



PROTOCOL

Protocolised trial of invasive and non-invasive weaning off ventilation

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CONTACT NAMES AND NUMBERS

| Role | Name, address, telephone |
|----------------------------|--|
| Lead Sponsor: | Ms Elizabeth Adey Heart of England NHS Foundation Trust MIDRU Birmingham Heartlands Hospital Bordesley Green East Birmingham, B9 5SS Tel: 0121 424 1633 Fax: 0121 424 2345 Email: Elizabeth.adey@heartofengland.nhs.uk |
| Co-Sponsor: | Mrs Jane Prewett University of Warwick Kirby Corner Road Coventry, CV4 8UW Tel: 02476 523716 Fax: 02476 524991 Email: jane.prewett@warwick.ac.uk |
| Chief Investigator: | Professor Gavin Perkins Warwick Clinical Trials Unit (WCTU) The University of Warwick Gibbet Hill Road Coventry, CV4 7AL Tel: 02476 750479 Fax: 02476 151136 Email: g.d.perkins@warwick.ac.uk |
| Trial Co-ordinator: | Beverley Hoddell Warwick Clinical Trials Unit (WCTU) The University of Warwick Gibbet Hill Road Coventry, CV4 7AL Tel: 02476 575849 Fax: 02476 151136 Email: b.hoddell@warwick.ac.uk |

| Role | Name, address, telephone |
|----------------------------|--|
| Trial Statistician: | Dr Ranjit Lall Warwick Clinical Trials Unit (WCTU) The University of Warwick Gibbet Hill Road Coventry, CV4 7AL Tel: 02476 574659 Fax: 02476 151136 Email: r.lall@warwick.ac.uk |
| Health Economist: | Professor Stavros Petrou Warwick Clinical Trials Unit (WCTU) The University of Warwick Gibbet Hill Road Coventry, CV4 7AL Tel: 02476 151124 Fax: 02476 151136 Email: s.petrou@warwick.ac.uk |

| Role | Name, address, telephone |
|----------------------------------|---|
| Trial Steering Committee: | <p>Professor Steve Goodacre School of Health and Related Research (SchARR) University of Sheffield</p> <p>Dr Simon Finney Royal Brompton Hospital</p> <p>Dr Shelia Harvey ICNARC Napier House</p> <p>Mr Barry Williams C/O The Intensive Care Society</p> <p>Mr Duncan Wells C/O The Intensive Care Society</p> <p>Professor Gavin Perkins University of Warwick, Heart of England NHS Foundation Trust</p> <p>Professor Simon Gates Warwick Medical School, Clinical Trials Unit</p> <p>Dr Ranjit Lall Warwick Medical School, Clinical Trials Unit</p> <p>Co-sponsor Representative University of Warwick</p> <p>Mrs Liz Adey Heart of England NHS Foundation Trust</p> <p>Dr Gary Mills Sheffield Teaching Hospitals</p> <p>Ms Beverley Hoddell Warwick Medical School, Clinical Trials Unit</p> <p>Ms Amanda Odell Royal Berkshire NHS Foundation Trust</p> |

| Role | Name, address, telephone |
|------------------|--|
| Observers | Trial Co-ordinator Sponsor representatives from Heart of England Foundation Trust and University of Warwick Representative from Research Network |

| | |
|--|--|
| Data Monitoring and Ethics Committee: | Professor Charles Hinds William Harvey Research Institute Dr Mark Griffiths Royal Brompton Hospital Dr David Harrison ICNARC Napier House Dr Ranjit Lall Warwick Medical School, Clinical Trials Unit |
|--|--|

For general queries, supply of trial materials and collection of data please contact the coordinating centre

Warwick Clinical Trials Unit (WCTU)
The University of Warwick
Gibbet Hill Road
Coventry, CV4 7AL
Tel: 02476 575849
Fax: 02476 151136

Randomisation:

<https://ctu.warwick.ac.uk/Breathe>

Randomisation telephone number if website is unavailable:
02476 150402 (9 a.m. – 5 p.m. Mon-Fri)

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LIST OF ABBREVIATIONS

| Abbreviation | Explanation |
|--------------|---|
| AE | Adverse Event |
| ALI | Acute Lung Injury |
| CAM-ICU | Confusion Assessment Method |
| CLRN | Comprehensive Local Research Network |
| CONSORT | <i>Consolidated Standards of Reporting Trials</i> |
| COPD | Chronic Obstructive Pulmonary disease |
| CRF | Case Report Form |
| CTU | Clinical Trials Unit |
| DMEC | Data Monitoring and Ethics Committee |
| EQ5D | EuroQol 5 Dimension |
| GCP | Good Clinical Practice |
| ICU | Intensive Care Unit |
| IMV | Invasive Mechanical Ventilation |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| MDT | Multi-Disciplinary Team |
| MRC | Medical Research Council |
| MREC | Multicentre Research Ethics Committee |
| NIV | Non-invasive Ventilation |
| NOK | Next of Kin |
| NSTS | NHS Strategic Tracing Service |
| PDSA | Plan, Do, Study, Act |
| PEEP | Positive End Expiratory Pressure |
| PSS | Personal Social Services |
| Psupp | Pressure Support Ventilation |
| QOL | Quality of Life |
| RCT | Randomised Controlled Trial |
| R&D | Research and Development |
| SAE | Serious Adverse Event |
| SBT | Spontaneous Breathing Trial |
| SF12 | 12 Item Short Form |
| SOP | Standard Operating Procedure |
| TSC | Trial Steering Committee |
| VAP | Ventilator Associated Pneumonia |
| VAO | Value of Information |
| WCTU | Warwick Clinical Trials Unit |

1. BACKGROUND

1.1 Epidemiology and burden of the condition

Approximately 60,000 people each year in the UK become critically ill and require sedation and invasive mechanical ventilation given via an endotracheal tube. While invasive mechanical ventilation can be lifesaving, it is also known to contribute to lung injury. Lung-derived inflammatory mediators spill over into the systemic circulation contributing to a systemic inflammatory response that can lead to multiple organ failure and death. Prolonged ventilation is associated with increased morbidity and mortality[2] and also increases cost[3]. Patients receiving prolonged (>48 h) mechanical ventilation account for 6% of all ventilated patients but consume 37% of intensive care unit (ICU) resources[4].

One of the main complications of prolonged ventilation is ventilator associated pneumonia (VAP). VAP is the commonest ICU acquired infection. Elimination of VAP is a target for international and NHS quality improvement initiatives[5]. Prevalence estimates vary widely but VAP is likely to affect around one third of ventilated patients [5-6]. VAP prolongs time spent on the ventilator, length of ICU stay, and length of hospital stay [6-7]. VAP adds an estimated cost of £10,000 to a typical hospital admission after adjustment for underlying diagnosis [8]. The attributable mortality linked to VAP has been cited to be as high as 50%. However recent data suggest the attributable mortality associated with VAP is overestimated by traditional-matched exposed–unexposed studies and biased by informative censor in survival models. Newer multistate and causal inference models suggest the attributable mortality for VAP is much lower at approximately 4-8% [9-10]. Other adverse consequences of prolonged ventilation include sinusitis [11], upper airway damage[12] and respiratory muscle weakness[12]. Invasive mechanical ventilation (IMV) is inextricably linked to sedation which is required for the patient to tolerate an endotracheal tube in their airway. Excessive use of sedation is linked to delirium, immobility and ICU acquired weakness[13]. For these reasons, minimising exposure to prolonged ventilation is likely to have important health and resource benefits.

Weaning is the process of liberating a patient from IMV. It involves transferring the work of breathing from the ventilator to patient. Observational and randomised controlled trials indicate that weaning accounts for a substantial proportion of the total time with ventilator assistance (40-50%)[1]. Weaning processes need to strike a balance between withdrawing ventilator support too early versus continuing IMV beyond when it is needed. Too early withdrawal runs the risk of a need for re-intubation. Such extubation failure is associated with adverse outcomes, including increased hospital mortality, prolonged hospital stay, higher costs, and greater need for tracheostomy [14-15]. By contrast, delayed weaning is associated with increased morbidity and mortality [16-17]. The observation that 10-15%[1] of patients require re-intubation during the weaning process and almost half of patients with an unplanned self-extubation during the weaning period do not require re-intubation[18] suggests there is scope for improvement in current approaches.

1.2 Usual Weaning Care

Weaning is a complex intervention which involves several stages. Delays or mistakes in any of these steps can prolong the duration of ventilation [1]. The first step is to identify the patient is ready to start the weaning process. The uses of simple criteria to allow daily assessment of readiness to wean are effective and can reduce the duration of ventilation [19]. There are a number of different tools that can be used for this purpose, with little evidence to show superiority of one tool over another [20]. In this scenario the feasibility and ease with which a tool can be applied (which will determine its use in practice) is of paramount importance. Members of our team have developed and validated a simplified daily checklist of metabolic, cardiorespiratory and neurological criteria which are now used daily by nursing staff as a trigger to commence a weaning protocol [21]. The addition of more complex physiological variables which included the rapid shallow breathing index did not improve the tools accuracy [22].

After determining readiness to wean, an assessment of readiness for discontinuation of mechanical ventilation is undertaken using a spontaneous breathing trial (SBT)[1]. During a spontaneous breathing trial the patient receive minimal support from the ventilator and a combination of clinical and physiological measurements are used to determine success or failure. Our surveys of members of the Intensive Care Society conducted in Summer 2010 (219 respondents) indicates that most ICUs in the UK use SBTs[23-24]. Three similar processes for the SBT are used in approximately equal proportions in the UK (T-piece; continuous positive airway pressure (CPAP); or Pressure Support ventilation (Psupp) of 5-8cmH₂O over positive end expiratory pressure (PEEP)[23-24]. The International Task Force review of weaning from mechanical ventilation concluded that there is little difference in the percentage of patients who pass the SBT of percentage successfully extubated between these three approaches[1].

Patients that pass the spontaneous breathing trial are extubated. This group of patients (which represents approximately 69% of ventilated patients) has a generally good prognosis (ICU mortality approximately 5%)[1]. Patients that fail the initial SBT (approximately 31%) are judged as not ready to sustain unsupported breathing and have poorer outcomes (mortality 25-30%)[1]. Those that fail the initial SBT are categorised as difficult / prolonged weaning. Weaning practices after failing an initial SBT are variable. Our surveys indicate that most UK ICUs use sequential reductions of pressure support for weaning whilst a minority (23%) use automated weaning systems (e.g. adaptive support ventilation, proportional assist ventilation, Smartcare™)[24]. Further SBT's are then repeated on a daily basis until either extubation or a tracheostomy is performed.

1.3 Non-invasive ventilation as an adjunct to weaning

Non-invasive ventilation (NIV) refers to the delivery of mechanical ventilation without the need for an endotracheal airway. Positive pressure ventilation is delivered to the patient through the mouth or nose via an interface such as a mask or helmet. In a similar way to invasive ventilation, NIV can reduce the work of breathing and improve gas exchange[25]. It however may avoid some of the complications of prolonged intubation (e.g. ventilator associated pneumonia, sinusitis, airway damage etc.)[26]. In the context of weaning, NIV has been used as an adjunct to early extubation, to

prevent respiratory failure after extubation and as a rescue therapy when respiratory failure occurs during the post extubation period[25].

1.4 Existing knowledge

Burns et al systematic review and meta-analysis on the use of NIV for weaning patients from invasive ventilation identified 12 trials which recruited 530 participants[27]. Compared with invasive weaning, NIV weaning was associated with reduced mortality (relative risk 0.55, 95% CI 0.38 to 0.79), ventilator associated pneumonia (0.29, 95% CI 0.19 to 0.45), length of stay in intensive care unit (weighted mean difference -6.27 days, 95% CI -8.77 to -3.78) and hospital (-7.19 days, 95% CI -10.80 to -3.58). Eight of the 12 trials included patients only with COPD. Of the four other trials, two included patients predominantly with COPD (58% [28] and 76% [29] COPD). The pooled effect on hospital mortality for these studies was not significant (RR 0.72 95% CI 0.39–1.32). The wide confidence intervals arose because of benefit in the two studies that had larger proportions of patients with COPD and no benefit in the studies that had fewer patients with COPD.

The interpretation of these studies and their relevance to UK practice is limited. Firstly, the treatment of an exacerbation of COPD has changed since these early trials were conducted. Many patients that would have previously received invasive mechanical ventilation for respiratory failure now have ward or ICU based NIV as a strategy to prevent the need for invasive ventilation[30]. The population of patients that require weaning in contemporary ICU practice differ from those in the historical studies above. Secondly, none of the trials recruited patients from the UK. An international survey of weaning practices clearly shows marked differences in weaning practices between countries[23]. Thirdly, three of the 12 studies (comprising nearly 20% of total patients) are either unpublished or published only as abstracts. Fourthly, where it was possible to assess methodological quality of index trials, quality was variable and eight studies had evidence of high risk of bias. There was variation in the methods used to identify patients for weaning (e.g. four trials used a unique resolution of pulmonary infection criterion which is rarely used in UK practice). There was also variability in approaches to titration and discontinuation of ventilator support. Finally, examination of the funnel plot suggests an absence of studies with non-significant results which might overinflate the overall estimate of treatment effect.

1.5 Need for a study

Although the results of the Cochrane review is encouraging, the size and limitations of studies conducted to date leave uncertainty of the net clinical benefit from the use of NIV as a routine tool to facilitate weaning from mechanical ventilation. This is likely to explain the limited penetration of this approach into UK ICU practice. This topic is important to the intensive care community. The need for additional trials in this area was identified in the Intensive Care Society Research Prioritisation Exercise (2008). With these considerations it is timely to conduct a well-designed, appropriately powered randomised controlled trial (RCT) to examine the clinical and cost effectiveness of NIV facilitated weaning in the NHS.

1.5.1 Context

The NIHR HTA Commissioning Board noted the need for such a study as a high priority to the NHS. The Board called for proposals for a study to determine the

clinical and cost effectiveness of using non-invasive ventilation as an intermediate step in weaning patients off invasive ventilation.

The specific brief is shown below.

- **Technology:** Non-invasive ventilation as an intermediate step in protocolised weaning of patients off invasive ventilation.
- **Patient group:** Patients with respiratory failure requiring invasive ventilation.
- **Setting:** Intensive care units.
- **Control or comparator treatment:** Protocolised weaning that does not include the use of non-invasive ventilation.
- **Design:** Randomised controlled trial with internal pilot study. The pilot study should include clear continuation criteria including an assessment of the likelihood of satisfactory recruitment to the full trial.
- **Important outcomes:** Re-intubation rate, time from extubation to meeting discharge criteria, ventilator days, cost effectiveness.
- **Other outcomes:** Adverse events, ICU days, mortality.
- **Minimum duration of follow-up:** 1 month.

1.6 Study name

The study will be known as the Breathe study. This study name was selected after consultation with patients and carers that had experience of being approached to participate in clinical studies. The overwhelming feedback was that they could identify with this title as it appeared relevant to what the study was investigating. Participants commented that studies with mnemonics of the intervention / study design were more difficult to understand and remember.

1.7 Hypothesis

In adult patients requiring invasive mechanical ventilation, protocolised weaning which includes non-invasive ventilation is more effective than protocolised weaning using invasive mechanical ventilation.

1.8 Good Clinical Practice

The Breathe study is not a Clinical Study of an Investigational Medicinal Product, and thus is not governed by the Medicines for Human Use (Clinical Trials) Regulations 2004. The study will be carried out in accordance with the Declaration of Helsinki, Medical Research Council (MRC) Good Clinical Practice Guidelines, and Warwick CTU Standard Operating Procedures (SOPs).

1.9 Ethical Considerations

The study will recruit patients, many of whom will lack capacity to consent due to the nature of the underlying disease process (critical illness, delirium) and the treatments they may be receiving (sedative medications, mechanical ventilation).

The study will be conducted in accordance with the ethical principles originating in the Declaration of Helsinki. We will apply separately for ethical approval to a REC flagged for trials involving patients without capacity in Scotland and England (see below). As a proportion of patients will lack capacity the trial will be subject to the requirements of the Mental Capacity Act 2005 (England, Wales and Northern Ireland) and the Adults with Incapacity (Scotland) Act 2000.

In the context of these legislative frameworks, the research is directly related to the treatment of the impairing condition. It is not possible to undertake research of a comparable effectiveness in people with capacity.

The study is comparing two different ways of helping someone to come off a ventilator (weaning). Both techniques are currently used in clinical practice but there is uncertainty about which one is most effective.

The research has the potential to benefit the participant (as one of the approaches to weaning may be more effective). The study will provide knowledge about the treatment of patients that find themselves in a similar situation in the future.

The success and speed of weaning are critical to patient outcomes. Delays in weaning leads to patients spending longer on intensive care and exposes them to the risk of serious infections such as ventilator associated pneumonia and other complications. Once a patient becomes ready to initiate the weaning process, delays in initiating weaning are associated with harm.

The approach to consent for this study is designed to maximise the opportunity for participation in the decision to take part in the trial, whilst at the same time avoiding potential harm from delaying weaning attempts solely to complete consent processes.

1.10 Consort

The study will be reported in line with the CONSORT (Consolidated Standards of Reporting Trials) statement (www.consort-statement.org).

2. STUDY DESIGN

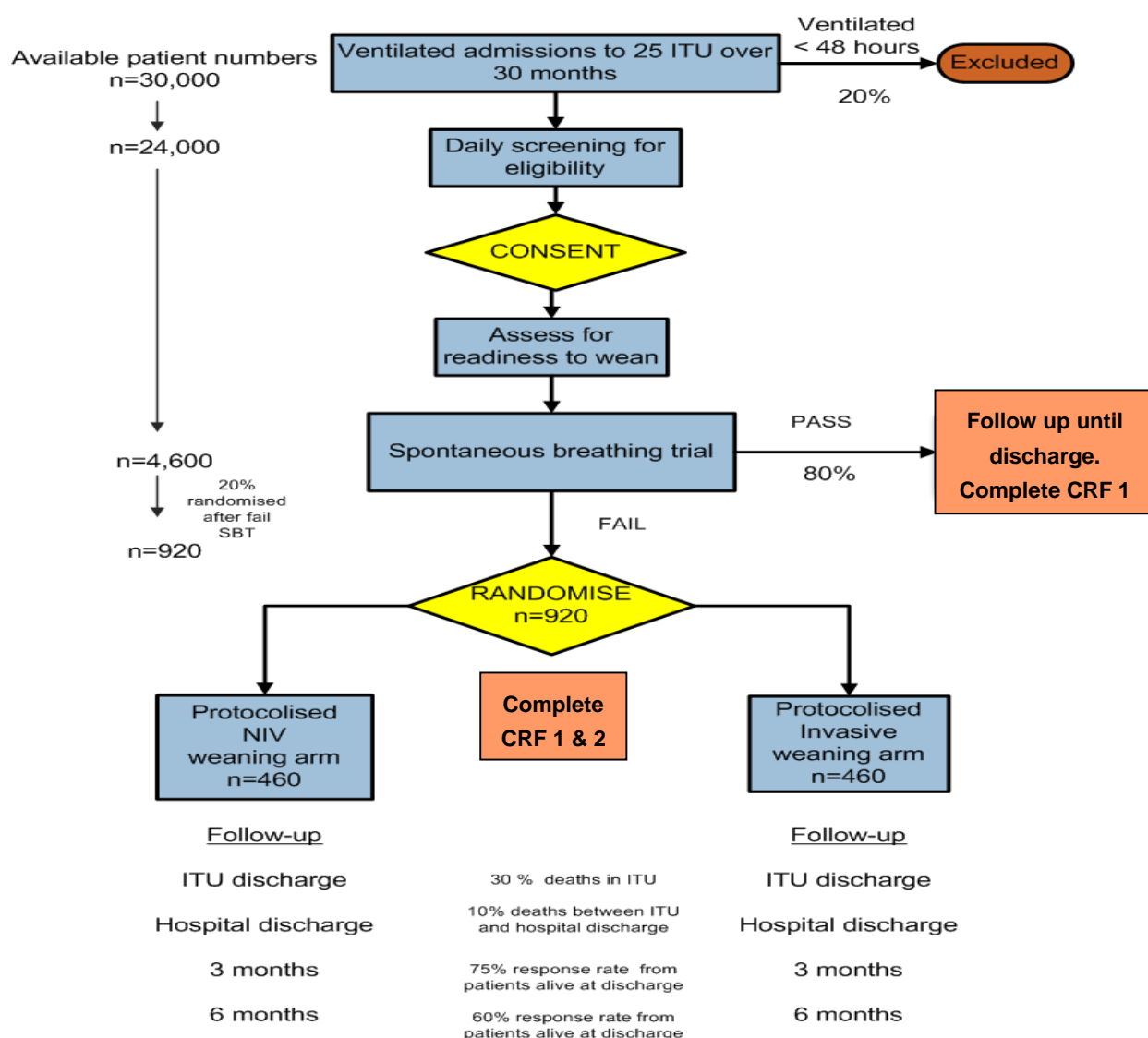
2.1 Study summary

The Breathe study will be a pragmatic, randomised controlled, open, multi-centre, effectiveness trial to determine if the use of NIV as an intermediate step in the protocolised weaning of patients off invasive ventilation is clinically and cost effective.

Patients with respiratory failure who have received invasive ventilation for more than 48 hours (from the time of intubation) and fail a spontaneous breathing test (SBT) will be randomised in a 1:1 ratio to invasive or non-invasive weaning strategies.

Data will be recorded by participating ICUs until hospital discharge, and all surviving patients will be followed up at three and six months post randomisation. A total of 364 patients will be recruited from about 40 ICUs in the UK, and an economic evaluation will be conducted alongside the study.

Figure 1: Flow Diagram



2.2 Objectives

2.2.1 Primary objective

To determine if invasive ventilation using protocolised weaning that includes non-invasive ventilation (NIV) as an intermediate step is clinically and cost effective compared to protocolised weaning without NIV.

Measurements of effectiveness include:

Primary clinical outcome: Time from randomisation to liberation from ventilation.

Secondary clinical outcomes: 30, 90 and 180 day all-cause mortality; duration of invasive mechanical ventilation (IMV) and total ventilator days (invasive and non-invasive ventilation); time to meeting ICU discharge criteria; hospital length of stay; proportion of patients receiving antibiotics for presumed respiratory infection;

antibiotic days for respiratory infection; total antibiotic days; re-intubation; placement of tracheostomy; adverse events, health related quality of life.

Primary economic outcome: Incremental cost per quality-adjusted life year (QALY) gained from the perspective of the NHS and personal social services (PSS).

Secondary economic outcomes: Cost of critical care stay (level 2/3 days); cost of hospital stay; utilisation of NHS and PSS resources after discharge.

2.2.2 Secondary objectives

To ensure screening, consent, recruitment, randomisation, protocol compliance and follow-up processes run smoothly we have included an internal pilot which is anticipated to lead directly into the main trial.

The pilot will run from months 3-9 and will follow the processes described in the main study section below. Pilot data will come from a minimum of five sites open to recruitment. The pilot will be used to confirm screening, consent procedures, recruitment rates, randomisation processes, data collection, protocol compliance and ensure follow-up processes run smoothly. Full details of the criteria for progression from the pilot study to the main study are given in section 0.

2.3 Outcome Measures

2.3.1 Efficacy

2.3.1.1 Primary outcome

The primary outcome is time from randomisation to liberation from ventilation.

Liberation from ventilation is defined based on the International Consensus Conference on Weaning recommendations[1] as the time point following which the patient is free of ventilatory (invasive or non-invasive) support for > 48 hours. This defines the duration of weaning process (randomisation to liberation from ventilation). Re-intubation as a consequence of weaning failure occurs within the first 12-48 hours[34], thus defining weaning success as after 48 hours from liberation of ventilation will capture weaning failures (requiring re-intubation within 48 hours) but will reduce confounding by late events un-related to the weaning process (e.g. the need for an un-related surgical procedure or other event requiring intubation and ventilation).

2.3.1.2 Secondary outcomes

Secondary outcome measures are:

Efficacy:

- Mortality at 30, 90 and 180 days
- Duration of IMV and total ventilator days (invasive and non-invasive ventilation)
- Time to meeting ICU discharge criteria (defined as no further requirement for level 2/3 care)

- Proportion of patients receiving antibiotics for presumed respiratory infection and total antibiotic days
- Re-intubation rates (protocolised end-point and actual event)
- Tracheostomy

Safety:

- Adverse events
- Serious adverse events

Patient focused outcomes:

- Health-related quality of life: EQ-5D, SF12 at baseline (estimated), 3 and 6 months

2.3.1.3 Economic evaluation

Primary economic outcome: Incremental cost per quality-adjusted life year (QALY) gained from the perspective of the NHS and personal social services (PSS).

Secondary economic outcomes: Cost of critical care stay (level 2/3 days); cost of hospital stay; utilisation of NHS and PSS resources after discharge.

We plan to undertake both a within-trial economic evaluation which will cover the follow-up period of the RCT namely to six months post-randomisation, and a modelling-based economic evaluation which will extrapolate cost-effectiveness over a lifetime time horizon. Both will be expressed in terms of incremental cost per QALY gained.

2.4 Eligibility Criteria

Patients are eligible to be included in the study if they meet the following criteria:

2.4.1 Inclusion criteria

- Age > 16 years
- Patients with respiratory failure who have received invasive ventilation for more than 48 hours (from the time of intubation)
- Patients who are ready for weaning
- Fail a spontaneous breathing trial (SBT)

2.4.2 Exclusion criteria

- Patient known to be pregnant
- Presence of tracheostomy
- Unable to protect airway due to profound neurological deficit

- Any absolute contraindication to NIV
- Home ventilation prior to ICU admission*
- Decision not to re-intubate or withdrawal of care anticipated
- Further surgery / procedure requiring sedation planned in next 48 hours
- Previous participation in the Breathe study
- Ventilator unavailable to deliver interventions

* This does not include nocturnal CPAP

2.4.3 Daily screening of patients for early identification for eligibility

This step is included to aid the early identification of potential patients for the study.

All ventilated patients will be assessed each morning for eligibility by ICU nursing / medical staff. Patients will be identified as potentially eligible if they fulfil the following criteria:

- anticipated or actual requirement for invasive ventilation for > 24 hours
- at least partial reversal of the condition precipitating invasive ventilation
- stabilisation of "other" organ system failures (i.e. no worsening)
- arterial oxygen saturation measured using pulse oximetry (SpO_2) \geq 90% with fractional concentration inspired oxygen (FiO_2) \leq 0.70
- PEEP \leq 12 cmH₂O
- the absence of trial exclusion criteria (above).

This approach is being used successfully in the Canadian WEAN study[25].

A screening log will be maintained at each site which includes the reasons for non-enrolment.

2.4.4 Identification of readiness to wean

Readiness to wean will be declared if the simple bedside Walsh criteria are met, namely:

- cooperative and pain free
- good cough
- PaO₂ : FiO₂ ratio >24 kPa
- PEEP <10 cmH₂O
- Hb >7 g dL⁻¹ axillary temperature 36 - 38.5°C
- vasoactive drugs reduced or unchanged over previous 24 h
- spontaneous ventilatory frequency >6 min⁻¹

Patients who fulfil the readiness to wean criteria if not already receiving pressure support ventilation will be started on a trial of pressure support ventilation. The level of pressure support (P_{supp}) will be titrated according to patient comfort to achieve tidal volumes of 6-8ml kg⁻¹ ideal body weight and a respiratory rate < 30 breaths min⁻¹.

Once the patient is stable on P_{supp} ventilation for at least 60 minutes, a SBT will be undertaken.

2.4.5 Spontaneous breathing trial

A spontaneous breathing trial will be performed in accordance with local unit practices (T-piece trial; CPAP or P_{supp} 5-7cm H₂O).

The spontaneous breathing trial should last at least 30 minutes. The duration of the spontaneous breathing trial may be increased up to 120 minutes in patients considered to be a higher risk of re-intubation (e.g. prolonged ventilation, past history of COPD, heart failure).

The patient will be monitored for the development of any the International Consensus Conference on Weaning *signs of distress or fatigue* [19]:

Physiological assessment:

- Heart rate $\geq 20\%$ of baseline or > 140 beats min^{-1}
- Systolic BP $\geq 20\%$ of baseline or > 180 mm Hg or < 90 mmHg
- Cardiac arrhythmias
- Respiratory rate $\geq 50\%$ of baseline value or > 35 min^{-1}
- Respiratory rate (min) / tidal volume (L) > 105 $\text{min}^{-1} \text{L}^{-1}$

Arterial blood gases:

- PaO₂ < 8 kPa on FiO₂ ≥ 0.5 or (SpO₂ $< 90\%$)
- PaCO₂ > 6.5 kPa or increase by > 1 kPa
- pH < 7.32 or fall by ≥ 0.07 units

Clinical assessment:

- Agitation and anxiety
- Depressed mental status
- Sweating / clammy
- Cyanosis
- Increased respiratory effort
(accessory muscle, facial distress, dyspnoea)

A patient will be considered to pass the SBT if no *signs of distress or fatigue* develop. These patients do not require further weaning and will not be randomised. Baseline data and outcome data will be collected and submitted to the trial office in an anonymised form (study ID). This is important for describing the patient population screened for this study and to allow clinicians to assess the generalizability of the study findings.

A patient that displays any *signs of distress or fatigue* will be judged to fail the SBT. This cohort of patients requires further weaning and will be randomised to invasive or non-invasive weaning arms of the trial. The patient should be placed back on supported ventilation and allowed to recover prior to commencing the respective protocolised weaning regime.

2.5 Consent Process

The approach to consent for this study is from the perspective of maximising patient capacity and choice. We have developed this approach in consultation with our patient representative.

The majority of patients will have altered consciousness caused by illness and therapeutic sedation (anaesthesia) and will lack capacity. People are advised not to sign any legal documents within 24 hours of having intravenous sedation / a general anaesthetic. For this reasons we will not rely solely on a patient indicating a general willingness to participate.

We will either approach a Personal Consultee / Relative / Welfare Attorney to establish their views about the patients willingness to participate (provided this does not introduce undue delay in the weaning process) or seek authority from a Registered Medical Practitioner (England, Wales, Northern Ireland only) unrelated to the organisation or conduct of the research project as described below.

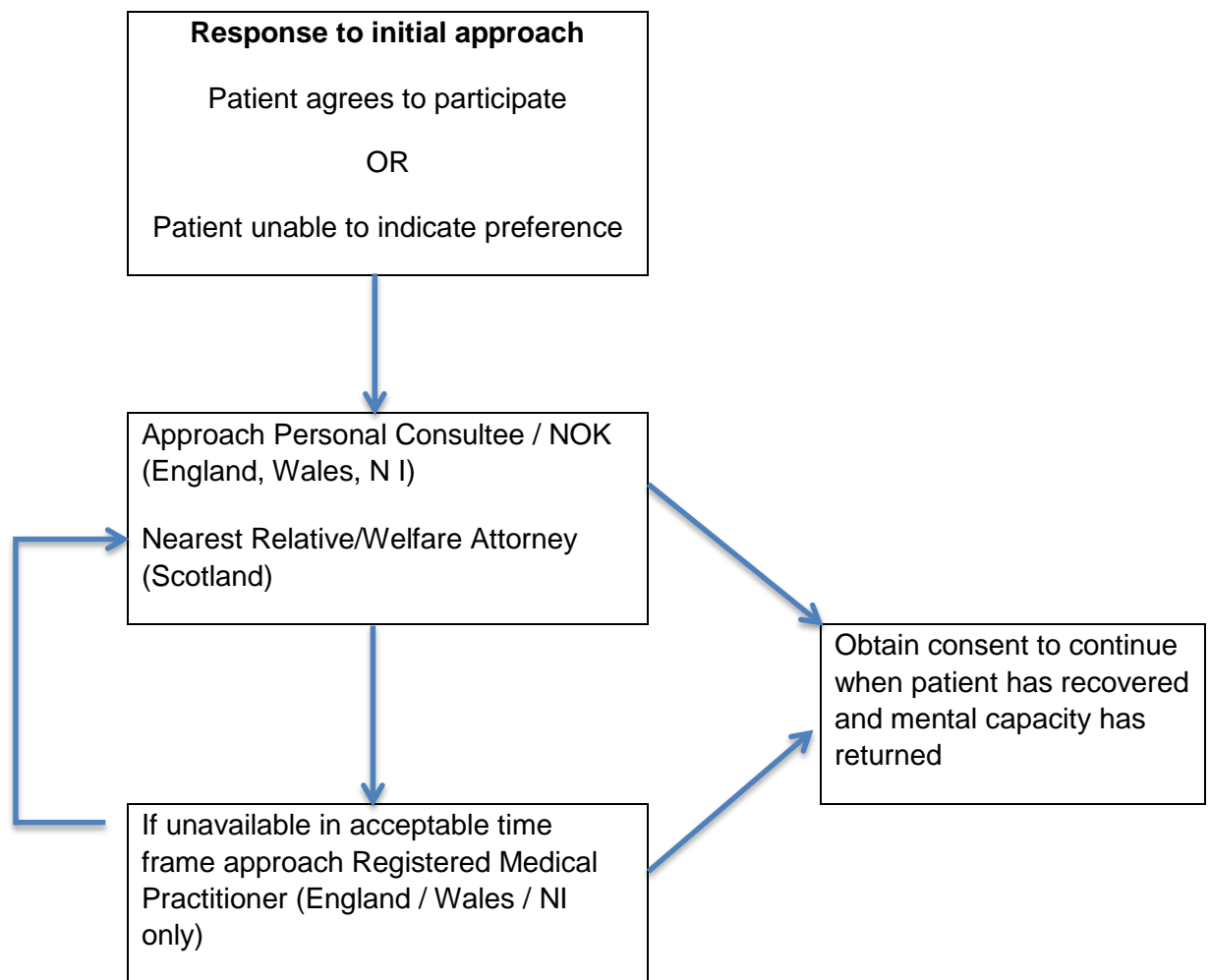
Consent / authorisation for enrolment must be obtained prior to randomisation; however it can be deferred until after the spontaneous breathing trial if the assessments for readiness to wean and conduct of the spontaneous breathing trial are part of the unit's standard clinical care.

Becoming critically ill is a rare event. It is not unusual for a patient to be potentially eligible for more than one study while they are in ITU. We will provide patients / their relative or guardian / personal consultee with the choice as to whether they may like to be considered to participate in more than one study.

In selecting which study's it may be possible to co-enrol with we will liaise with the Chief Investigators of other studies and we will ensure no potential interaction between the proposed treatments. Detailed guidelines have been developed around co-enrolment by the NIHR critical care speciality group. We will follow these guidelines.

The different approaches for informed consent in England/Wales/Northern Ireland and Scotland are summarised below.

Figure 2: Consent Process



2.5.1 Informing patients about the study

Context: The study will be recruiting critically ill patients, receiving sedative (anaesthetic) medications. This will impair / disturb the functioning of the mind / brain. Patients will also be receiving mechanical ventilation through a tube placed through the mouth directly into the trachea - this makes it impossible for the patient to speak. However some patients may be able to communicate their wishes with non-verbal cues such as hand signals, nodding / shaking their heads.

Patients will be assessed for their ability to understand verbal communication and to communicate a reply. If they are able, the researcher / clinician will provide a short verbal summary about the study, for example:

- We are going to try to see if we can help you off the ventilator now
- We would like to collect some information about how we do this as part of a research study
- We will talk to the doctors and / or your relatives as well.
- Is it OK with you if we include you in this study?
- We will let you know more details once the tube is out of your mouth and you are able to speak.

If it is clear that the patient expresses an unwillingness to participate they will not be enrolled.

If the patient indicates a willingness to participate (or if they are unable to communicate a preference), the researcher will record this in the clinical record and will proceed with consulting a Personal Consultee / Relative / Welfare Attorney or Registered Medical Practitioner as described below to obtain authorisation to randomise the patient in the study.

2.5.2 Personal Consultee (England, Wales) / Next of kin (Northern Ireland)

The researcher will seek advice from a Personal Consultee (England, Wales) or Next of Kin (Northern Ireland). This should normally take place during a face to face meeting. If this is not possible the researcher may contact the Relative / Welfare Attorney by telephone and seek verbal consent (witnessed by a 2nd member of staff) and record in the clinical record. Written consent will then be obtained as soon as possible. The researcher will provide the consultee / Next of Kin with information about the study and seek their views about whether the patient should take part in the study. They will be asked about their opinion of the wishes and feelings of the patient if they had capacity.

If the Consultee / Next of Kin agree, the patient will be randomised.

2.5.3 Nearest Relative / Welfare Attorney (Scotland)

The researcher will seek consent from a Nearest Relative / Welfare Attorney. This will usually take place during a face to face meeting. In the event that a Nearest Relative / Welfare Attorney is not immediately available at the time that the decision is taken to commence weaning, and in the view of the treating clinician weaning should not be delayed until their arrival, the researcher may contact the Nearest Relative / Welfare Attorney by telephone and seek verbal consent (witnessed by a 2nd member of staff) and record in the clinical record. Written consent will be obtained when they next visit the patient or when the patient regains capacity. These processes have worked successfully in similar studies previously (e.g. age of blood evaluation – ABLE).

The researcher will provide the Nearest Relative / Welfare Attorney with information about the study and seek their consent to include the patient in the study.

2.5.4 Approval by a Registered Medical Practitioner (England, Wales, Northern Ireland)

In the event that a Personal Consultee / Next of Kin (NI) is not immediately available at the time that the decision is taken to commence weaning, and in the view of the treating clinician weaning should not be delayed until their arrival, authorisation to randomise the patient will be sought from a Registered Medical Practitioner unrelated to the study conduct or organisation in accordance with the waiver of consent provision of the Mental Capacity Act (section 32(9)).

The doctor will be informed about the trial by a member of the research team and given a copy of the patient information sheet. If the doctor decides that the patient is

suitable for entry into the study they will be asked to complete the relevant authorisation form.

In the event that a patient is randomised in the study by a Registered Medical Practitioner, the Personal Consultee / Next of Kin will be informed at the earliest opportunity and consent to continue with data collection will be sought using the process described below. If there is no Personal Consultee / Next of Kin the authorisation from the Medical Practitioner will remain in place.

2.5.5 Follow-up stage: participant consent to continue

Once the participant has recovered from the condition / treatment causing incapacity, and once free from sedative medications for more than 24 hours they will be approached to obtain permission to continue in the study. This will usually take place just prior to or after intensive care discharge. If consent to follow-up is not obtained prior to discharge, the hospital will contact the patient at their place of residence to seek consent to continue.

The consent to continue process will include assessment and documentation of capacity; providing written information about the study; allowing sufficient time for the patient to understand the material and ask questions; obtaining written informed consent.

If the participant agrees to continue in the study they will be asked to sign the Patient Consent Form which will then be counter signed by a member of the research team.

If the participant declines on-going participation in the study no further follow-up will take place. Data collected up until that point will be anonymised before returning to the coordinating centre.

In the rare event that the patient does not regain capacity or the hospital staff have been unable to obtain consent to continue, the consent from the Registered Medical Practitioner and / or the Personal Consultee / Next of Kin will continue.

2.5.6 Responsibilities

The Principal Investigator is responsible for ensuring that the consent processes described above are followed. Appropriate signatures and dates must be obtained prior to randomisation and collection of trial data. The consultation / consent process may be undertaken by any registered medical practitioner or allied health practitioner that has received training on taking consent, has been briefed about this study and has the approval of the site PI.

2.6 Randomisation

Once authorisation has been obtained for the patient to participate in the study the patient will be randomised to invasive or non-invasive weaning strategies. Patients will be randomised by web-based secure electronic randomisation; the randomisation telephone number if the website is unavailable will be as follows: 02476 150402 (9 a.m. – 5 p.m. Mon-Fri)

Randomisation will be minimised by centre; presence / absence of COPD and post-operative / non-operative reason for admission. Participants will be allocated to invasive or non-invasive weaning strategies on a 1:1 allocation using a randomisation sequence. These processes will ensure that allocations remain secure prior to randomisation.

The randomisation service will ask to be provided with the patients' initials, date of birth and recruitment centre, confirmation that the patient fulfils the trial entry criteria and data for minimisation.

At the time of randomisation, each patient will be allocated a unique Participant Study Number which will be used throughout the study for participant identification.

Where possible the clinical record will be flagged to indicate enrolment in this study. An entry will be recorded in the clinical record noting the time of enrolment and the name of member of staff that authorised enrolment.

2.6.1 Post-randomisation withdrawals and exclusions

Participants may be discontinued from the study treatment and/or the study at any time without prejudice. Unless a participant explicitly withdraws their consent to follow-up, they should be followed-up wherever possible and data collected as per the protocol until the end of the trial.

Participants may be withdrawn from the study at the discretion of the Investigator and/or Trial Steering Committee due to safety concerns.

2.6.1.1 Withdrawal of consent

Participants may withdraw or be withdrawn (by their personal consultee or the intensive care consultant responsible for their care) from the study at any time without prejudice. In the event that the participant is withdrawn during the protocolised weaning element of the study, the clinician responsible for their care will determine the safest and most appropriate way to continue the weaning process outside of the study protocols.

In the event of a request to withdraw from the study, the researcher will determine which elements of the study are to be withdrawn from the following possibilities:

- The protocolised weaning intervention
- On-going data collection during hospital admission
- Confirmation of status at 30/90/180 days
- Contact for follow-up questionnaires

In the event that the participants requests withdrawal from all four elements, only anonymised data recorded up to the point of withdrawal will be included in the study analysis.

3. STUDY INTERVENTIONS

The health technology being assessed is the use of NIV as an adjunct to protocolised weaning compared to protocolised weaning that does not include NIV following a failed spontaneous breathing trial.

3.1 Protocolised invasive weaning arm

The Breathe study manual provides detailed information on the protocolised weaning guidelines.

The patient should be allowed to recover prior to commencing the weaning regime.

Causes for distress / fatigue / weaning failure should be sought and corrective treatments initiated as appropriate.

Invasive weaning protocol

The patient will be restarted on pressure supported ventilation at the previous settings.

The level of pressure support (P_{supp}) should be titrated to achieve patient comfort and respiratory rate <30 breaths min⁻¹.

Assess the patient at least 2 hourly.

If there are no *signs of distress / fatigue* then the level of P_{supp} will be reduced by 2 cmH₂O. This cycle will be repeated as tolerated. If at any stage the patient develops signs of distress / fatigue then the P_{supp} should be increased by 2 cmH₂O. FiO₂ will be titrated to maintain SaO₂ > 90%.

A further SBT will take place each morning. This cycle will continue until the patient has either been extubated (due to passing the SBT or tolerating P_{supp} 5 cmH₂O) or a tracheostomy is performed.

If a patient continues to show signs of distress or fatigue despite increases in pressure support and treating any reversible causes they may be taken temporarily off the weaning protocol. The treating clinician will determine the off protocol ventilation strategy. It may include for example increase in sedation and / or an alternative ventilation mode. The patient should be re-assessed at least daily (or more frequently at the discretion of the clinician) for readiness to wean. When the patient is ready to wean, the weaning protocol should be re-started.

This active weaning protocol should occur between 8am-10pm. Unless the patient develops signs of fatigue or distress, ventilator settings will not be changed overnight. The invasive weaning regime should continue until either the patient is extubated or a tracheostomy is performed.

3.2 Protocolised non-invasive arm

The Breathe study manual provides detailed information on the protocolised weaning guidelines.

The patient should be allowed to recover prior to commencing the weaning regime.

Causes for distress / fatigue / weaning failure should be sought and corrective treatments initiated as appropriate.

Non-invasive weaning protocol

Patients allocated to the NIV arm will be extubated and immediately provided with NIV with an equivalent level of pressure support and PEEP to the ventilator settings prior to extubation.

The level of pressure support (IPAP) should be titrated to achieve patient comfort and respiratory rate <30 breaths min^{-1} .

Assess the patient at least 2 hourly.

If *no signs of distress / fatigue* occur then either remove the NIV and allow the participant to undergo a self-ventilation trial OR reduce IPAP by 2cm H_2O . Supplemental oxygen (equivalent to the previous FiO_2) should be provided via a standard oxygen mask.

If *no signs of distress or fatigue* develop during the self-ventilation trial, Reassess the patient and consider continuing unsupported ventilation with inhaled oxygen being provided as required.

If the participant subsequently develops *signs of distress or fatigue*, NIV will be re-started (as below). Otherwise the participant will continue with unsupported self-ventilation. FiO_2 will be titrated to maintain $\text{SaO}_2 > 90\%$.

If *signs of distress or fatigue* develop NIV will be re-instated at the previous settings. The level of pressure support (Psupp) will be titrated to achieve participant comfort and a respiratory rate < 30 breaths min^{-1} . Causes for distress / fatigue / weaning failure will be sought and corrective treatments initiated as appropriate. The participant will be reassessed every 2 hours. If there are *no signs of distress / fatigue* then a further trial of self-ventilation will be commenced as described above.

If a patient continues to show signs of distress or fatigue despite increases in IPAP and treating any reversible causes they may be taken temporarily off the weaning protocol. The treating clinician will determine the off protocol strategy which may include re-intubation, cautious use of sedation and / or an alternative ventilation mode. The patient should be re-assessed at least daily (or more frequently at the discretion of the clinician) for readiness to wean. When the patient is ready to wean, the weaning protocol should be re-started.

This active weaning protocol should occur between 8am-10pm. Unless the patient develops signs of fatigue or distress, ventilator settings will not be changed overnight.

The NIV weaning protocol should stop when the participant tolerates 12 hours unsupported spontaneous ventilation.

3.3 Standardised care protocols

3.3.1 Criteria for re-intubation

The decision to re-intubate a participant is a clinical decision and will be made by the clinician responsible for the participant at the time of assessment. The decision to re-

intubate or not re-intubate can be complex and may include factors outside the pre-defined re-intubation criteria below (for example where a subsequent decision to limit treatment has been taken).

The CRF will record when a participant meets the pre-defined re-intubation criteria below and when they are actually re-intubated.

Pre-defined re-intubation criteria will be any of the following:

- cardiac or respiratory arrest
- respiratory pauses with loss of consciousness or gasping for air
- severe psychomotor agitation inadequately controlled by sedation
- persistent inability to remove respiratory secretions
- heart rate ≤ 50 or ≥ 140 bpm with loss of alertness
- haemodynamic instability unresponsive to fluids and vasoactive drugs
- requirement for surgery or other interventional procedure which requires deep sedation or anaesthesia

3.3.2 Criteria for tracheostomy

The decision for timing of tracheostomy rests with the treating clinician. We suggest that tracheostomy may be considered after at least 7 days has elapsed from the time of initial intubation. Indications for tracheostomy are (i) persistent requirement for invasive mechanical ventilation (ii) inability to protect airway (iii) persistent inability to remove respiratory secretions.

3.3.3 Standardised ventilation bundle

The Department of Health “High Impact Intervention No.5 – Care bundle for ventilated patients” mandates ICUs to have in place sedation protocols; prevention of ventilator associated pneumonia (head up position; oral decontamination; sedation hold; peptic ulcer prophylaxis (drug or enteral feeding). We will ensure each site have relevant protocols for these requirements in place. Compliance will be recorded on the case report form.

3.4 Adherence

Protocol adherence with sedation, weaning and ventilator bundles will be recorded daily. The proportion of time operating “within protocol” will be monitored for each site and across the study. Differences between the proportion of time spent “within protocol” will provide an early alert to potential differences between arms. Regular audit, feedback and corrective actions will minimise the likelihood of protocol non-compliance. We will monitor withdrawal rates in both arms of the trial closely.

Adherence will be classified as:

- full adherence ($> 75\%$ of 24 hour period within protocol)
- partial adherence ($\leq 75\%$ of 24 hour period within protocol)
- off protocol (weaning protocol suspended. Record reason for suspending weaning protocol in CRF).

3.5 Blinding

By the nature of the interventions it is not possible to blind clinicians to whether a participant has been randomised to the invasive or non-invasive treatment arm. We

have therefore given careful consideration to the strategies that we will use to minimise the risk of bias as a consequence of this knowledge.

The use of secure electronic randomisation with a randomisation sequence of variable block size will reduce the risk of selection bias. The use of standardised adjunctive care bundles will decrease the likelihood of performance bias. The risk of detection bias will be minimised by the use of protocols with clear, unambiguous criteria for discontinuation of invasive and NIV. Intensive care clinical charts provide contemporaneous, hour by hour records of the participant physiology and current treatments. This will enable outcomes to be verified by both site staff and the coordinating centre. It is our experience that in this patient group (ICU patients) withdrawal rates are typically < 2%. On the rare occasions that a patient or their legal representative chooses to withdraw from the study we will seek their permission to retain data collected up until that point and to continue to collect the main outcome data. Our experience is that participants are normally happy to proceed on this basis. These approaches should minimise the risk of attrition bias. Source verification (from clinical records) and hospital computer records will be used to minimise the risk of reporting bias. The main clinical and resource utilisation outcomes of this study (e.g. ventilation status (hourly); death; level 2/3 care; adverse events, antibiotic uses are recorded contemporaneously on patient clinical records and hospital information systems.

4. METHODS AND ASSESSMENTS

4.1 Schedule of delivery of intervention and data collection

Study assessments are summarised in Table 1. It is anticipated that after randomisation, most participants will be in intensive care for on average for 5-10 days, followed by a hospital stay of similar duration. Clinical data will be recorded daily during ICU stay. The only daily clinical data that will be collected after ICU discharge are antibiotic usage (for antibiotics started in intensive care).

Table 1: Study Assessments

| Visit | Initial | ICU stay | Hospital stay | 30 day | 3 month | 6 month |
|------------------------------|---------|----------|---------------|--------|---------|---------|
| Informed consent | ✓ | | | | | |
| Medical history | ✓ | | | | | |
| Inclusion/exclusion criteria | ✓ | | | | | |
| Intervention | ✓ | ✓ | | | | |
| Clinical variables | ✓ | ✓ | ✓ | | | |

| Visit | Initial | ICU stay | Hospital stay | 30 day | 3 month | 6 month |
|---|---------|----------|---------------|--------|---------|---------|
| Quality of Life/Health Economic Outcomes | | | ✓ | | ✓ | ✓ |
| Adverse events | | ✓ | ✓ | ✓ | | |
| Survival status | | ✓ | ✓ | ✓ | ✓ | ✓ |

5. ADVERSE EVENT MANAGEMENT

5.1 Definitions

5.1.1 Adverse Events (AE)

An adverse event is defined as any untoward medical occurrence in a subject and which does not necessarily have a causal relationship with this treatment.

The following are expected adverse events and will be recorded in the CRF:

- Nasal / skin / mouth sores / irritation
- Vomiting
- Gastric distension
- Barotrauma
- Non-respiratory infection

- Arrhythmia

These events will be included as part of the safety analysis for the trial and do not need to be reported separately to the Trial Coordinating Centre.

5.1.2 Serious Adverse Events (SAEs)

A serious adverse event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Any other important medical condition which, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed.

The causality (i.e. relationship to trial treatment) and expectedness (expected or unexpected) will be assessed by the investigator(s) and recorded on the SAE form.

Table 2: Relationship of SAEs to study intervention

| Relationship to study intervention | Description |
|------------------------------------|---|
| Unrelated | There is no evidence of any causal relationship |
| Unlikely to be related | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication or device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment). |
| Possible relationship | There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments). |
| Probable relationship | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. |
| Definitely related | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. |

Related and unexpected SAEs that occur between trial entry and 30 days post randomisation will be reported using the mechanism described in Section 5.2.

5.1.3 Expected SAEs that do not require separate reporting

Because the Breathe study is recruiting a population that is already in a life-threatening situation, it is expected that many of the participants will experience SAEs. Events that are expected in this population and those that are collected as outcomes of the trial should not be reported as SAEs. This includes:

- Death
- Organ failure
- Pneumonia
- Re-intubation
- Tracheostomy

5.2 Reporting SAEs

All serious adverse events (SAE) as defined above will be entered onto the Serious Adverse Event reporting form and faxed to dedicated fax at WCTU within 24 hours of the investigator becoming aware of them.

Once received, causality and expectedness will be confirmed by the Chief Investigator. SAEs that are deemed to be unexpected and related to the study will be notified to the Research Ethics Committee (REC) within 15 days. All such events will be reported to the Sponsor, Trial Steering Committee and Data Monitoring Committee at their next meetings.

All participants experiencing SAEs will be followed-up as per protocol until the end of the trial.

6. END OF STUDY

The study will end when 920 participants have been randomised and the last participant has completed final follow-up.

The study will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Data Monitoring and Ethics Committee (DMEC)
- Funding for the trial ceases

The Ethics Committee that originally gave a favourable opinion of the study will be notified in writing if the study has been concluded or terminated early.

7. DATA MANAGEMENT

7.1 Training issues

To ensure accurate, complete and reliable data, the Study Coordinating Centre will do the following:

- Provide instructional material to the trial site(s)
- Provide support to the site PI in running a site initiation meeting. This session will give instructions on the protocol, the completion of Case Report Forms and study procedures
- Make periodic visits to the study sites
- Be available for consultation and stay in contact with the study site personnel by mail, telephone and/or fax
- Review and evaluate Case Report Form (CRF) data, source data (as required), detect errors in data collection and request data clarification

7.2 Data collection and management

All data for an individual participant will be collected by each Principal Investigator or their delegated nominees and recorded in the CRF. Participant identification in the CRF will be through their unique Participant Study Number allocated at the time of randomisation and initials. Data will be collected from the time the patient is considered for entry into the trial through to their discharge from hospital. In the event that a participant is transferred to another hospital, the trial team will liaise with the receiving hospital to ensure complete data collection.

Data will be collected in duplicate using non-carbon required forms. Once a participant has been discharged from hospital and all data entered into the CRF, the top copy of each form will be returned to the Study Coordinating Centre. The bottom copy of the CRF will be retained at the recruiting centre. The study number, name, address and other contact details of all participants who survive will be supplied to the Study Coordinating Centre at the time of hospital discharge to allow follow-up questionnaires to be posted to the participant at three and six months.

Submitted data will be reviewed for completeness and entered onto a secure, backed-up bespoke database. Due care will be taken to ensure data safety and integrity, and compliance with the Data Protection Act 1998.

Data collection will use instruments optimised using data collection pilots before recruitment starts. Data collection will be restricted to variables required to define patient characteristics at enrolment, to monitor the treatment received, to monitor adverse effects and to determine quality of life and the use of healthcare resources.

In brief the data set will include:

Variables describing baseline characteristics

- Patient identifiers
- Inclusion and exclusion criteria
- APACHE II (at admission)
- Admission diagnosis
- Presence of COPD (defined by BTS/NICE criteria OR current treatment for COPD)
- Measured or estimated height and weight and calculated BMI
- Duration of ventilation prior to randomisation
- CAM-ICU

Variables collected daily from randomisation until discharge from ICU

- Ventilation status (IMV, NIV, self-ventilating)
- Organ support requirements (defined by the mandatory DH Critical Care Minimum Dataset)
- Level of critical care support required (level 0-3, where 0 and 1 define readiness for ICU discharge)
- Antibiotic use for respiratory and non-respiratory infection
- Tracheostomy
- Criteria met for re-intubation and actual re-intubation
- Adverse events

- Deaths
- Sedation usage
- Weaning and ventilator bundle compliance

Variables collected after ICU discharge

- Antibiotic use for respiratory and non-respiratory infection started within ICU
- Acute hospital discharge date and status (to calculate acute hospital length of stay).

Variables collected after hospital discharge

- Vital status up to 180 days post randomisation
- EQ-5D and SF-12 questionnaire at three and six months, after verification of vital status with telephone follow-up for non-responders. Incentives will be used to improve return rates[48].
- Healthcare resource use questionnaire at three and six months after verification of vital status with telephone follow-up for non-responders. Incentives may be used to improve return rates (e.g. £5-£10 voucher).

Participant survival after discharge from hospital will be determined using the NHS Strategic Tracing Service.

Following being informed of a participants discharge, WCTU will send a card thanking them for their participation in the study and reminding them we will be back in touch in three months' time.

All survivors will be followed up at three and six months after randomisation by postal questionnaire. Any deaths after discharge from hospital will be identified using the NHS Strategic Tracing Service (NSTS), to avoid sending questionnaires to patients who have died. Study participants will be asked to let the Coordinating Centre know if they move house at any time after hospital discharge; NSTS will enable us to locate any who move without informing the Coordinating Centre. The follow-up questionnaire will collect data on disability and health-related quality of life, using the EQ-5D and SF-12 questionnaires. If questionnaires are not returned a maximum of two telephone contacts will be made to the study participant to check that the questionnaire has been received and the participant is happy to complete it, followed by a second copy of the questionnaire and telephone contacts in the event of non-return. If the second questionnaire is not returned the participant will be contacted and the outcome data collected over the telephone where possible.

7.3 Database

The database will be set up by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer, statistician and trial coordinator.

7.4 Data Storage

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

7.5 Archiving

Study documentation and data will be archived for five years after completion of the study. Trial Master File and associated data will be archived by WCTU, trial data generated at study sites will be archived according to local policy.

8. DATA ANALYSIS

8.1 Power and Sample Size

The original sample size was set at 920 patients to detect a hazard ratio of 0.8 between the intervention and control groups for the primary outcome with 80% power, allowing for time to discontinuation of ventilation to be undefined for a 30% of participants because of death in the ICU, and 2% of participants to have missing outcome data because of withdrawal from the trial. This equated to a 36 hour difference in the time to liberation from ventilation based an average of 6.4 days in the standard care group drawn from a 5 centre audit of weaning duration in the UK.

The trial management group reviewed the sample size requirements eighteen months in to the trial in light of slower than anticipated recruitment. Analysis of the duration of ventilation amongst patients in the control arm noted the distribution of data was skewed, indicating that the median duration of weaning, which was 2.9 days) would be a better estimate for the sample size calculation.

Using a median value of 2.9 days and a minimally clinically important difference of 24 hours provides an associated hazard ratio (HR) of 1.53. However, it is anticipated that the hazards may not be constant over time (as assumed for the exponential distribution) and that the hazards are quite likely to decrease over time. For this reason we used a Weibull distribution, as it computes a shape parameter, p , which allows for non-constant hazards. The value of p was estimated to be 0.918, thus giving a HR of 1.48.

Based on these data, a minimum sample size of 280 would provide 90% power to detect a clinically meaningful median difference of 24 hours between the intervention and control group for the primary outcome at a 5% significance level. However, we anticipate that around 23% will be lost to follow-up. Thus, inflating the above sample size estimate by 23%, to allow for loss to follow-up results in a final sample size of 364 (182 patients in each arm).

The revised sample size was approved following review by the Data Monitoring Committee, Trial Steering Committee and the National Institute for Health Research (NIHR).

8.2 Statistical analysis

Analysis of the study will be by intention to treat i.e. all participants will be analysed as part of the group to which they were originally randomised. A per protocol sensitivity analysis will be performed in the event of substantial non-compliance. Analysis of the primary outcome, time to liberation from ventilation, and other time to event outcomes, will use survival analysis methods to estimate the hazard ratio and 95% confidence interval. The analysis is complicated by the fact that a proportion of participants will die before the end of ventilation, and hence their time to liberation from ventilation is undefined. It is incorrect to treat such cases as missing or censored data, or to impute a value for time to liberation from ventilation. Survival analysis methods that correctly allow for the competing risk of death have been developed [35, 49] and will be used. Mortality at 30, 90 and 180 days will be compared between the NIV and control groups by calculating risk ratios and 95% confidence intervals. Continuous outcomes such as health related quality of life will be compared by mean differences and 95% confidence intervals. Sensitivity analyses will explore the effects of adjustment for any potential baseline differences between the groups. Three pre-specified subgroup analyses will be undertaken: (1) responsibility for weaning processes (physician led; multi-professional); (2) presence/absence of COPD (3) post-operative / non-operative. Subgroup analyses will be performed, for the primary outcome, by inclusion of interaction terms in Cox regression models.

The study will be monitored by a DMEC, and interim analyses of the accumulating data will be performed on a schedule determined by the DMEC. A detailed statistical analysis plan will be drawn up by the study statistical team during the trial, and will be approved by the DMEC before any final analysis is undertaken.

8.3 Economic Evaluation

An economic evaluation will be integrated into the study design. The economic evaluation will be conducted from the recommended NHS and personal social services (PSS) perspective[37]. Data will be collected on the health and social service resources used in the treatment of each trial participant during the period between randomisation and six months post-randomisation. Trial data collection forms will record the duration of each form of hospital care by level of intensity, adjunctive interventions, analgesic and broader medication profiles, tests and procedures. Observational research may be required to detail additional staff and material inputs associated with clinical complications. At three and six months post-randomisation, trial participants or, where necessary, appropriate proxies will be asked to complete economic questionnaires profiling hospital readmissions and post-discharge health and social community care resource use. For the purposes of a sensitivity analysis that will conduct the economic evaluation from a societal perspective, out-of-pocket expenses, and costs associated with lost productivity will also be measured. Current UK unit costs will be applied to each resource item to

value total resource use in each arm of the trial. A per diem cost for each level of hospital care, delineated by level of intensity, will primarily be calculated using national tariffs. However, primary research that uses established accounting methods may also be required to estimate costs unique to this trial. This may entail obtaining costs from NHS finance departments and apportioning these to different categories of patient using a 'top-down' methodology. Trial participating centres will be visited to ensure consistency in cost apportionments.

The unit costs of community health and social services will largely be derived from national sources[38], although some calculations from first principles using established accounting methods may also be required[39]. Trial participants or, where necessary, appropriate proxies will be asked to complete the EuroQol EQ-5D[40] and SF-12[41] measures at three months and six months post-randomisation. In addition, health-related quality of life immediately prior to the critical illness will be retrospectively recalled at three months post-randomisation using the EQ-5D and SF-12 by the trial participants themselves or, where necessary, appropriate proxies[42]. Responses to the EQ-5D and SF-12 will be converted into multi-attribute utility scores using established algorithms [43-44].

An incremental cost-effectiveness analysis, expressed in terms of incremental cost per quality-adjusted life year (QALY) gained, will be performed. Results will be presented using incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs) generated via non-parametric bootstrapping. This accommodates sampling (or stochastic) uncertainty and varying levels of willingness to pay for an additional QALY. Due to the known limitations of within-trial economic evaluations[45] we will also construct a decision-analytical model to model beyond the parameters of the proposed trial the cost-effectiveness of NIV in this clinical population. The model will be informed partly by data collected as part of the proposed trial, but also by data collected from other primary and secondary sources, including observational[46] and research (BALTI-2; OSCAR; ABLE) datasets held by the research team. Survival analysis models will be used to estimate life expectancy with and without NIV beyond the time horizon of the trial[47]. Long term costs and health consequences will be discounted to present values using discount rates recommended for health technology appraisal in the United Kingdom[37]. A series of probabilistic sensitivity analyses will be undertaken to explore the implications of parameter uncertainty on the incremental cost-effectiveness ratios. Probabilistic sensitivity analyses (PSAs) will also explore the effects of extending the study perspective, target population, time horizon and decision context on the incremental cost-effectiveness ratios. In addition, cost-effectiveness acceptability curves will be constructed using the net benefits approach. Value of information analysis (VOI) will be performed both overall and for specific parameters in the model. Modelling and PSAs will be undertaken in TreeAge using Monte Carlo simulation; VOI analysis will be undertaken in TreeAge and Excel. Sampling information for the PSAs and VOI analysis will be extracted prospectively within-trial, as well as from existing literature and observational datasets held by the research team where necessary.

9. STUDY ORGANISATION AND OVERSIGHT

9.1 Sponsor

The Heart of England NHS Foundation Trust and University of Warwick will act as Co-sponsors for the study. Agreed responsibilities will be sub-contracted to the University of Warwick, as employer of the Chief Investigator and coordinating centre for the study.

Sub-contracts delegating responsibilities to research sites will be established using our standard contracting processes with NHS organisations.

9.2 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk.

The University of Warwick provides indemnity for any harm caused to patients by the design of the research protocol.

9.3 Study timetable and milestones

Allowing conservative set up times, we will open the first site within 3 months of initiating the grant and have all sites open within 12 months. The internal pilot will run between 3-9 months from grant initiation. Following successful confirmation of recruitment rates the internal pilot will run seamlessly into the main trial. If necessary, additional study sites will be recruited. As most ICU's have the necessary equipment to deliver NIV, it is not anticipated this will present a challenge.

Table 3: Study timetable

| Project activity (months) | <0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 | 36 | 39 | 42 | 45 | 48 |
|--------------------------------|--------------|-------|-------|------|------|------|------|------|------|------|------|------|------|------|-----------|-----------|----|
| Trial stage | trial set up | pilot | pilot | main | main | main | main | main | main | main | main | main | main | main | follow up | reporting | |
| Set-up | | | | | | | | | | | | | | | | | |
| Recruit research staff | * | | | | | | | | | | | | | | | | |
| Ethics approval | * | | | | | | | | | | | | | | | | |
| Refine protocol | * | | | | | | | | | | | | | | | | |
| Pilot study | | | | | | | | | | | | | | | | | |
| R+D approvals | * | * | * | | | | | | | | | | | | | | |
| Sites open | | 5 | 7 | | | | | | | | | | | | | | |
| Patient recruitment | | * | * | | | | | | | | | | | | | | |
| 3 month follow-up | | * | * | | | | | | | | | | | | | | |
| 6 month follow-up | | * | * | | | | | | | | | | | | | | |
| Patient accrual (pilot) | | 11 | 32 | | | | | | | | | | | | | | |
| Main trial | | * | * | * | * | * | * | * | * | * | * | * | * | * | | | |
| R+D approvals | | * | * | * | | | | | | | | | | | | | |
| Sites open | | | | 15 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | | | |
| Patient recruitment | | | | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| 3 month follow-up | | | | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| 6 month follow-up | | | | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| Trial management / reporting | | | | | | | | | | | | | | | | | |
| Data processing | | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| Data analysis | | | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| DMEC meeting | | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| TSC meeting | | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| Monitoring reports | | | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| HTA monograph | | | | | | | | | | | | | | | * | * | * |
| Other publications | | | | | | | | | | | | | | | * | * | * |
| Patient accrual (pilot + main) | | 11 | 32 | 77 | 190 | 302 | 415 | 527 | 640 | 752 | 865 | 977 | 1090 | | | | |

9.4 Criteria for progression to main study

The following criteria will determine progression from the pilot to the main study:

- Recruitment > 75% of target (target 32 patients – see recruitment justification below)
- Protocol compliance (>75%)
 - daily sedation hold (Yes / No)
 - compliance with allocated intervention (IMV or NIV use)
 - proportion of weaning time within relevant protocol (assessed daily)
 - adherence with ventilator care bundle (Yes / No)

9.5 Administration

The study will be coordinated at the Warwick Clinical Trials Unit. All day-to-day coordination of the study will be the responsibility of the Trial Coordinator. All clinical coordination of the study will be the responsibility of Professor Gavin Perkins.

The study is managed by a multi-disciplinary team.

The study office team will assist and facilitate the setting up of centres wishing to collaborate in the study. In addition the study office team will:

- Distribute the standardised data collection forms to collaborators
- Organise the telephone randomisation service for formal study entry
- Monitor the collection of data, process data and seek missing data
- Train local staff with regards to data collection
- Ensure the confidentiality and security of all study forms and data
- Conduct extensive data checking and cleaning
- Organise any interim and main analyses
- Organise Steering Committee, DMEC and Collaborators meetings

The study office will receive completed data forms, via the postal service. Upon receipt, data forms will be checked for completeness and entered into a study specific dedicated computer programme which will check the data validity.

9.6 Trial Management Group (TMG)

The TMG will meet at least monthly. Meetings will be minuted and a list of actions recorded.

9.7 Trial Steering Committee (TSC)

The role of the TSC is outlined in the HTA Research Governance Guidelines. <http://www.hta.ac.uk/investigators/TSCDataMonitoringCommitteeGuidance.pdf>

The role of the TSC is to provide overall supervision for a trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

The main features of the TSC are as follows:

- To provide advice, through its Chair, to the Chief Investigator(s), the Study Sponsor, the Trial Funder, the Host Institution and the Contractor on all appropriate aspects of the trial

- To concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question
- The rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society
- To ensure appropriate ethical and other approvals are obtained in line with the project plan
- To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
- To provide advice to the investigators on all aspects of the trial

The TSC will adhere to the following guidelines:

- A minimum of 75% majority will be independent members. Only appointed members will be entitled to vote and the chair will have a casting vote.
- The minimum quoracy for a meeting to conduct business is 67% of appointed members.
- The chair and members to sign and maintain a log of potential conflicts and/or interests.
- Attendance at TSC meetings by non-members is at the discretion of the chair. The primary TSC reporting line is via the chair to the NIHR HTA Programme Director

Further information is provided in the WCTU's standard operating procedures.

9.8 Data Monitoring and Ethics Committee (DMEC)

A DMEC will be appointed comprising two clinicians with experience in undertaking clinical trials / caring for subjects who are critically ill and a statistician who are independent of the trial.

During the period of recruitment into the trial, interim analyses of the proportion of patients alive at 28 days and analyses of deaths from all causes at 28 days will be supplied, in strict confidence, to the chairman of the DMEC, along with any other analyses that the committee may request. The intervals for these analyses will be determined by the committee.

The DMEC will advise the Chairman of the Steering Committee if, in their view, the randomised comparisons have provided both (i) 'proof beyond reasonable doubt' that for all, or some, the treatment is clearly indicated or clearly contra-indicated and (ii) evidence that might reasonably be expected to materially influence future patient management.

Following a report from the DMEC, the Steering Committee will decide what actions, if any, are required. Unless the DMEC request cessation of the trial the Steering Committee and the collaborators will remain ignorant of the interim results.

9.9 Essential Documentation

A Trial Master File will be set up according to WCTU SOPs and held securely at the coordinating centre.

9.10 Monitoring and quality assurance of study procedures

9.10.1 Definitions

9.10.1.1 Trial protocol deviation

Deviations from clinical trial protocols and GCP occur commonly in clinical studies. The majority of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial. These cases should be documented in the protocol deviation section of the case report form for the trial and appropriate corrective and preventative actions taken. Deviations will be included and considered when the clinical study report is produced, as they may have an impact on the analysis of the data. Please note that a clinical decision to take the patient “off protocol” [for the weaning protocol] should be recorded in the weaning log as opposed to a trial protocol deviation. Adherence with the weaning regime should be recorded in the CRF under the adherence section in the daily data record.

9.10.1.2 Serious breach

A serious breach is defined as any protocol deviation or breach of the principles of good clinical practice in connection with the Breathe study that has a significant effect on the safety or physical or mental integrity of the subjects or the scientific value of the study.

9.10.2 Local monitoring of protocol compliance

The following elements related to protocol compliance will be assessed daily and recorded on the CRF by a member of the local research team.

- daily sedation hold (Yes / No)
- compliance with allocated intervention (IMV or NIV use)
- proportion of weaning time within relevant protocol (assessed daily)
- adherence with ventilator care bundle (Yes / No)

9.10.3 Monitoring

All sites will be monitored by WCTU during the first few weeks after their first recruit. Monitoring will seek to ensure protocol compliance, quality of data collection, storage of documentation. Monitors will require access to relevant participant notes / charts and study documentation. The primary purpose of the monitoring visit is to ensure the safety of study participant and integrity of the study data. Monitoring visits will be conducted in a supportive manner with the objective of supporting centres in delivering the study safely and in accordance with the principles of GCP.

Participating institutions will permit study-related monitoring, audits, REC review and regulatory inspections, providing direct access to source data/documents as required.

9.10.4 Reporting

Protocol deviations (and actions taken to prevent recurrence) will be recorded in the CRF. Deviations from the weaning protocol will be recorded in the weaning log and daily data form.

Any serious breaches of the study protocol or GCP should be immediately reported to the Chief Investigator. The Chief Investigator in consultation with the PI will take whatever immediate action is required to safeguard the wellbeing of participant. The Chief Investigator will notify the Sponsor immediately and Ethics committee within 7 days of becoming aware of the serious breach.

10. DISSEMINATION AND PUBLICATION

The approach will be informed by WCTU SOP 22 'Publication & Dissemination'.

The results of the study will be reported first to study collaborators. The main report will be drafted by the study coordinating team, and the final version will be agreed by the Steering Committee before submission for publication, on behalf of the collaboration.

The success of the study depends on the collaboration of doctors, nurses and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the study.

The study will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

Participants (or personal consultee) will be asked if they would like to be informed of the study results at the time of obtaining consent. Following the conclusion of the study, summary information will be sent to surviving participants (or personal consultee in the event of the participant not surviving) who recorded a desire to receive this information.

11. FINANCIAL SUPPORT

Research costs:

Research costs for this study are funded by the NIHR HTA (reference 10/124/06).

NHS Service Support Costs:

This study is included on the NIHR portfolio and is eligible for NHS service support costs. NHS service support costs have been produced through our lead CLRN (West Midlands South CLRN). The costing is based on their experience of similar trials in this setting and is calculated as £79.65 per patient.

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