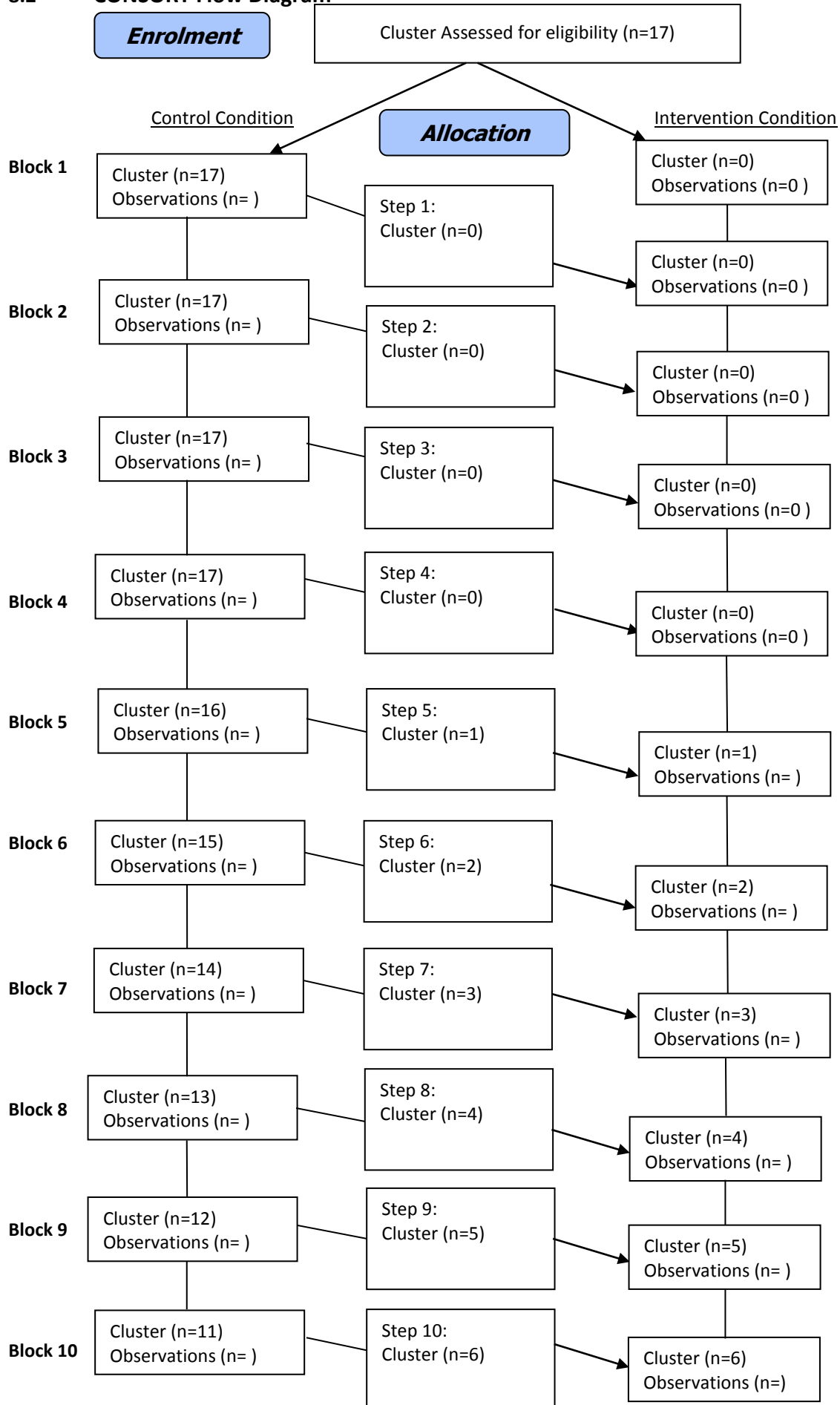
## **8. ANALYSIS DETAILS**

The results of the analyses will be reported following the principles of the ICH E3 guidelines on the Structure and Content of Clinical Study Reports.

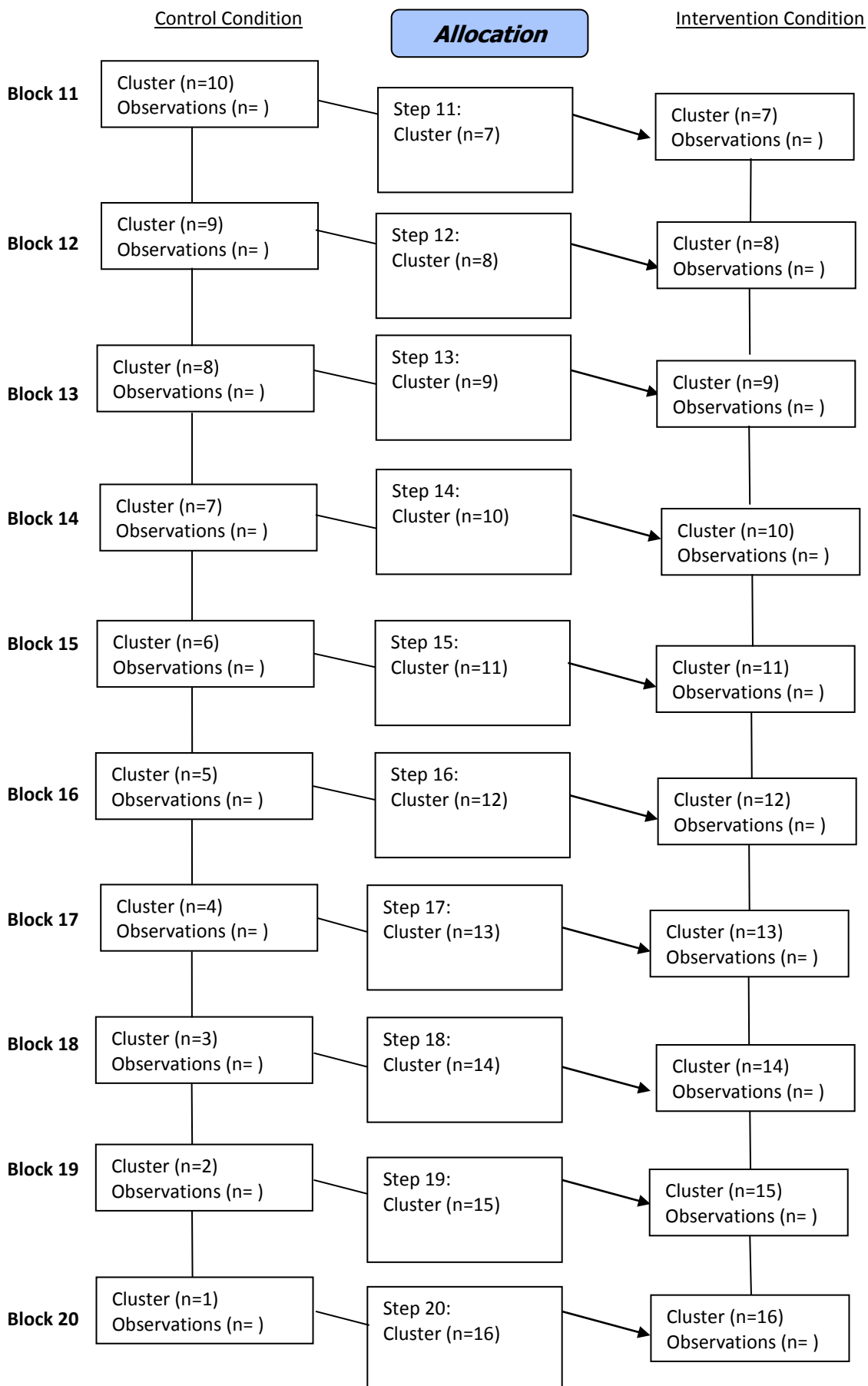
### **8.1 Recruitment and follow-up patterns**

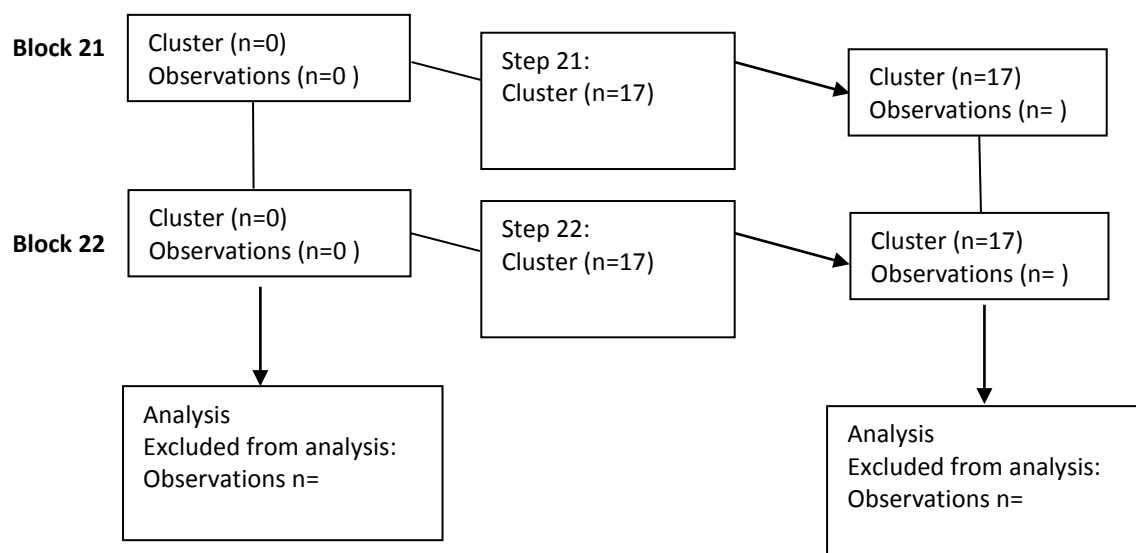
- Recruitment by site
- Withdrawals by site

8.2 CONSORT Flow Diagram









There are 17 clusters which will begin to crossover to the intervention phase at block 5 (in block 1 and 2 everyone is in control phase and in block 3 and 4 the first site to crossover is in training) of the trial recruitment period. As one hospital (GOSH) has two PICU units, although separate, due to the likely contamination between the two units for the purpose of randomisation will be treated as one cluster, this results in 17 clusters comprising of 18 PICUs.

### 8.3 Baseline Characteristics

- Gender, no. (%) by treatment arm
- Age on admission, mean (SD) by treatment arm
- Gestational age at delivery, mean (SD) by treatment arm
- Intubated prior to PICU arrival, no. (%) by treatment arm
- Previous ICU admission (during current hospital stay), no. (%) by treatment arm
- Location from where child was admitted, no. (%) by treatment arm
- Paediatric Index of mortality score, mean (SD) by treatment arm
- Primary diagnostic group, no. (%) by treatment arm
- Type of admission, no. (%) by treatment arm

### 8.4 Ventilation Parameters

A comparison of the ventilator parameters below at the point patients were eligible for the trial by treatment arm will be carried out. As well as a comparison of ventilator parameters for all those who were extubated. The values at the beginning of the SBT will be used for the Intervention arm (if within 2 hours +/- 1 hour of extubation) and the values 2 hours prior to extubation will be used for the Control arm. The following parameters will be compared:

- FiO<sub>2</sub>, mean (SD) by treatment arm
- PIP, mean (SD) by treatment arm
- PEEP, mean (SD) by treatment arm
- Ventilator Rate, mean (SD) by treatment arm
- Tidal Volume, mean (SD) by treatment arm
- Level of Pressure Support above PEEP, mean (SD) by treatment arm

### 8.5 Trial Outcomes

- Duration of IMV (1<sup>st</sup> successful extubation), median (IQR) by treatment arm, HR and 95% CI
- Incidence of successful extubations, no. (%) by treatment arm. RD and 95% CI, RR and 95% CI
- Incidence of unplanned extubations, no. (%) by treatment arm. RD and 95% CI, RR and 95% CI
- Incidence of reintubations, no. (%) by treatment arm. RD and 95% CI, RR and 95% CI

- Total duration of IMV, median (IQR) by treatment arm, HR and 95% CI
- Incidence of post-extubation use of non-invasive mechanical intubation, no. (%) by treatment arm. RD and 95% CI, RR and 95% CI
- Duration of post-extubation use of non-invasive mechanical intubation, median (IQR) by treatment arm, HR and 95% CI
- Total duration of mechanical ventilation (IMV and NIV) median (IQR) by treatment arm, HR and 95% CI
- Incidence of tracheostomy insertions, no. (%) by treatment arm. RD and 95% CI, RR and 95% CI
- Incidence of post-extubation stridor, no. (%) by treatment arm. RD and 95% CI, RR and 95% CI
- PICU length of stay, median (IQR) by treatment arm , HR and 95% CI
- Hospital length of stay in survivors, median (IQR) by treatment arm , HR and 95% CI
- Incidence of mortality occurring within ICU, no. (%) by treatment arm. RD and 95% CI, RR and 95% CI
- Incidence of mortality occurring in the Hospital, no. (%) by treatment arm. RD and 95% CI, RR and 95% CI

### 8.6 Toxicity/ Symptoms

- Adverse Event Rate, no. events (%) by treatment arm and Classification, no. patients (%) by treatment arm. RR and 95% CI.
- Serious Adverse Event, no. events (%) by treatment arm and Classification, no. patients (%) by treatment arm. RR and 95% CI.
- Unexpected Serious Adverse Reaction, no. events (%) by treatment arm and Classification, no. patients (%) by treatment arm. RR and 95% CI.

### 8.7 Health Economics

Details of the Health Economics analysis will be outlined in a separate Health Economics Analysis Plan.

## 9. ADDITIONAL INFORMATION

### 9.1 Trial Steering Committee (TSC)

A group of experienced clinicians, a statistician, and patient and public representatives will be appointed to the TSC. The TSC will have at least 75% independent membership. It will include the CI and will have independent members (one of whom will act as Chair).

The TSC will provide oversight with respect to the conduct of the study on behalf of the Funder and Sponsor. The TSC will meet approximately every 6-12 months during the course of the study and observers may be invited and be in attendance at TSC meetings, such as the Sponsor or Funder representatives or the Trial Manager to provide input on behalf of the NICTU. The discussions of the TSC will be formally minuted and a record kept in the TMF.

A TSC Charter will be drawn up to detail the terms of reference of the TSC including membership and roles and responsibilities.

### 9.2 Data Monitoring Committee (DMC)

The role of the DMC is to safeguard the rights, safety and wellbeing of trial participants, monitor data and make recommendations to the TSC on whether there are any safety reasons why the trial should not continue and monitor the overall conduct of the study to ensure the validity and integrity of the study findings.

The DMC will comprise independent members with at least one statistician and one clinician with expertise in the relevant area. The DMC will meet approximately every 6-12 months during the course of the study. The discussion of the DMC will be formally minuted and a record kept in the TMF.

A DMC Charter will be drawn up to detail the terms of reference of the DMC including membership and roles and responsibilities.

## 10. SIGNATURES OF APPROVAL

Date: 25<sup>th</sup> February 2020

Version: 1.0 final

This document has completed a final review and is understood and approved by the following:

<u>Bronagh Blackwood</u> Chief Investigator Name	<u>B. Blackwood</u> Chief Investigator Signature	<u>25/2/2020</u> Date dd/mm/yyyy
<u>Cliona McDowell</u> Head of Statistics Name	<u>C. McDowell</u> Head of Statistics Signature	<u>25/02/2020</u> Date dd/mm/yyyy
<u>Cliona McDowell</u> Study Statistician Name	<u>C. McDowell</u> Study Statistician Signature	<u>25/02/2020</u> Date dd/mm/yyyy

## 11. REFERENCES

[1] Clémence Leyrat, Katy E Morgan, Baptiste Leurent, Brennan C Kahan, Cluster randomized trials with a small number of clusters: which analyses should be used?, *International Journal of Epidemiology*, Volume 47, Issue 1, February 2018, Pages 321–331, <https://doi.org/10.1093/ije/dyx169>

## 12. APPENDIX 1: EXAMPLE DRAFT SUMMARY TABLES

Figure xxx. Recruitment

Figure xxx. CONSORT

Table x.x.x. Baseline Characteristics at trial entry

Baseline Characteristics		Observation period		Total
		Control	Intervention	
		n=<n>	n=<n>	
Gender	Male	n(%)	n(%)	n(%)
	Female	n(%)	n(%)	n(%)
	Ambiguous	n(%)	n(%)	n(%)
	Not known	n(%)	n(%)	n(%)
Age on admission (months)		xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Gestational age at delivery (if patient is under 2 years old)				
Intubated prior to PICU arrival				
	Yes			
	No			
Previous ICU Admission				
	ICU			
	PICU			
	NICU			
	None			
	Not Known			
Location from where child was admitted				
	Same hospital			
	Other hospital			
	Outpatient clinic			
	Home			
Paediatric Index of Mortality Score				
Primary Diagnostic Group				

Respiratory			
Cardiovascular			
Neurological			
Gastroenterology			
Infection			
Oncology			
Other			
Type of admission			
Planned – following surgery			
Unplanned – following surgery			
Planned – other			
Unplanned - other			

Mean (SD) presented for continuous variables and no. (%) for all categorical variables.

**Table x.x.x Main Clinical Outcome variables**

Main Clinical Outcomes	Observation period		Difference \$ (95% CI)	ICC (95% CI)
	Control	Intervention		
	n=<n>	n=<n>		
Duration of IMV (1 <sup>st</sup> successful extubation)				
Successful extubations				
Unplanned extubations				
Reintubations				
Total duration of IMV				
Incidence of Post-extubation use of non-invasive mechanical intubation				
Duration of Post-extubation use of non-invasive mechanical intubation				
Total duration of IMV and NIV				
Tracheostomy insertions				
Post-extubation stridor				
PICU length of stay				
Hospital length of stay				
Status at discharge <ul style="list-style-type: none"> <li>• Alive</li> <li>• Dead</li> </ul>				
Location following discharge <ul style="list-style-type: none"> <li>• Home</li> <li>• Other</li> </ul>				
Mortality occurring within ICU				
Mortality occurring within the Hospital				

Mean (SD) presented for treatment arms

#No. (%) for treatment arms and Risk Ratio and 95% CI presented

\$ HR, RD, RR and mean differences with 95% CIs will be presented based on output from STATA and SAS

**Table x.x.x Ventilation**

This table will include a summary of ventilation parameters at the point patients were eligible for the trial as well as prior to extubation.

Trial Treatment	Observation period	
	Control	Intervention
	n=<n>	n=<n>
Ventilator Rate, mean (SD) by treatment arm		
FiO <sub>2</sub>		
PIP		
PEEP		
Tidal Volume		
Level of Pressure Support above PEEP		

**Figure x.x.x. Kaplan Meier Curve**

Time to death and no. of deaths on x-axis while in PICU

**Table x.x.x. Protocol Deviations**

Category	Observation Period	
	Control	Intervention
Eligibility	n(%)	n(%)
Late Reporting of SAE	n(%)	n(%)
Other	n(%)	n(%)
<b>Total</b>	n	n



**Table x.x.x. Safety by Treatment Group**

		Number of events			Number of patients			RR(95%CI)	p-value
		Total n	Observation Period		Total n (%)	Observation Period			
			Control n (%)	Intervention n (%)		Control n (%)	Intervention n (%)		
AEs, SAEs,	Total SAEs								
	Related to intervention								
	Total AEs								
	Related to intervention								
	Related to intervention and unexpected								
SAEs	Classification 1								
	Classification 1								
	....								
AEs	Classification 1								
	Classification 1								
	....								
Unexpected Related SAEs	Classification 1								
	Classification 1								
	....								

For no. of events %s are calculated within total SAEs, AEs, respectively within treatment arm.

**Figure x.x.x. Forest plot for subgroups**