# SANDWICH

## Sedation AND Weaning In CHildren

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| Chief Investigator: | Professor Bronagh Blackwood<br>Wellcome-Wolfson Institute for Experimental Medicine<br>Wellcome-Wolfson Building<br>Queen's University Belfast<br>97 Lisburn Road<br>Belfast<br>BT9 7BL |

# PROTOCOL AUTHORISATION

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| Protocol Title | Sedation AND Weaning In CHildren |
| Protocol Acronym (if applicable) | SANDWICH |
| Protocol Number | B17/13 |
| Protocol Version Number/Date | V5.0 Final 12th March 2019 |
| Protocol Amendments | Amendment 1: minor amendment<br>Amendment 2: v2.0 Final 26/10/2017<br>- Key changes: changes to exclusion criteria & secondary outcomes<br>Amendment 3: minor amendment<br>Amendment 4: v3.0 Final 18/04/2018<br>- Key changes:<br>i) Process of safety reporting clarified; list of expected AEs expanded.<br>ii) Eligibility is a delegated task.<br>iii) Only co-enrolment of patients in interventional studies to be reviewed by the TMG.<br>iv) "legal representatives" should be supplied with an information leaflet for deemed consent, and withdrawal of consent.<br>v) listing of additional data variables described within the protocol.<br>vi) clarification of variables used for calculations and identifying patients<br>Amendment 5: v4.0 Final 27/07/2018<br>- Key change: addition of pregnancy to the exclusion criteria<br>Amendment 6: v5.0 Final XXX<br>- Key change: sample size recalculation |

A review of the protocol has been completed and is understood and approved by the following:

| | | |
|---|---|---|
| BRONAGH BLACKWOOD | B Blackwood | 13 / 3 / 19 |
| Chief Investigator | Signature | Date |
| CLIONA MCDOWELL | C McDowell | 13 / 03 / 2019 |
| Statistician | Signature | Date |

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# LIST OF ABBREVIATIONS

| Abbreviation / Acronym | Full Wording |
|---|---|
| AE | Adverse Event |
| BHSCT | Belfast Health and Social Care Trust |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CRN | Clinical Research Network |
| CTU | Clinical Trials Unit |
| DMC | Data Monitoring Committee |
| DMP | Data Management Plan |
| EU | European Union |
| FiO2 | Fraction of Inspired Oxygen |
| GCP | Good Clinical Practice |
| HR | Hazard Ratio |
| HRG | Health-care Resource Group |
| HTA | Health Technology Assessment |
| ICER | Incremental Cost-Effectiveness Ratio |
| ICH | International Conference of Harmonisation |
| ICC | Intracluster Correlation Coefficient |
| ICU | Intensive Care Unit |
| IMV | Invasive Mechanical Ventilation |
| ISF | Investigator Site File |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| MRC | Medical Research Council |
| NICTU | Northern Ireland Clinical Trials Unit |
| NIHR | National Institute of Health Research |
| NHS | National Health Service |
| PCCMDS | Paediatric Critical Care Minimum Data Set |
| PE | Process Evaluation |
| PEEP | Positive End Expiratory Pressure |
| PI | Principal Investigator |
| PIP | Peak Inspiratory Pressure |
| PICANet | Paediatric Intensive Care Audit Network |
| PICU | Paediatric Intensive Care Unit |
| QUB | Queen's University Belfast |
| RCT | Randomised Controlled Trial |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SBT | Spontaneous Breathing Trial |
| SOP | Standard Operating Procedure |
| SW | Stepped Wedge |
| TMF | Trial Management File |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| WTP | Willingness-to-pay |

# 1 STUDY SUMMARY

| | |
|---|---|
| Scientific title | Sedation AND Weaning In CHildren: the SANDWICH trial |
| Public title | Weaning children from the breathing machine in the children's intensive care unit |
| Health Condition(s) or problem(s) studied | Children admitted to paediatric intensive care units (PICU) requiring invasive mechanical ventilation (IMV) |
| Study Design | Cluster-randomised stepped wedge (SW) clinical and cost-effectiveness trial with an internal pilot and a process evaluation (PE) |
| Study Aim and Objectives | <u>Aim</u><br>To determine if a protocol-based intervention, incorporating co-ordinated care with greater nursing involvement, to manage sedation and ventilator weaning can reduce the duration of IMV and is cost effective compared with usual care in children in PICUs.<br><br><u>Primary Objective</u><br>To determine if the intervention reduces the duration of IMV in children expected to be ventilated for a prolonged period of time<br><br><u>Secondary Objectives</u><br>To determine if the intervention:<br>• Reduces total duration of IMV<br>• Reduces length of PICU and hospital stay<br>• Does not cause additional harm<br>• Is cost effective in the National Health Service (NHS)<br>• Is sustainable and acceptable to staff delivering care<br><br>Alongside the trial a process evaluation will be conducted using the principles of the Medical Research Council (MRC) |
| Study Intervention | A protocol-based intervention incorporating:<br>• co-ordinated care with greater nursing involvement<br>• patient-relevant sedation plans linked to regular assessment using the COMFORT scale<br>• regular assessment of ventilation parameters with a higher than usual trigger for undertaking an extubation readiness test<br>• a spontaneous breathing trial (SBT) on low levels of respiratory support to test extubation readiness |
| Comparator | Usual care: this is non-protocol-based and primarily medically-driven. Sedation levels are often assessed using the COMFORT scale. Ventilator weaning generally involves slow, gradual reduction of |

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| | pressure support to very low levels to test readiness for extubation |
| Primary Outcome | Duration of IMV measured in hours from initiation of invasive ventilation until the first successful extubation (success defined as still breathing spontaneously 48 hours following extubation).<br><br>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. |
| Key Secondary Outcomes | • Successful extubation<br>• Number of unplanned extubations<br>• Number of reintubations<br>• Incidence and duration of post-extubation use of non-invasive ventilation<br>• Tracheostomy<br>• Post-extubation stridor<br>• Any adverse events<br>• PICU length of stay<br>• Hospital length of stay<br>• Mortality occurring within the ICU<br>• Mortality occurring within the hospital<br>• Cost per respiratory complication avoided at 28 days |
| Key Inclusion and Exclusion Criteria | <u>Unit inclusion criteria</u><br>UK NHS PICUs willing to comply with the protocolised weaning intervention once randomised to crossover to the intervention period<br><br><u>Patient inclusion criteria</u><br>All invasively mechanically ventilated children (<16 years old)<br><br><u>Patient exclusion criteria</u><br>Children who would not reach the primary endpoint. |
| Countries of Recruitment | UK |
| Study Setting | Paediatric Intensive Care Units |
| Target Sample Size | 9520 |
| Study Duration | 36 months |

# 2 STUDY TEAM

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|---|---|
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| Sponsor | Queen's University Belfast |
| Primary Sponsor's Reference | B17/13 |
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# 3 BACKGROUND AND RATIONALE

## 3.1 Background Information

Currently there is no UK consensus on weaning from invasive mechanical ventilation (IMV) in Paediatric Intensive Care Units (PICUs). Our feasibility study highlighted considerable variation in ventilator weaning practice: usually a slow reduction in ventilator support to a very low level prior to extubation and no test for early readiness for extubation on higher levels of support using a trial of spontaneous breathing [1]. Furthermore, nurses' roles are not optimally utilised to adjust ventilator settings due to lack of protocols to guide ventilator weaning and discontinuation [2]. In a large number of PICUs, very few nurses are engaged in weaning, most PICUs suspend changes to ventilator settings overnight and weaning only happens during the day [1].

Mechanically ventilated children require sedative therapy with associated clinical benefit such as reduced agitation, but over-sedation can result in protracted weaning time. A recent National Institute for Health Research (NIHR) study of sedatives in PICUs reported that only about one-third of children were adequately sedated; and that almost 18% were over-sedated [3]. Our feasibility study of site visits highlighted limited guidance on target sedation scores, and nurses reported they more often increased than decreased sedatives to ensure patient comfort [1]. Only two PICUs adopted a sedation protocol to guide sedative dose adjustment to sedation score. While there is some evidence of an association with using sedation protocols and reduced PICU length of stay, there is a paucity of high-quality evidence to guide this practice[4].

Pressure on resources is a daily occurrence in the current National Health Service (NHS) and admissions to PICU are increasing year by year. Children who are ventilator dependent generally remain in PICU, requiring specialised care and frequent monitoring. In the current climate of limited availability of PICU beds, maximising use of limited resources is an important goal of providing care to critically ill patients. From 2004 to 2013 there was an increase of 15% in PICU admissions in England and Wales from 13,982 to 16,100; and overall UK admissions for 2014 were 19,760. There is seasonal variation in the number of admissions with peaks seen in the winter months from November to January when pressure for beds is greater. Around 67% of admissions to PICU require IMV for acute respiratory failure. In general, 25% of children are discharged within 24 hours, 33% remain from 1 up to 3 days; 23% from 3 up to 7 days; and 19% for more than 7 days [5].

Weaning from ventilation is a complex process involving a number of stages: i) recognition that the child is ready to begin the weaning process; ii) steps to reduce ventilation while optimising sedation in order not to induce distress; and iii) removing the endotracheal tube. Delay at any stage can prolong the duration of IMV, therefore an intervention targeted at assisting clinicians to safely expedite this process will minimise the risks associated with IMV. The judgement and experience of clinicians is critical in guiding weaning from ventilation, however, as data from our feasibility study on paediatric usual practice show, there is wide variation both in sedation and ventilator weaning practices and junior staff are rarely involved in the process [1]. Various intensive care unit (ICU) studies have reported associations between rates of high inter-professional collaboration and lower patient mortality [6, 7]; and improved clinician-to-clinician communication with reductions in ICU length of stay [8]. A team-led approach that maximises engagement of all staff in early recognition of readiness and preparation for weaning ventilation could potentially reduce duration of IMV and PICU length of stay and relieve pressures for beds. As 67% of nurses employed in UK PICUs are Band 5 (junior) nurses, this would greatly maximise nursing contribution to the weaning process [5]. Our feasibility study identified very few policies that specifically addressed sedation and weaning guidelines and staff interviews confirmed that a strategy for weaning sedation and ventilation was an important priority in most PICUs [1]. Staff also disclosed continuing uncertainty about readiness to wean, the benefits of an extubation readiness test and its potential impact on

duration of IMV in the UK. Importantly, the overwhelming majority of PICUs (83%) were willing to take part in a cluster Randomised Controlled Trial (RCT).

The proposed trial has the capacity to generate new knowledge on the intervention, its cost-effectiveness and the implementation process. First, it will be large enough to provide reliable evidence for or against a combined ventilator/sedation weaning protocol allowing clear, strong recommendations to be made on the use of this potentially low cost intervention. Second, it will determine the main organisational and process factors considered important for ensuring the intervention is optimally implemented in PICUs.

## 3.2 Rationale for the Study

A Cochrane review of weaning protocols in mechanically ventilated children highlighted only three RCTs [9]. A two-centre trial (n=260), using an intervention incorporating daily screening and a spontaneous breathing trial (SBT), demonstrated a significant reduction of 32 hours (95% CI 8-56 hours) in duration of IMV without additional harms [10]. The smaller pilot studies using computer-driven protocols showed non-significant effects in duration of IMV, but significant reductions in weaning times (106 hours, 95% CI 28-184; and 21 hours, 95% CI 9-32) [11, 12]. In adults, a Cochrane review of protocolised weaning (17 trials) showed a 26% reduction in duration of IMV in favour of protocols and the most commonly used protocol was daily screening and SBT[13]. Although results from adults cannot be applied to the paediatric population, the use of SBT as a weaning strategy shows promise and the paediatric review indicates a state of clinical equipoise that is worthy of further evaluation.

Sedation levels in PICU are generally suboptimal and over sedation is common. Strategies to improve sedation management include guidelines, algorithms or protocols, but there is weak evidence to support effectiveness in children [14]. A recent paediatric multi-centre cluster RCT conducted in the United States (n=31 sites) evaluated a sedation weaning protocol that included a SBT and found no significant reduction in duration of IMV [15]. However, the main focus of this intervention was the stringent sedative regime (targeted sedation, arousal assessments, extubation readiness testing, sedation adjustment every 8 hours, and sedation weaning). A process evaluation was not conducted alongside this trial, therefore the reasons for a lack of effect are uncertain and we cannot determine if this was due to intervention and/or implementation failure.

The paediatric review showed low quality evidence emanating from small, mainly single-centred sites [9]. This indicates a state of clinical equipoise: considerable promise that the intervention will be effective, but an evidence base that is currently too weak to warrant routine roll-out without further evaluation in a large, robust, multi-centre RCT. That sedation and ventilator weaning are inextricably linked and shown to impact on duration of ventilation, provides the rationale for evaluating a combined approach in the trial. Additionally, the process evaluation will augment the interpretation of the trial outcomes [16].

## 3.3 Rationale for the Intervention

The health technology being assessed is a protocol-based intervention incorporating co-ordinated care with greater nursing involvement; patient-relevant sedation plans linked to regular assessment using the COMFORT tool; regular assessment of ventilation parameters with a higher than usual trigger for undertaking an extubation readiness test; and a SBT on low levels of respiratory support to test extubation readiness.

There is strong evidence that co-ordinated care improves quality and saves money in healthcare, but it depends on the approach used, how well it is implemented and on the particular environment [17]. Within ICU, the dynamic, complex and time-pressured environment necessitates a team approach to care delivery that requires effective communication and

collaboration [18]. Various studies in ICU have reported associations between rates of high inter-professional collaboration and patient mortality [6, 7]; and improved clinician-to-clinician communication with reductions in ICU length of stay [8]. Qualitative research indicates that inter-professional collaboration and communication are major factors that influence weaning and adoption of weaning protocols [19].

In ventilator weaning, there is strong evidence that mechanically ventilated patients should have their readiness to wean assessed daily and weaning should be initiated on the basis of objective clinical criteria, rather than the clinician's subjective impression[20]. Weaning generally involves either a period of spontaneous breathing (a SBT) or a gradual reduction in the amount of ventilator support. The SBT was developed to identify patients who are ready to discontinue ventilation [20]. The test aims at monitoring signs of respiratory muscle fatigue while the patient is still intubated. Adult studies have shown that most patients do not need gradual weaning; when assessed with a daily evaluation and SBT, approximately 75% of patients are ready to be extubated [21]. Early paediatric studies have shown similar results[22-23]. However, although the introduction of weaning protocols has resulted in decreased ventilation times in adult patients [13], only one study (n=260) has shown that a similar protocol can benefit the paediatric population [10].

In sedation weaning, a Cochrane review of two single-centre adult trials (n=633) [24] and a recent multi-centre paediatric trial (n=2449) [15] showed no clear evidence that protocol-directed sedation is more effective than non-protocolised care. However, systematic review evidence from six observational studies including 2011 children reported a beneficial association between the use of sedation guidelines and reduced PICU length of stay, frequency of unplanned extubation, prevalence of patients experiencing drug withdrawal, total doses delivered and duration of sedation [4].

Sedation and weaning are inextricably linked and clinical co-ordination of care is an important priority. Therefore, it makes sense to package these together in a way that is not overly complicated: (a) daily evaluation and SBT; (b) sedation assessment and a strategy to minimise sedation; and (c) maximisation of engagement of staff. While the individual components have been evaluated separately, the evidence to support them is still limited due to its low quality, and they have not been combined and evaluated in this particular way.

## 3.4 Rationale for the Comparator

The control arm is intended to reflect current best practice in NHS PICUs. Sedation and ventilator weaning in standard care is currently non-protocol-based and medically-driven. Sedation levels will be assessed and recorded with a validated sedation tool and ventilator weaning will involve a slow reduction in ventilator support until low levels are achieved consistent with readiness for extubation. Conducting a SBT from higher levels of pressure support is not a component of current practice.

## 3.5 Rationale for the Study Design

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.

# 4 STUDY AIM AND OBJECTIVES

## 4.1 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.

## 4.2 Study Aim

To deliver a UK multi-centre stepped wedge cluster 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 IMV and is cost effective compared with usual care in children in PICUs.

## 4.3 Study Objectives

### 4.3.1 Primary objective

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

### 4.3.2 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

### 4.3.3 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.

# 5 STUDY DESIGN

## 5.1 Study Design

This is a stepped wedge (SW) cluster randomised clinical and cost-effectiveness trial with an internal pilot phase and a process evaluation.

In PICO terms:

Population: Children admitted to eligible PICUs who require IMV.
Intervention: A protocol-based intervention incorporating co-ordinated care with greater nursing involvement to managing sedation and weaning ventilation.
Comparator: Usual care: sedation and ventilation weaning that is non-protocol-based and primarily medically-driven.
Outcome: Duration of IMV.

### 5.1.1 Stepped Wedge Trial Design

The SW design 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. In sites where two PICUs are participating, the pair of PICUs will be randomised to cross from control to intervention together to avoid intervention contamination within the site. 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.

To assess for intervention contamination in units not yet randomised (control phase), sedation and ventilation weaning steps will also be monitored by collecting daily information on ventilation parameters (mode of IMV, fraction of inspired oxygen (FiO2), positive end expiratory pressure (PEEP) and peak inspiratory pressure (PIP), ventilator rate, tidal volume, and the level of pressure support above PEEP) and sedation scores (COMFORT) prior to extubation will be measured. This will enable changes in practice across time to be detected.

Fidelity to the intervention will be monitored as follows during the trial period. Fidelity to the sedation and ventilation weaning steps will be monitored by collecting daily information on ventilation parameters (mode of IMV, FiO2, PEEP, PIP, ventilator rate, tidal volume, and the level of pressure support above PEEP) and sedation scores (COMFORT) in the pre-weaning stage and the ventilation parameters and sedation score prior to the SBT.

Adherence to elements of the intervention will be monitored in the following ways:

- ward round sedation and ventilation planning
- assessment of COMFORT
- assessment of criteria for readiness to wean
- progression to SBT when readiness criteria are fulfilled

### 5.1.2 Internal Pilot Study

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

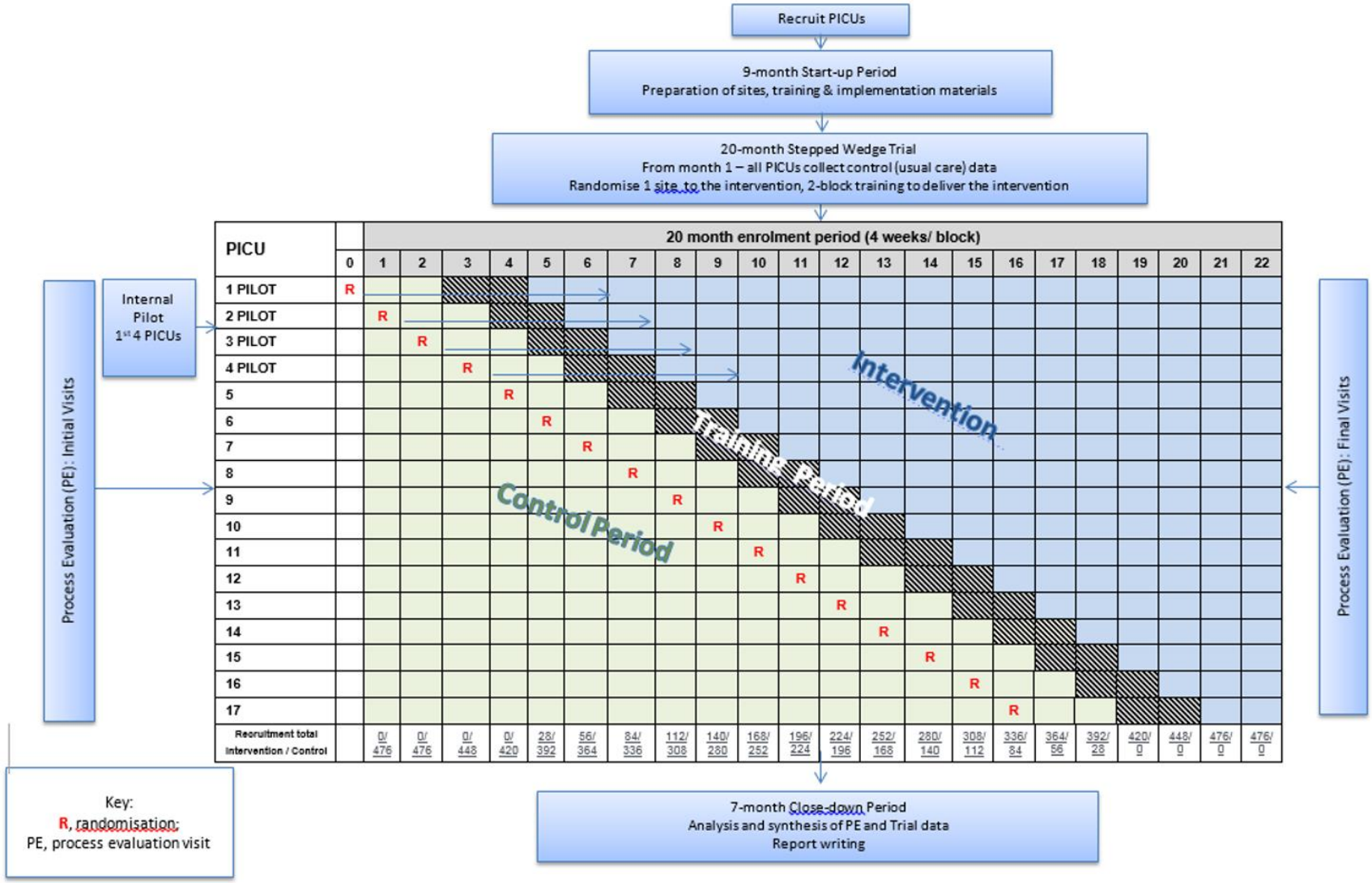
Specifically, the following criteria will be considered:

- 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.

Alongside the internal pilot the process evaluation will be conducted. At the pilot sites information will be collected on feasibility and acceptably from baseline visits about usual practice and resources; the implementation process during the training period; and interviews with key staff approximately two months following the training period.

## 5.2 Example Study Schematic Diagram



## 5.3 Study Timeline

The total study duration will be 36 months. The first 9 months will constitute the start-up period and all participating units 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 units 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.

| 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 | | | | | 2,147 | 4,293 | 6,440 | 8,586 | 10,733 | 12,879 | 14,310 | | |
| 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 |
| TSC Meetings | | | X | | | | X | | | X | | | X |
| Data Analysis | | | | | | | | | | | | X | X |
| Health Economics Analysis | | | | | | | | | | | | X | X |
| Trial Report | | | | | | | | | | | | | X |
| Dissemination | | | | | | | | | | | | | X |

## 5.4 End of Study

For the purposes of submitting the end of trial notification to the Sponsor and Research Ethics Committee (REC), the end of the trial will be considered to be when database lock occurs for the final analysis. The trial will be stopped prematurely if:

- Mandated by REC
- Mandated by the Sponsor (e.g. following recommendations from the Data Monitoring Data Monitoring Committee (DMC)
- Funding for the trial ceases

The REC that originally gave a favourable opinion of the trial will be notified in writing once the trial has been concluded or if it is terminated early.

# 6 OUTCOMES

## 6.1 Outcome Measures

### 6.1.1 Primary Outcome Measure

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.

### 6.1.2 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
- Tracheostomy insertion
- 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.

# 7 STUDY SETTING AND ELIGIBILITY

## 7.1 Study Setting

The trial will be conducted in at least 13 PICUs in the UK with a case mix typical of UK critical care practice. The PICUs recruited all participate in the Paediatric Intensive Care Audit Network (PICANet). PICANet is an international audit of paediatric intensive care that collects data on all children admitted to PICUs in the UK and Ireland (www.picanet.org.uk). Participating organisations provide clinical audit data to the PICANet database. A list of the study units participating in the SANDWICH trial will be maintained in the Trial Master File (TMF).

## 7.2 Eligibility Criteria for Clusters (Site)

The PICUs must provide evidence that medical and nursing staff have clinical equipoise for protocolised weaning, must nominate a local champion and agree to comply with the protocolised weaning intervention once randomised to cross over to the intervention. Staff must also document a willingness to participate in training.

## 7.3 Patient Eligibility Criteria

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

### 7.3.1 Inclusion Criteria

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

### 7.3.2 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

## 7.4 Co-enrolment Guidelines

Patients enrolled in SANDWICH may be enrolled in other observational studies.

Patients enrolled in other interventional studies are potential candidates for SANDWICH. The PI or other unit staff should notify the trial team at the Clinical Trials Unit (CTU) with details of the interventional study. The study details will be reviewed by the Chief Investigator in consultation with the Trial Management Group (TMG). Where applicable, the TMG may consult with the Chief Investigator of the other study before making a decision on whether co-enrolment is acceptable.

# 8 RECRUITMENT

## 8.1 Recruitment Strategy

All PICUs will be recruited prior to starting the trial to enable all units to begin baseline data collection at the same time point. The trial will be conducted in at least 13 units.

## 8.2 Screening Procedure

All invasively mechanically ventilated children in the PICU will be screened for eligibility for inclusion in data analysis. Eligibility will be confirmed by authorised nursing/medical staff on the delegation log. A screening log will be maintained at each unit that will include details of the number of participants excluded and the reason for exclusion. Recording this information is required to establish an unbiased study population and for reporting according to the CONSORT statement [26].

## 8.3 Informed Consent

A non-confirmed deemed consent (opt-out) approach will be taken in this cluster randomised stepped wedge trial. The hospital site is the cluster and one site per month will be informed that they have been randomised to receive training on the intervention; they will continue using the intervention until the end of the trial. In the recruiting clusters, leaflets will be provided to parents, or legal representative, of children, informing them that the PICU is involved in a study and that staff will be collecting anonymised patient level information during that time. Individual patient consent will not be confirmed with parents. This study is assessing how well a new approach to weaning and sedation works and all clinical staff will follow the same protocol for weaning and sedation after their PICU is randomized to the intervention. This deemed consent (opt-out) approach is considered appropriate for the following reasons:

1. In line with guidance from the Ottawa Statement [27] and feedback from proposed guidance on consent in cluster trials from the NHS Health Research Authority [28], there is broad support for taking different approaches to seeking consent in low-risk trials where the patient is likely to receive the research intervention as part of their standard treatment. The trial falls into this category because the intervention is non-invasive and directed at clinician behaviour change.
2. During feasibility work the Clinical Research Network (CRN): Children's Young Persons' Advisory Group and a parent research group at Alder Hey were consulted on their views regarding consent. Parents and young people indicated that written informed consent was unnecessary due to the low-level of risk and non-invasive nature of the intervention and preferred posters and leaflets [2925].
3. Posters and leaflets will be displayed in prominent areas to explain that a trial is taking place with the PICU. The leaflets provided to parents will include details of who can be contacted to get more information or to request that their child's data is not included in the data analysis. This method is already established practice and works well in PICUs for informing parents of patient data collection for the national audit of Paediatric Intensive Care occurring in the participating ICUs.
4. The units routinely submit clinical data to the PICANet database. These data are used locally by participating PICUs to monitor activity and performance. We will use PICANet data. PICANet will produce a facility for units to download a pseudoanonymised dataset for the SANDWICH trial.

## 8.4 Patient Withdrawal

Children may be withdrawn from outcome data collection on the request of parents or legal representatives who decline participation in the research. If parents opt out from the research

before any data has been collected for their child this will be noted on the screening log, which will be held at the unit; the Chief Investigator (CI) and the units Principal Investigator (PI) will be informed. If at any other stage in the study children are withdrawn, units will inform their PI and the clinical trials unit. Withdrawal should also be noted by the unit in the patient record and on PICANet. Units will maintain a log with details of the number of patients withdrawn and the reasons for withdrawal. Any data collected up to the point of withdrawal will not be included in the data analysis.

# 9 ASSIGNMENT OF INTERVENTION

## 9.1 Intervention Description

A protocol-based intervention incorporating co-ordinated care with greater nursing involvement is being assessed; patient-relevant sedation plans linked to regular assessment using a COMFORT scale; regular assessment of ventilation parameters with a higher than usual trigger for undertaking an extubation readiness test; and a SBT on low levels of respiratory support to test extubation readiness.

The intervention comprises a number of components including:

- Greater inter-professional collaboration in regularly reviewing sedation management including:
    a) review of COMFORT scores, sedative regimen and setting targets
    b) ventilation and setting ventilation goals
- Measurement of sedation using COMFORT
- Regular daily assessment of criteria for readiness to perform a SBT by bedside nursing staff
- A SBT and if no distress, a discussion about the decision to extubate

A full description of the protocol-based intervention will be available in the study-specific guideline. This will be provided to units once they are randomised and have entered the intervention-training period, so as not to influence usual practice at units during their control period.

## 9.2 Assignment of Intervention

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 annual report). A restricted randomisation process will be used to ensure that the study is balanced with respect to site size across exposed and unexposed “arms” of the trial. The randomisation will be completed in real time and will create a balance of large and small units.

## 9.3 Blinding

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.

# 10 DATA COLLECTION & DATA MANAGEMENT

## 10.1 Data Collection

The trial will collaborate with PICANet to make best use of the established data collection infrastructure which exists in all PICUs in the UK. All participating PICUs routinely submit clinical data to the national audit of Paediatric Intensive Care. These data are used locally by participating PICUs to monitor activity and performance. They have full access to, and ownership of the data. Data are validated on entry and centrally on the PICANet server. PICANet produce a download facility that allows participating units to extract data required for the trial, thus reducing the burden of data collection for unit staff.

When submitting individual patient data to PICANet unit staff will indicate which patients are eligible for inclusion in the data analysis and will add a unique trial number. PICANet will produce a pseudoanonymised dataset for the SANDWICH trial which can be downloaded by unit staff at required intervals during the study. The data download for SANDWICH will not include any patient identifiable information.

The PICANet data required for the trial will be transmitted from the participating centres to the Northern Ireland Clinical Trials Unit (NICTU) electronically using a secure method.

PICANet currently does not fully collect data to measure the primary outcome (duration of mechanical ventilation in hours) and several of the secondary outcomes. Additional variables to assess compliance with sedation and ventilation parameters would also not be captured by PICANet. Instead, these data will be collected and recorded on the electronic case report form (CRF) by the PI or designee at each unit. The data collected in the electronic CRF will not include any patient identifiable information.

## 10.2 Data Variables

Data collection will be restricted to variables required to define patient characteristics at enrolment; to monitor the intervention received and adverse events; determine quality of life; and use of health care resource. Data collection includes the variables detailed below (* denotes data collected through PICANet):

<u>Baseline Data (for both usual care and intervention)</u>

- Inclusion/exclusion criteria and eligibility screen
- Patient Number (Event ID generated in PICANet; Patient No. generated in the CRF*)
- Sex*
- Age on admission (in months)*
- Gestational age at delivery (if patient is under 2 years old)*
- Date/time of admission
- Previous ICU Admission (during current hospital stay)*
- Location from where the child was admitted (same hospital, other hospital, outpatient clinic or home)*
- Paediatric Index of Mortality score (including breakdown of reason for this admission)*
- Primary diagnosis for this admission*
- Date/time of intubation

Daily data collection (for both usual care and intervention periods) up to 90 days or PICU discharge (whichever is earlier)

- Once daily, at 8 am or as close to this time as possible, the mode of IMV, FiO2, PEEP, PIP, ventilator rate, tidal volume, and the level of pressure support above PEEP (depending on the mode of ventilation) (whilst the child is ventilated through an endotracheal tube)
- Adverse events
- Paediatric Critical Care Minimum Dataset (for obtaining the healthcare resource group for each PICU admission) *

Additional data collected during the intervention phase up to 90 days or PICU discharge (whichever is earlier) (whilst the child is ventilated through an endotracheal tube)

- COMFORT scoring and ward round sedation and ventilation planning
- Readiness to wean criteria
- Date/time of start/end of SBT and outcome (if applicable)
- Mode of IMV, FiO2, PEEP, PIP, ventilator rate, tidal volume, and the level of pressure support above PEEP and COMFORT score (*prior to SBT*) (if applicable)

Additional data collected during the control phase (whilst the child is ventilated through an endotracheal tube)

- Mode of IMV, FiO2, PEEP, PIP, ventilator rate, tidal volume, and the level of pressure support above PEEP (2 *hours prior to extubation)*
- COMFORT score (*2 hours prior to extubation or score recorded closest to this time-point prior to extubation*)

Outcome data collection up to 90 days or PICU discharge (whichever is earlier)

- Successful extubation
- Unplanned extubations
- Reintubation (including date and time)
- Date/time of start/end of post-extubation use and duration of non-invasive ventilation
- Post-extubation stridor
- Date and time of tracheostomy
- Date and time of extubation
- PICU mortality (status on discharge)*
- PICU length of stay *
- Location where child was discharged to from the PICU*

Data collected after PICU discharge.

- Hospital length of stay (calculated from the date/time of hospital discharge)
- Destination following hospital discharge
- Hospital mortality (status on discharge)

Data censorship for each patient will occur at 90 days after admission to ICU. However, at the end of the 20-month enrolment period, patients will be followed-up for a maximum of 28 days.

## 10.3 Study Instruments

COMFORT Scale

The COMFORT and COMFORT Behaviour scale is used to assess sedation in critically ill children requiring mechanical ventilation. The scale has various indicators such as alertness; calmness/agitation; respiratory response; physical movement; blood pressure; heart rate; muscle tone and facial tension. Units will use either the COMFORT or COMFORT Behaviour Scale depending on usual practice at the unit.

## 10.4 Data Management of Non-PICANet Data

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.

## 10.5 Data Quality

Data integrity and study credibility depend on factors such as ensuring adherence to the protocol and using quality control measures to establish and maintain high standards for data quality.

The CI and the NICTU will provide training to unit staff on trial processes and procedures including CRF completion and data collection.

Monitoring during the trial will check adherence to the protocol, trial specific procedures and Good Clinical Practice (GCP).

Within the NICTU, the clinical data management process is governed by SOPs which help ensure standardisation and adherence to International Conference of Harmonisation Good Clinical Practice (ICH-GCP) guidelines and regulatory requirements.

For data collected in the electronic CRF, data validation will be implemented and discrepancy reports will be generated following data entry to identify data that may be out of range, inconsistent or protocol deviations based on data validation checks programmed into the clinical trial database. Changes to data will be recorded and fully auditable. Data errors will be documented and corrective actions implemented.

PICANet's data validation methodology includes real-time data validation reporting back to data suppliers using clinical advice on appropriate ranges for clinical data. There is comprehensive checking of outcome variables and data used for risk adjustment. Missing data, excessive use of exception values and data anomalies are reported and progress chased until resolved. Stringent data quality, logic and range checks are built into the web-based data collection system which provides real-time data validation reporting. By using a standardised format for data entry and upload PICANet maintains a consistent data quality. In addition, validation visits to units by the PICANet research nurse check the accuracy of data transcription from clinical notes.

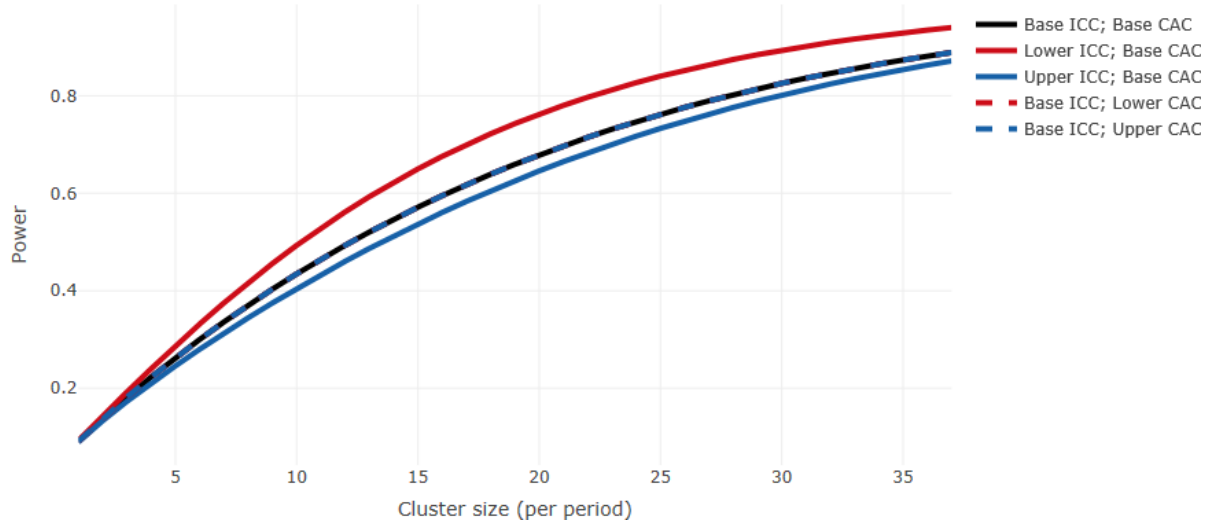
A Data Monitoring Committee (DMC) will be convened for the study to carry out reviews of the study data at intervals during the study.

# 11 STATISTICAL CONSIDERATIONS

## 11.1 Sample Size

The primary aim of this study is to determine whether the intervention can reduce the average number of hours on ventilation in eligible children. To inform the 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 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[38]. 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.




## 11.2 Data Analysis

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. The primary aim of the study is to evaluate whether there is a difference in the duration of hours on ventilation before and after exposure to the intervention: that is, does it improve clinical outcomes for the child. 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. 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 know exact survival times (i.e. times until successful extubation) for most children, but children who either die on ventilation, are transferred to another unit, are not weaned before transitioning to the training phase, or are not weaned by 90 days will not have a known extubation time. We will treat these types of events as censored observations. That means we will make the assumption that children who died on ventilation, not weaned before transitioning to the training phase, were not weaned by 90 days or who were transferred to another unit on ventilation, will have an extubation time (i.e. were removed from ventilation) greater than the time until they died or were transferred.

For children who are transferred to another unit, we will also make the assumption that their actual time to extubation is longer than their recorded time until extubation. This is again a plausible assumption, as children who are lost to follow up due to transfer would have been ventilated at the time of transfer and certainly for at least a short time beyond this. For children who are not weaned by 90 days we will make the assumption that their actual time until extubation is longer than 90 days. For children who die on ventilation, it will be unknown how long they would have been ventilated had they have survived. By treating these observations as censored, we will be making the assumption that their time on ventilation is greater than the time until they died. For children who are transferred or discharged post extubation but prior to determining it is successful we will make the assumption that it has been a successful extubation.

We will explore various models, but anticipate fitting a Cox proportional hazards model, perhaps with some treatment by covariate interaction to incorporate any non-proportionality. 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 along with 95% CIs. Time adjustment is essential because this is a SW trial.

Secondary analysis will adjust for individual and cluster level covariates such as the adherence score and these will be pre-specified in the Statistical Analysis Plan. 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 for binary outcomes and mean differences for continuous outcomes (all adjusting for cluster and time effects).

Full details of the analyses will be given in the statistical analysis plan.

## 11.3 Health Economic Evaluation

A within-trial economic evaluation will be undertaken to measure the cost-effectiveness of the intervention compared with standard care. The perspective of the analysis will be the hospital. The incremental cost-effectiveness ratio (ICER) is a measure of the additional cost per additional unit of effect produced by one intervention compared with another. We will calculate the cost per complication avoided at 28 days. The occurrence of the following respiratory

complications at 28 days will be measured; reintubation, unplanned extubations, tracheostomy, post-extubation non-mechanical ventilation and post-extubation stridor.

We will estimate total hospital costs until 28 days for each participant by applying appropriate unit costs from the NHS Schedule of Reference Costs [32] to resource use data collected prospectively via the CRF or PICANet, as appropriate. Data on the level of care for PICU bed-days will be obtained via PICANet through the routine collection of the Paediatric Critical Care Minimum Data Set (PCCMDS). The PCCMDS consists of items recorded for each PICU bed-day that can be used to define the level of care and appropriate health-care resource group (HRG). For patients discharged from hospital prior to 28 days, data on any PICU readmissions within 28 days will come from PICANet but data on readmissions to general hospital wards within this time will not be collected. This is expected to lead to only minimal data loss, as the readmission rate within 30 days in a similar paediatric population was observed to be low (5%) with a mean hospital length of stay of less than 1 day [33].

Descriptive statistics will be used to summarise hospital service use, costs and respiratory complications. Multilevel mixed-effects regression modelling will be used for total costs and respiratory complications. We will adjust for calendar time and clustering, ensuring consistency with the other models being constructed as part of the main analysis of the trial. We will estimate adjusted incremental (differential) total costs and adjusted incremental effects (respiratory complications). To explore the uncertainty in the estimates of costs and effects, the regression models will be bootstrapped to obtain at least 1000 bootstrapped adjusted incremental costs and adjusted effects which will be plotted on the cost-effectiveness plane as ICER replicates. Cost-effectiveness acceptability curves will be constructed from the scatterplots by placing a series of lines on the plane which represent different willingness-to-pay (WTP) thresholds. The WTP threshold is the maximum amount of money that the decision-maker would be willing to pay per additional unit of effect. The proportion of ICER replicates falling below each WTP threshold equates to the probability of the intervention being cost-effective at that threshold. Since there is no generally accepted threshold value for cost per respiratory complication avoided a range of plausible thresholds will be explored.

Sensitivity analysis will be performed to assess the robustness of the cost-effectiveness results to changes in key parameters. Since the time horizon of the analysis is less than 1 year, it will not be necessary to discount costs and effects.

## 11.4 Additional Analyses

Exploratory analysis will be reported using 99% confidence intervals for subgroups including size of unit and type of condition. The SW design will also allow us to investigate intervention effect heterogeneity across clusters and time.

# 12 PROCESS EVALUATION

## 12.1 Justification

The intervention under investigation in this trial is complex in that it includes a number of interdependent and interrelated components. Adding to that complexity, the intervention is being tested in multiple units comprising variable characteristics and so it is susceptible to variations between units concerning how it is implemented, received and delivered [34]. Therefore, we will evaluate the process of the implementation of the intervention to answer the question 'does it work?' in a way that will help us distinguish between intervention failure and implementation failure. Additionally, this evaluation will deliver important evidence concerning the barriers and facilitators to adoption. This cannot only help to explain trial outcomes, but also determine factors requiring attention if, after the study, the intervention is to be further disseminated to other PICUs and sustained in practice. We will follow the guidance from the MRC on the process evaluation (PE) [16]. Additionally, our evaluation will be guided by on-going work of an MRC Network of Trials Methodology Hubs' PhD Fellowship student (supervised by Blackwood, McAuley and Clarke), who is developing a framework for PEs in critical care trials.

## 12.2 Aims and Objectives

The aim of the process evaluation is to explore the processes involved in delivering the intervention, in order to identify factors and the mechanisms of their interaction likely to impact on trial outcomes. The objectives are:

1. To establish the extent to which the intervention is implemented as intended (implementation fidelity), over time and across different PICUs.
2. To ascertain how participants receive (e.g. understand and respond to) the intervention, over time and across different PICUs.
3. To explore the context over time and across different PICUs and determine factors (including managerial support, economic, organisational and work level) that affect implementation.

## 12.3 Data Collection Methods

The methods used to conduct the PE will be:

- Initial unit visits to undertake familiarisation with the PICU and to obtain information on context and usual practice. This information will be collected through interviews and/or focus groups with staff involved in the implementation and delivery of the intervention, as well as research staff (PIs and Research Nurses). We will employ purposive sampling to obtain a range of participants according to grade and profession.
- Telephone interviews with unit research staff and local champions in the intervention phase to obtain information regarding the implementation process; acceptability of the intervention; barriers; clinical decisions affecting the use of protocol.
- Final unit visits to undertake individual and/or focus group interviews with staff involved in implementation or intervention delivery. Interviews will explore clinician experiences and understandings, including those relating to barriers and facilitators to the delivery and receipt of the intervention. These final visits will be staggered to allow time for transcription and analysis of qualitative data. Again, we will employ purposive sampling to obtain a range of participants according to grade and profession.

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## 12.4 Data Analysis Methods

We will use the framework approach to analyse qualitative data [35]. This will allow us to use themes identified *a priori* alongside those that emerge *de novo* in the development of the final analytical framework. The analysis will look for patterns and exceptions to these patterns that cross-cut the entire dataset. To ensure confirmability and trustworthiness, a sample of textual data will be double coded and the independent analyses shared to identify key differences and similarities in pursuit of an agreed final analysis. Using this approach, we will generate a body of evidence on the barriers and facilitators related to the implementation, receipt and setting of the protocol.

## 12.5 Integrating Process and Outcome Data

The integration of process and trial outcome data and subsequent analyses will be secondary and explanatory, and separate from the primary effectiveness analysis. The qualitative evidence will be systematically combined with outcome data to identify the processes mediating protocol implementation, receipt and setting and observed outcomes.

For example, in relation to assessment of implementation fidelity, we will use an adapted version of the Conceptual Framework for Implementation Fidelity [36]. Accordingly, we will assess each key component of the protocol to answer the following questions:

- Fidelity: were the intervention components implemented as planned?
- Dose: how much of the intended intervention was delivered? (i.e. to what extent changes were made in delivering the components and decisions taken for operating 'off protocol').
- Reach: what proportion of staff were trained and to what extent were they engaged in the intervention components?

We will identify potential moderating factors that may impact on adherence to the key components, using evidence gathered as part of the PE. This will allow us to score each of the participating PICUs according to adherence to each component. Adherence will be 'scored' on a categorical scale ranging from 0 to 3, with 0 representing 'no adherence', 1 representing 'some adherence', 2 representing 'mostly adhering', and 3 representing 'full adherence'. Following Sheard *et al.* [34], each intervention component will be independently scored by three members of the research team, with consensus agreement on the final score for each ICU. The final score will be available to use as a covariate in secondary analyses.

Throughout the integration of process and outcome data, and in line with recommended practice, we will draw on relevant theory to help understand the observed relationships between (components of) the evidence uncovered through the process evaluation and trial outcome data [37].

# 13 SAFETY REPORTING

## 13.1 Definitions

As the current study is not investigating medical products, adverse event reporting will follow the Health Research Authority guidelines on safety reporting in non-clinical trial investigational medicinal product studies.

### 13.1.1 Adverse Event

Events and complications associated with the patient's underlying medical condition will not be considered adverse events (AE). An AE is defined as any untoward medical occurrence in a study participant.

### 13.1.2 Serious Adverse Event

A serious adverse event (SAE) is defined as an untoward occurrence that:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation*;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect; or
- is otherwise considered medically significant by the investigator.

*Hospitalisation is defined as an inpatient admission regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

### 13.1.3 Assessment of Causality

The PI or medically qualified designee should make an assessment of causality, i.e. the extent to which it is believed that the event resulted from delivery of the SANDWICH intervention:

- **Not Related**: Temporal relationship of the onset of the event, relative to delivery of the intervention, is not reasonable or another cause can by itself explain the occurrence of the event.
- **Unlikely**: Temporal relationship of the onset of the event, relative to delivery of the intervention, is likely to have another cause which can by itself explain the occurrence of the event.
- **Possibly***: Temporal relationship of the onset of the event, relative to delivery of the intervention, is reasonably resulted from the intervention but the event could have been due to another, equally likely cause.
- **Probably***: Temporal relationship of the onset of the event, relative to delivery of the intervention, is reasonable and the event is more likely a result of the intervention than any other cause.
- **Definitely***: Temporal relationship of the onset of the event, relative to delivery of the intervention and the event is reasonably a result of the intervention and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

* Where an event is assessed as possibly, probably or definitely related, the event is considered 'related' to the SANDWICH intervention.

## 13.2 Reporting and Recording

AEs and SAEs will be recorded and reported for each patient until PICU discharge or 90 days after admission (whichever is earlier). All reported adverse events will be recorded in the medical notes of the patients.

Adverse events expected within the trial population include the events listed below:

- Unplanned extubation**
- Unplanned extubation requiring reintubation**
- Unplanned removal of arterial line
- Unplanned removal of an arterial line requiring reinsertion
- Unplanned removal of central line
- Unplanned removal of a central line requiring reinsertion
- Unplanned removal of a urinary catheter
- Unplanned removal of a urinary catheter requiring insertion
- Unplanned removal of a chest drain
- Unplanned removal of a chest drain requiring insertion
- Unplanned removal of any other indwelling line, tube or drain
- Unplanned removal of any other indwelling line, tube or drain requiring insertion
- Tracheostomy**
- Post-extubation stridor**
- Need for non-invasive mechanical ventilation (post extubation)**
- Reintubation**
- Bradycardia requiring intervention
- Hypoxia/desaturation requiring intervention
- Need for cardiopulmonary resuscitation (CPR)

**These events are being collected as outcomes in the study and so will not be reported separately as an AE or SAE.

## 13.3 Serious Adverse Event Reporting

All SAEs (other than those defined in the protocol as not requiring reporting) should be reported to the NICTU within 24 hours of the unit research team becoming aware of the event. SAEs will be reported using the SAE report form. The form must be emailed to the NICTU using the following dedicated email address:

**clinicaltrials@nictu.hscni.net**

The NICTU will acknowledge receipt of the SAE Form within two working days by email to the unit. The unit should not wait until all information about the event is available before notifying the NICTU of the SAE. Information not available at the time of the initial report must be documented and submitted as it becomes available.

If in the opinion of the PI or other medically qualified designee, an SAE occurring to a research participant is classified as:

- *Related*: that is, it resulted from delivery of the intervention, and
- *Unexpected*: that is, the type of event is not listed in the protocol as an expected occurrence

the CTU will be responsible for reporting the SAE to the sponsor and to the REC which issued the favourable ethical opinion. The CTU will submit the SAE (using the SAE report for non-

CTIMPs published on the Health Research Authority website) within 15 days of the PI becoming aware of the event.

## 13.4 Urgent Safety Measures

If the PI or designee becomes aware of information that necessitates an immediate change in study procedure to protect research participants from any immediate hazard, they can implement this immediately prior to approval by REC.

If an urgent safety measure is taken, the PI should notify the REC that provided the favourable opinion for the study immediately by telephone. The PI should also immediately notify the NICTU at the following email address:

**clinicaltrials@nictu.hscni.net**

The NICTU will notify the Sponsor and CI. The CI will then notify the REC within 3 days (in writing) setting out the reasons for the urgent safety measures and the plan for further action.

# 14 DATA MONITORING

## 14.1 Access to Study Data

Prior to commencement of the study, the PI at each unit will give permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. The patients' confidentiality will be maintained and their identity will not be made publicly available to the extent permitted by the applicable laws and regulations.

## 14.2 Monitoring Arrangements

The NICTU will be responsible for trial monitoring. Monitoring will be conducted in accordance with the trial monitoring plan. Monitoring will be an on-going activity from the time of initiation until trial close-out and will comply with the principles of GCP. The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial Sponsor.

Before the trial starts at a participating unit, they will be provided with training on the trial to ensure that unit staff are fully aware of the trial protocol and procedures. Checks will be completed to ensure that all relevant essential documents are in place.

Monitoring during the trial will check the adherence to the protocol, procedures and GCP, and the progress of recruitment and follow up.

The close-out procedure at each unit will commence once the final patient enrolled has completed all follow-up required by the protocol.

# 15 TRIAL COMMITTEES

## 15.1 Trial Management Arrangements

The CI will have overall responsibility for the conduct of the study. The NICTU will undertake trial management including preparing clinical trial applications (REC and research governance), pharmacovigilance, unit initiation/training, monitoring, analysis and reporting. The Trial Manager/Co-ordinator will be responsible on a day-to-day basis for overseeing and co-ordinating the work of the multi-disciplinary trial team. Additional trial specific oversight committees will be convened for the SANDWICH trial. These will include a TMG, TSC and DMC. The NICTU will facilitate the setting-up and the co-ordination of these trial committees.

## 15.2 Trial Management Group (TMG)

A TMG will be established and Chaired by the CI. The TMG will have representation on it from the NICTU and other investigators/collaborators who are involved in the study and provide trial specific expertise (e.g. trial statistician). This group will have responsibility for the day-to-day operational management of the trial, and regular meetings of the TMG will be held to discuss and monitor progress. The discussions of the TMG will be formally minuted and a record kept in the TMF.

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

## 15.3 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.

## 15.4 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.

# 16 REGULATIONS, ETHICS AND GOVERNANCE

The trial will comply with the principles of GCP, the requirements and standards set out by the EU Directive 2001/20/EC and the applicable regulatory requirements in the UK and the Research Governance Framework.

## 16.1 Sponsorship

Queen's University Belfast (QUB) will act as Sponsor for the study and the CI will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor and each organisation who will undertake Sponsor delegated duties in relation to the management of the study.

## 16.2 Funding

This study is funded by the NIHR HTA Programme. This funding covers staff cost, travel, consumables, training, trial registration fees, software licenses and open access publication fees.

This study is funded as a result of a commissioned call from the NIHR and the protocol was developed in response to review by NIHR HTA.

## 16.3 Contributorship

All the applicants (Bronagh Blackwood, Kevin Morris, Duncan Macrae, Mark Peters, Mike Clarke, Karla Hemming, Joanne Jordan, Roger Parslow, Cliona McDowell, Ashley Agus, Danny McAuley, Lyvonne Tume and Timothy Walsh) contributed to the study design; and along with the TMG were involved in the development and finalisation of the protocol. Blackwood brings expertise in the evaluation of complex interventions in ICU, particularly considering strategies for weaning from mechanical ventilation. Jordan brings expertise in ethnography for the process evaluation. Tume has undertaken robust feasibility work to underpin this study and provides nursing leadership in education, training and implementation of the weaning protocol. Walsh brings expertise in complex intervention in cluster trials. Both Clarke and Hemming provide expertise in clinical trials and stepped wedge design. Parslow is an experienced epidemiologist and manages the PICANet dataset. Morris, Macrae, Peters, McAuley and Walsh bring clinical intensive care expertise including clinical trial leadership and management expertise. McDowell will co-ordinate the statistical aspects of the study including analyses and Agus will conduct the economic analysis for the study.

## 16.4 Patient and Public Involvement

Consultation interviews were undertaken with parents, a 15 year old PICU survivor and 13 young people who were members of the NIHR Clinical Research Network: Children, Young Person's Advisory Group Service about the proposed trial.

## 16.5 Competing Interests

The research costs were funded by NIHR HTA. The CI and members of the TMG have no financial or non-financial competing interests and the members of the TSC and DMC will be asked to confirm that they have no conflict of interest. In the event that a TSC or DMC member reports a conflict of interest, advice will be sought from the Sponsor.

## 16.6 Indemnity

Queen's University Belfast (QUB) will provide indemnity for the management and design of the UK cohort of the study. QUB will provide indemnity for negligent and non-negligent harms caused to patients by the design of the research protocol. The NHS indemnity scheme will apply with respect to clinical conduct and clinical negligence.

## 16.7 Ethical Approvals

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee.

## 16.8 Good Clinical Practice

The trial will be carried out in accordance with the principles of the ICH-GCP guidelines (www.ich.org).

## 16.9 Study Protocol Compliance

A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented.

A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The PI or designee is responsible for ensuring that serious breaches are reported directly to the NICTU within one working day of becoming aware of the breach.

Study protocol compliance will be monitored by the NICTU who will ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRFs) is being completed appropriately.

## 16.10 Protocol Amendments

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee. Changes to the protocol may require ethics committee approval/favourable opinion prior to implementation. The NICTU in collaboration with the Sponsor will submit all protocol modifications to the research ethics committees for review in accordance with the governing regulations.

## 16.11 Patient Confidentiality

In order to maintain confidentiality, all study reports and communication regarding the study will identify the patients and participants by the assigned unique trial number only. Databases where information will be stored will be password protected. Patient confidentiality will be maintained at every stage and their identities will not be made publicly available to the extent permitted by the applicable laws and regulations.

## 16.12 Record Retention

The PI will be provided with an Investigator Site File (ISF) by the NICTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The TMF will be

held by the NICTU within the Belfast Health and Social Care Trust (BHSCT) and the essential documents that make up the file will be listed in an SOP. On completion of the trial, the TMF and study data will be archived by the NICTU according to the applicable regulatory requirements and as required by the Sponsor. Following confirmation from the Sponsor the CTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the NICTU and Sponsor.

# 17 DISSEMINATION/PUBLICATIONS

## 17.1 Trial Registration

The trial will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) register.

## 17.2 Trial Publications

The analyses for the final study report will be provided by the Trial Statistician; it is anticipated that the study findings will be published in national and international peer reviewed journals and that the preparation of the report will be led by the CI. In addition, study findings may be presented at both national and international meetings and to appropriate patient groups.

A dissemination strategy will be devised to ensure that findings from this commissioned study are reported in a timely and relevant manner to influence health service policy to deliver public benefit. The strategy will target a variety of service users including the UK paediatric intensive care community, the NHS and the public.

## 17.3 Authorship Policy

Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org). Authorship of parallel studies initiated outside of the TMG will be according to the individuals involved in the project but must acknowledge the contribution of the TMG and the Study Co-ordination Centre.

## 17.4 Data Access

Following the publication of the study outcomes, there may be scope to conduct additional analyses on the data collected. In such instances formal requests for data will need to be made in writing to the CI who will discuss this with the TMG. In the event of publications arising from such analyses, those responsible will need to provide the CI with a copy of any intended manuscript for approval prior to submission. Authorship will need to take the format of “[name] on behalf of” or something similar, which will be agreed by the TMG.

## 17.5 Data Sharing Statement

Requests for data sharing will be reviewed on an individual basis by the CI and the TMG.

# 18 REFERENCES


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