DOMAIN PROTOCOL

Airway Pressure Release Ventilation (APRV) vs conventional ventilation for patients with moderate to severe acute hypoxemic respiratory failure: The RELEASE trial

To be read in conjunction with CoReCCT Master Protocol

CoReCCT (Confederation of Respiratory Critical Care Trials)

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TRIAL SUMMARY

Trial Title	Airway Pressure Release Ventilation (APRV) vs conventional ventilation for patients with moderate to severe acute hypoxemic respiratory failure: The RELEASE trial
Internal ref. number (or short title)	RELEASE
Clinical Phase	Phase III effectiveness & cost-effectiveness
Purpose of research	To investigate, using a multi-centre, parallel group, pragmatic, randomised controlled trial design, the clinical and cost effectiveness of early APRV compared to conventional lung protective invasive mechanical ventilation in patients with moderate-severe acute hypoxic respiratory failure (AHRF).
Trial Design	Parallel group randomised controlled trial with internal pilot and cost effectiveness analysis
Trial Participants	Critical Care Unit (CCU) patients with moderate to severe acute hypoxaemic respiratory failure (AHRF)
Planned sample size	710
Inclusion Criteria	1. Age ≥ 18 years 2. Receiving invasive mechanical ventilation 3. Moderate to severe acute hypoxaemic respiratory failure, defined as a single measurement showing a PaO_2/FiO_2 ratio <20 kPa while receiving a Positive End-Expiratory Pressure (PEEP) of ≥5 cmH_2O, assessed at any point within the first 60 hours after the initiation of invasive mechanical ventilation 4. Expected to stay on invasive mechanical ventilation for >48hrs
Exclusion Criteria	1. Receiving invasive mechanical ventilation ≥ 60 hours at time of screening as will be unable to deliver early APRV 2. Primary reason for invasive mechanical ventilation is one of the following: a. Asthma b. Severe Chronic Obstructive Pulmonary Disease (COPD) c. Pulmonary embolism (massive or sub-massive) (as cause of hypoxaemia is not primarily due to collapse of lung tissue) d. Existing neuromuscular disease such as Motor Neurone Disease, Guillain Barre or Myasthenia Gravis (as the cause of respiratory failure is not primarily lung-related) 3. Refractory shock (systolic blood pressure < 90 mmHg, despite fluid administration and vasoactive drugs) 4. Severe hypercapnic respiratory acidosis (pH <7.20 on the arterial blood gas assessed for trial inclusion) 5. Ongoing air leak (e.g., unresolved pneumothorax at time of screening) 6. Traumatic brain injury with uncontrolled intracranial hypertension 7. Likely death or treatment withdrawal in next 24 hours 8. Home ventilation or home oxygen therapy prior to admission 9. Receiving, or decision to commence, ECMO in the next 24 hours

Intervention	Airway Pressure Release Ventilation (APRV). APRV is a method of invasive mechanical ventilation which uses longer inspiration times followed by a brief expiration. The longer inspiration time enables alveolar recruitment and oxygenation while the short expiration time maintains lung volume. This reduces shear-stress damage to the alveoli, whilst maintaining adequate ventilation.
Control	Standard lung protective invasive mechanical ventilation
Follow-up Duration	6 months
	Objectives
Primary Outcome	Duration of mechanical ventilation (time from randomisation to first successful unassisted breathing or death)
Secondary Outcomes	1. All-cause mortality at 2 and 6 months 2. Time to first successful extubation 3. Need for reintubation prior to achieving first successful unassisted breathing 4. Use of non-invasive ventilation following extubation but prior to achieving first successful unassisted breathing 5. CCU and hospital length of stay 6. Serious adverse events up to hospital discharge 7. Health related quality of life (EQ-5D-5L) at 2 and 6 months after randomisation 8. Acute health care use at 2 and 6 months after randomisation We will conduct a within-trial cost-utility analysis from an NHS hospital care perspective
Statistical methods	Intention to treat and per protocol analyses. Cox proportional hazard regression model to estimate the treatment difference reporting hazards ratios and their 95% confidence intervals (CIs), using both unadjusted and adjusted estimates. Mean difference with 95% CIs using linear regression.

LIST OF ABBREVIATIONS/GLOSSARY

AHRF	Acute Hypoxaemic Respiratory Failure
APRV	Airway Pressure Release Ventilation
ARDS	Acute Respiratory Distress Syndrome
CCU	Critical Care Unit (both ICU and HDU)
CI	Chief Investigator
CIs	Confidence Intervals
eCRF	electronic Case Report Form
DMC	Data Monitoring Committee
ECMO	Extracorporeal Membrane Oxygenation
HEAP	Health Economics Analysis Plan
HES	Hospital Episode Statistics
HDU	High Dependency Unit
HFNC	High flow nasal cannula
HrQoL	Health-related Quality of Life
ICF	Informed Consent Form
ICNARC	Intensive Care National Audit & Research Centre
ICU	Intensive Care Unit
ISRCTN	International Standard Registered Clinical/soCial sTudy Number
NIV	Non-invasive ventilation
PaO_2/FiO_2	Ratio of partial pressure of oxygen in arterial blood (PaO_2) to the fraction of inspiratory oxygen concentration (FiO_2)
PEEP	Positive-end expiratory pressure
P_{EF}	Peak Expiratory Flow
P_{high}	Positive pressure applied during the inspiratory phase
PI	Principal Investigator
P_{low}	Positive pressure applied during the expiratory phase
PPI	Public and Patient Involvement
QALY	Quality Adjusted Life Year
R&D	Research and Development
RASS	Richmond Agitation Sedation Scale
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event

T_{high}	Time spent in the inspiratory phase
T_{low}	Time spent in the expiratory phase
TMG	Trial Management Group
TSC	Trial Steering Committee
VILI	Ventilator Induced Lung Injury

1. BACKGROUND

1.1 Epidemiology and burden of the condition

Approximately 130,000 adults are admitted to critical care units (CCUs) in the UK each year, 40-45% of whom require invasive mechanical ventilation[1]. Acute hypoxaemic respiratory failure (AHRF) is the most common reason for invasive mechanical ventilation and is associated with serious morbidity and a mortality which remains high at ~40%[2]. Although lifesaving, invasive mechanical ventilation can cause additional lung injury (termed ventilator induced lung injury - (VILI)[3].

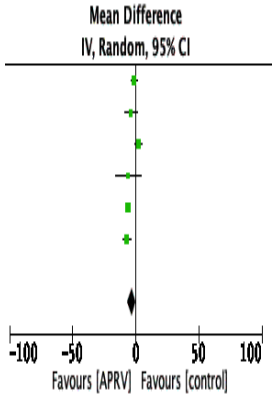
To minimise VILI, UK guidelines recommend using invasive mechanical ventilation with a low tidal volume and low inflation pressure, generally with a short time for inspiration (breathing in) and longer time for expiration (breathing out)[4]. However, injured lungs inflate slowly and deflate quickly. Consequently, most injured lungs need more time (i.e., longer inspiration) so that they can achieve a more gradual and complete inflation. A shorter expiration prevents lung collapse and injury. Therefore, the currently recommended method of invasive mechanical ventilation may perpetuate VILI leading to more days on a ventilator and increased risk of death.

Airway Pressure Release Ventilation (APRV) is an innovative ventilatory strategy available on all CCU ventilators at no additional cost to the National Health Service (NHS). APRV may improve gas exchange and minimise VILI by reducing excessive lung stretch and preventing lung collapse[5, 6].

1.2 Existing knowledge

APRV is one of three interventions not currently standard of care in the NHS (others are corticosteroids and non-invasive ventilation) with evidence of potential effectiveness which requires further study[7]. Four recent systematic reviews (totalling 10 studies, 519 participants) on APRV[8-11] suggest APRV reduces time spent on the ventilator and mortality. One review[9] (7 trials, 405 participants) found an increased number of ventilator free days at day 28 with APRV compared to conventional ventilation (mean difference 5.4 days). Three reviews [9, 10, 12] report a mortality benefit favouring APRV while two report improved gas exchange but no difference in mortality and ventilation free days[11, 13]. One subsequent trial (65 participants)[14] reported no difference in mortality or invasive mechanical ventilation duration, although median CCU length of stay was 5 days shorter in the APRV arm.

Figure 1: Meta-analysis of ventilation duration (unpublished data)



	APRV			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Ibarra-Estrada 2022	9	5.925	45	10	5.185	45	19.9%	-1.00 [-3.30, 1.30]
Kucuk 2021	9.84	8.033	32	13.52	12.826	33	14.4%	-3.68 [-8.87, 1.51]
Maxwell 2010	10.49	7.23	31	8	4.01	32	18.9%	2.49 [-0.41, 5.39]
Ota 2009	17	17	17	23	20	40	7.2%	-6.00 [-16.18, 4.18]
Putensen 2001	15	2	15	21	2	15	21.1%	-6.00 [-7.43, -4.57]
Zhou Y 2017	8	6.67	71	15	11.11	67	18.5%	-7.00 [-10.08, -3.92]
Total (95% CI)			**211**			**232**	**100.0%**	**-3.26 [-6.60, 0.09]**

Heterogeneity: Tau² = 13.23; Chi² = 37.08, df = 5 (P < 0.00001); I² = 87%
Test for overall effect: Z = 1.91 (P = 0.06)

To obtain data on invasive mechanical ventilation duration, we conducted a meta-analysis of the studies reporting invasive mechanical ventilation duration (Figure 1) and we found that APRV was associated with a mean reduction in invasive mechanical ventilation duration of 3.3 days (95% CI -6.6 to 0.1 days) (I^2=87%). However, evidence certainty is low, due to methodological limitations and trial heterogeneity. Most of the trials are small and few primarily recruit patients with moderate AHRF early in the course of invasive mechanical ventilation. Furthermore, no study to-date has reported on cost-effectiveness of APRV.

1.3 Hypothesis

Our primary hypothesis is that adult CCU patients requiring invasive mechanical ventilation for moderate-severe AHRF will have a shorter duration of mechanical ventilation if ventilated with APRV compared to usual care.

1.4 Need for a trial

Many patients require invasive mechanical ventilation for AHRF which is associated with significant morbidity and mortality which may in part be attributable to the current way invasive mechanical ventilation is delivered in the NHS. Furthermore, significant NHS costs are incurred to care for these patients (average CCU cost is £1648/day[15], with an average invasive mechanical ventilation duration of 6 days). Total costs increase with longer duration of invasive mechanical ventilation. Therefore, it is likely that optimisation of invasive mechanical ventilation could reduce lung damage, favour faster healing, thereby reducing invasive mechanical ventilation duration, mortality, and costs. In addition, survivors of AHRF experience reduced health-related quality of life[16] with many unable to return to previous levels of activity including work and education. This results in substantial costs to the NHS and to society. If APRV reduces the time spent receiving invasive mechanical ventilation this may shorten time to return to pre-CCU quality of life.

The RELEASE trial addresses a James Lind Alliance Priority Setting Partnership CCU top priority 'What is the best way of preventing lung damage of patients receiving respiratory support?'[17] A NIHR research priority setting exercise highlighted the need for robust UK data on the effect of APRV[18]. Finally, this proposed trial received the 2022 UK Intensive Care Society Research Prioritisation Exercise award (providing £50K pump priming funds) highlighting it as the trial given the highest priority for conduct by the UK CCU community. Our Patient, Public Involvement (PPI) work also endorsed the study importance and helped us refine our research questions and the outcomes to be measured.

To inform this proposal, we queried the UK Severe Respiratory Failure Referral Database. Over the last two years 740/3650 (21%) patients were on APRV at referral for extracorporeal membrane oxygenation (ECMO). From Feb to April 2022, we surveyed CCU consultants referring these patients. Of 160 consultants representing 92 of the 128 UK hospitals making referrals to the Severe Respiratory Failure service, we found 108 (80%) used APRV for patients with AHRF, although it was mainly used as a rescue mode (73/108 consultants, 68%). In addition, 83% felt more evidence on APRV was needed and 75% would consider taking part in a trial further highlighting the equipoise in the clinical community [19].

1.5 Assessment and management of risk

While APRV is commonly used in the NHS, there is significant variation in its use likely due to the limited evidence for its clinical and cost effectiveness, or absence of harm. If effective, our group will work with clinicians, professional societies, and NICE to implement APRV more widely to improve patient outcomes and reduce NHS costs. If ineffective or harmful, our group will work to de-implement this intervention.

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

We will conduct a multi-centre, randomised, allocation concealed, controlled, open label, pragmatic, parallel group clinical and cost effectiveness trial with an internal pilot. The internal pilot will run for 8 months in 20 sites (with staggered starts to facilitate site initiation visits and site support). The internal pilot will use identical processes as the main trial and will assess site set-up, screening, participant recruitment, protocol adherence, and cross over rates. Progression criteria are outlined below in section 2.3.1.2. All participants included in the internal pilot will be included in the final analyses.

PICO Summary

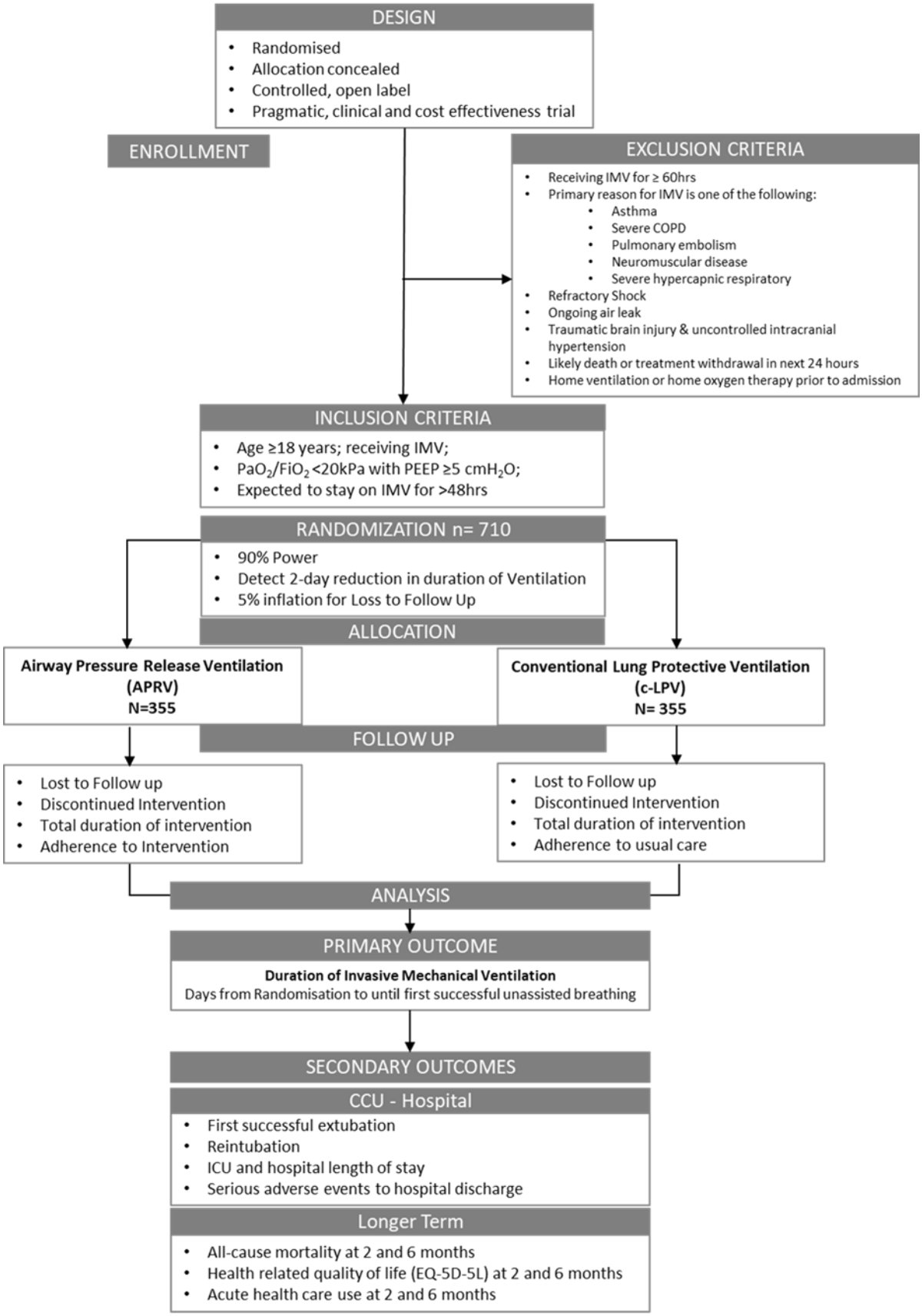
Population: Patients receiving invasive mechanical ventilation for moderate to severe AHRF.

Intervention: Early APRV.

Comparator: Standard conventional lung protective invasive mechanical ventilation (no APRV).

Outcome: Duration of mechanical ventilation from randomisation (primary clinical effectiveness), plus cost-utility at 6-months.

Figure 2: Trial flow diagram



2.2 Trial setting

The RELEASE trial will be conducted in approximately 40 UK CCUs with a proven track record of participating in CCU research. The CCUs must provide evidence that they have access to the trial population, that consultants in the CCU have clinical equipoise for APRV in this clinical setting and agree to maintain trial allocation in patients randomised by their colleagues.

Staff must also demonstrate and document a willingness to comply with the protocol, standard operating procedures, the principles of GCP (Good Clinical Practice) and regulatory requirements and be prepared to participate in training. All new sites will be provided with education on APRV and mentoring on APRV during trial conduct from the research team.

2.3 Internal Pilot

The trial will include an internal pilot that will run for 8 months (months 8 to 15 from grant activation) with all participants recruited in the pilot included in final analyses. The pilot will take place in 20 representative sites with a staggered start. We will recruit 78 patients with a target of 0.6 participants /site for the first 5 months and subsequently 0.7/site for the remaining 3 months.

Table 1: Internal Pilot Recruitment Rates

Trial Activity	**Trial month (from grant activation)**							
	8	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Site Activation	4	8	12	16	20	20	20	20
Participant Recruitment	2	5	7	10	12	14	14	14
Cumulative Participant Recruitment	2	7	14	24	36	50	64	78

The internal pilot will establish our ability to recruit to target, protocol fidelity, crossover rates, and data collection completeness.

During the internal pilot, we will audit screening logs, recruitment rates, reasons for exclusion, protocol fidelity, and crossover rates. We will measure dataset completeness, including completeness of the primary outcome, which we anticipate should be >95% as this is routinely documented in the medical record of all ventilated patients.

Table 2: Progression Criteria

	Red Unable to progress to main trial	**Amber** Review screening log & protocol; adjust protocol & research processes; explore additional sites	**Green** Progress to main trial
% Threshold (patient recruitment based on 0.7 patients/site/month)	<50%	51-99%	100%
Recruitment rate/open site/month	<0.4	<0.6	0.7
Number of pilot sites opened	<10	10-19	20
Total number of participants recruited	<40	59-77	78
Total number of participants with crossover	>5%	4-5%	<4%

We will use a traffic light system to guide progression as recommended in best practice guidelines[20].

Green: Progress to main trial with review of screening logs and protocol addressing any barriers to recruitment.
Amber: Progress to main trial with ongoing site set-up, review of screening logs and protocol deviations, and protocol amendment where necessary.
Red: Unable to progress to main trial.

The Data Monitoring Committee (DMC), Trial Steering Committee (TSC), and HTA secretariat will review internal pilot data and make recommendations in terms of trial progression.

2.4 Aims and objectives

This is a non-commercial, UK, multi-centre, parallel group, pragmatic, randomised controlled trial that aims to determine the clinical and cost effectiveness of early APRV compared to conventional lung protective invasive mechanical ventilation in patients with moderate-severe AHRF.

2.4.1 Primary objective

To determine the effectiveness of APRV for reducing the duration of mechanical ventilation compared to conventional lung protective ventilation. Duration of ventilation is defined as the time from randomisation to first successful unassisted breathing or death.

2.4.2 Secondary objective

To determine the effect of APRV compared to conventional lung protective ventilation on the following:

- All-cause mortality at 2 and 6 months
- Time to first successful extubation
- Need for reintubation prior to achieving first successful unassisted breathing
- Use of non-invasive ventilation following extubation but prior to achieving first successful unassisted breathing
- CCU and hospital length of stay
- Serious adverse events up to hospital discharge
- Health related quality of life (EQ-5D-5L) at 2 and 6 months after randomisation
- Acute health care use at 2 and 6 months after randomisation
- Within-trial cost-utility analysis from an NHS hospital care perspective (see Section 6.5).

2.4.3 Primary and secondary endpoints

We have included as our trial outcomes, the core outcome set for trials of interventions intended to modify mechanical ventilation duration developed by members of our group[21].

Our primary outcome is duration of mechanical ventilation in days commencing at randomisation and discontinuing at first successful unassisted breathing or death.

Unassisted breathing is defined as remaining able to breathe unassisted at 48 hours without inspiratory support (i.e., invasive or non-invasive ventilation) or extracorporeal lung support. Duration of assisted breathing includes time receiving extracorporeal lung support, invasive

mechanical ventilation and non-invasive ventilation delivering volume or pressure support ventilation.

This duration **excludes** time receiving high-flow oxygen therapy or use of continuous positive airway pressure (either delivered via the ventilator or via mask interface).

This definition was agreed through an international consensus process, involving clinician, researcher, patient and family representatives, and industry during developing of the core outcome set for trials of interventions designed to effect the duration of mechanical ventilation. This primary outcome was chosen with PPI input.

Secondary outcomes are listed in section 2.4.2. Time to first successful extubation is defined as free from all tubes, endotracheal tube, and tracheostomy. Success is defined as remaining free from tubes at 48 hours. Time does not include the 48-hour success period.

2.4.4 Cost-effectiveness Objective

To estimate the cost-effectiveness of APRV compared to conventional lung protective ventilation.

2.5 Eligibility criteria

Our eligibility criteria will enrol a population clinically and pragmatically likely to benefit from the intervention. Our exclusion criteria are designed to ensure early use of APRV, inclusion of a population of critically ill patients with moderate to severe AHRF most likely to benefit, and exclusion of patients unlikely to benefit due to their underlying condition or at increased risk of a complications from the intervention.

Patients who meet all the following inclusion criteria and none of the exclusion criteria are eligible to participate in the trial.

2.5.1 Inclusion criteria

1. Age ≥ 18 years

2. Receiving invasive mechanical ventilation

3. Moderate to severe acute hypoxaemic respiratory failure, defined as a single measurement showing a PaO_2/FiO_2 ratio <20 kPa while receiving a Positive End-Expiratory Pressure (PEEP) of ≥5 cmH_2O, assessed at any point within the first 60 hours after the initiation of invasive mechanical ventilation*

4. Expected to stay on invasive mechanical ventilation for >48hrs

*(once inclusion criteria are met, patients will remain eligible and may be randomised into the RELEASE trial at any time during this 60-hour window).

2.5.2 Exclusion criteria

1. Receiving invasive mechanical ventilation ≥ 60 hours at time of screening as will be unable to deliver early APRV

2. Primary reason for invasive mechanical ventilation is one of the following:

   a) Asthma

b) Severe COPD

c) Pulmonary embolism (massive or sub-massive) (as cause of hypoxaemia is not primarily due to collapse of lung tissue)

d) Existing neuromuscular disease such as Motor Neurone Disease, Guillain Barre or Myasthenia Gravis (as the cause of respiratory failure is not primarily lung-related)

3. Refractory shock (systolic blood pressure < 90 mmHg, despite fluid administration and vasoactive drugs)*

4. Severe hypercapnic respiratory acidosis (pH <7.20 on the arterial blood gas assessed for trial inclusion)*

5. Ongoing air leak (e.g. unresolved pneumothorax at time of screening)*

6. Traumatic brain injury with uncontrolled intracranial hypertension*

7. Likely death or treatment withdrawal in next 24 hours

8. Home ventilation or home oxygen therapy prior to admission

9. Receiving, or decision to commence, ECMO in the next 24 hours

*(patients can be recruited if this resolves and remain within the eligibility window or <60 hours of invasive mechanical ventilation).

2.6 Participant identification / Screening

All invasively ventilated CCU patients will be screened daily for eligibility by the research team in consultation with the clinical team. Each site will maintain a screening log which will include data on the numbers of patients potentially meeting eligibility criteria but not entered into the trial, those for which consent is given but are then not randomised, numbers not meeting inclusion criteria and reasons for non-enrolment. A fully anonymised patient-level minimal dataset (including age, sex, ethnicity, and reasons for non-enrolment) will be recorded to establish an unbiased trial population and for reporting according to the CONSORT statement [27,28].

2.7 Informed consent

It is the responsibility of the Principal Investigator (PI) (or designee) to ensure that written informed consent is obtained for each participant prior to entry into the trial. Consent may be obtained by the PI; or an appropriately trained member of the research team provided they are GCP trained, suitably qualified and experienced and have been delegated this duty by the Principal Investigator on the delegation log.

Patients will be unable to give informed consent because of sedation, infection, delirium and mechanical ventilation. Consent will therefore be obtained in line with the legal requirements for obtaining consent in patients without capacity and a personal or professional consultee will be approached. An animated information video may be provided in addition to written information leaflets to support the informed consent process.

For centres in Scotland, if there is a person willing and able to take on the responsibilities of Welfare Attorney/Welfare Guardian/Nearest Relative, they will provide consent for inclusion. In cases where

no Welfare Attorney/Welfare Guardian/Nearest Relative is available it will not be legally possible to enrol the patient (specific to the Adults with Incapacity Act Scotland for non-CTIMP trials).

Further details on the consent process are detailed in section 4.2.3 of the CoReCCT master protocol.

Once a participant who initially lacks capacity, regains capacity, they will be informed about the trial and invited to consent to continue in the trial.

2.8 Randomisation

2.8.1 Randomisation

Randomisation will occur once eligibility has been confirmed and consent obtained. Participants will be randomised via randomly permuted blocks using an automated web-based system on a one-to-one basis, stratified by site and prior enrolment into the Awake Prone Positioning and Protect Airways trials, using a computer-generated randomisation schedule managed by the Warwick CTU. We have selected a parallel group RCT design to minimise selection bias and ensure against accidental bias.

2.8.2 Post-randomisation withdrawals

Participants (or their legal representative) are free to withdraw or discontinue from the trial at any time, without having to give a reason. Withdrawing from the trial will not affect them or their care in any way. Where participants have given consent, the research team will keep information already collected prior to withdrawal, unless specified by the participant. Participants may also be asked for permission to collect further outcome data from their medical records or data linkage. Where participants regain capacity to consent and then choose to withdraw, participants will be asked if they are happy for data collected prior to withdrawal to be kept.

2.9 Trial intervention

2.9.1 Intervention arm (APRV protocol)

We will compare APRV to standard lung protective invasive mechanical ventilation. All commercially available ventilators used in the NHS can provide APRV. APRV is a method of invasive mechanical ventilation which uses longer inspiration times (CPAP phase) followed by a brief expiration (release phase). The longer inspiration time enables alveolar recruitment and oxygenation while the short expiration time maintains lung volume. This reduces shear-stress damage to the alveoli, whilst maintaining adequate ventilation.

APRV has four main control settings. Two of which determine the inspiratory cycle (CPAP phase): inspiratory or high pressure (P_{high}) and inspiratory time, or time at high pressure (T_{high}). The other two control settings determine the expiratory cycle: expiratory or low pressure (P_{low}) and time at low pressure (T_{low}) which make up the expiratory or Release Phase.

In accordance with current clinical practice for APRV, expiratory time will be individualised for each patient based on their respiratory mechanical characteristics, which will vary during the course of the disease.

Guidance on delivery of APRV is outlined in the RELEASE study intervention manual. Patients randomised to the intervention arm MUST continue to receive APRV (or CPAP when weaning) until extubation. There are few parameters considered mandatory to the study protocol, these are outlined below:

- The P_{low} must always be set to 0 cmH_2O without exception
- Pressure support must NOT be added to APRV due to the risk of barotrauma

- Pressure support must NOT be added to CPAP in the weaning phase, as this is the weaning method used in the control arm and would be considered crossover
- The release phase must target a T_{low} that terminates expiration at approximately 75% of the peak expiratory flow (P_{EF})

For detailed information regarding transitioning to APRV, optimising ventilation, weaning from ARPV, and troubleshooting, refer to the RELEASE study intervention manual.

2.9.2 3Additional Therapies

Patients in the APRV arm should receive all other treatments (e.g., prone position, neuromuscular blockade, or consideration for ECMO) as per usual standard of care at the discretion of the clinical team.

Participants randomised to the control arm will receive standard ventilation as per local guidance and practice. Current evidence-based best practice of conventional lung protective mechanical ventilation for management of moderate to severe acute respiratory failure is shown in Table 5. This is only a guide, there is no protocolisation of standard ventilation or other clinical management within the RELEASE trial.

Table 3: Evidence-based standard of care from published guidance

All patients	**Patients with PaO_2/FiO_2 ratio<20 kPa**
Tidal volume of <6 ml/kg ideal body weight	Prone positioning at least 12 hours per day
Conservative fluid management strategy	Consider ECMO

Faculty of Intensive Care Medicine; Intensive Care Society, and British Thoracic Society endorsed guideline for management of acute respiratory distress (ARDS)[4].

During site initiation visits, sites will be asked to confirm compliance with the evidence-based standard of care outlined above.

2.9.2.1 Weaning in the control arm

Weaning will be conducted according to the usual practices of the participating site (low level pressure support, CPAP or T-Piece) and may or may not include a spontaneous breathing trial. There is no protocolisation of weaning in the control arm in the RELEASE trial.

2.9.3 Both trial arms

2.9.3.1 Refractory Hypoxaemia

If the treating physician is concerned about hypoxaemia, measures such as prone positioning, continuous neuromuscular blockade infusion, inhaled pulmonary vasodilators, or referral for consideration of extracorporeal membrane oxygenation (ECMO) can be applied in either arm of the trial as per standard care in the UK. These interventions will be recorded in the CRF up to Day 10 post-randomisation or CCU discharge if sooner.

2.9.3.2 Other Clinical Management

Responsibility for all other management decisions remains the responsibility of the attending physicians and CCU team.

The intervention (APRV or control) will continue until one of the following criteria is met:

- 60 days after randomisation
- Successful unassisted breathing (at 48 hours with no further requirement for invasive or non-invasive inspiratory support or extracorporeal lung support. See section 2.4.3 for full definition)
- Trial intervention-related serious adverse event
- Death or discontinuation of active treatment
- Withdrawal of consent

2.9.3.3 Crossover

Crossover from the control arm to APRV is not allowed. This will be monitored during the trial. If any site despite re-training continues to experience crossover, the site will be closed to recruitment.

We will allow brief periods of conventional ventilation (maximum of 6 hours) for patients randomised to APRV for the purposes of:

- Transport out of the CCU for diagnostic or surgical procedures or other purposes
- Management of a new complication that would be considered an exclusion criterion such as a new air leak or cardiovascular instability

2.9.3.4 Site Staff Training

All sites will complete a training package prior to opening to recruitment. The training package will include set up, optimisation, and weaning of APRV; trouble shooting guides; and a review of standard of care approaches for the management of patients with moderate to severe AHRF. This training will be delivered by on-site, remote or hybrid training with a research education nurse, and also via modules on the online training platform LearnPro.

2.9.4 Compliance/contamination

We will record the APRV settings for participants randomised to the intervention arm or ventilator settings for participants randomised to standard care. We will also record duration of received APRV and standard care ventilation. This will be collected daily up to Day 10 post-randomisation or CCU discharge if sooner. The statistical analysis plan will define adherence to the trial intervention.

2.10 Blinding

2.10.1 Methods for blinding and measures to avoid bias

Our trial is an open-label pragmatic design. This design means that patients, clinicians and outcome assessors are aware of treatment allocation. Although we considered blinding during trial design meetings, this is not feasible as we cannot blind clinical teams to ventilator settings. These and the patient response must be visible to guide clinical decision making and ensure patient safety. While lack of blinding can introduce bias, we have safeguards in place to mitigate against this risk as described below.

To mitigate against potential sources of bias with an open label design, we will:

- undertake source verification (from the electronic (or paper) medical record) to minimise the risk of reporting bias. The main clinical and resource utilisation outcomes of this trial (e.g., ventilation duration, death, length of stay and adverse events) are recorded contemporaneously in the patient medical record by a member of the clinical team as part of routine documentation.

- use duration of ventilation as our primary outcome as this is objectively measured and documented in the medical record. Other secondary outcomes are objective; only health-related quality of life requires participant self-report.

- use a short duration of follow-up for the primary outcome (i.e., 48 hours to determine successful unassisted breathing) to minimise the risk of attrition bias with withdrawal rates typically < 5% resulting in minimal loss to follow-up. On the rare occasion that a patient or their representative chooses to withdraw, we will retain data collected up until that point and seek permission to continue to collect the main outcome data from their medical records. Our experience is that patients or their representatives normally are happy to proceed on this basis.

- monitor usual care (lung protective ventilation) in the control arm over the duration of the trial to decrease the likelihood of performance bias. We will feedback monitoring data to sites monthly and provide additional training if required.

- collect measures of intervention fidelity over the duration of the trial and feedback monitoring data to sites monthly. If poor fidelity is found, we will provide additional training and support to sites and continue to monitor fidelity. Sites with ongoing issues with intervention fidelity will be closed to recruitment.

We have selected outcomes and measures with demonstrated validity and reliability recommended in the core outcome set for trials of interventions to modify mechanical ventilation duration developed by members of our team (McAuley and Rose[20]). Health-related quality of life will be collected by blinded assessors independent of the clinical team involved in delivering the intervention.

We have used the SPIRIT guidelines and checklist to inform the development of our protocol. We have registered the trial (ISRCTN17158033) and will make a full trial protocol publicly available. To ensure our trial reporting is accurate, comprehensive, and transparent, we will use the CONSORT-reporting guidelines to report out trial findings. We will document participant flow through the trial, including screening, baseline and follow up assessments using a CONSORT flow diagram. To avoid selective reporting, we will report all outcomes as outlined a priori in our trial protocol.

We will use Warwick standard operating procedures for trial conduct.

2.11 Co-enrolment into other trials

The RELEASE trial investigators will consider co-enrolment of RELEASE trial participants to other interventional trials outside of CoReCCT where there are no possible treatment interaction, and this does not conflict with the trial objectives. Co-enrolment will be permitted with non-interventional observational studies without the need for a co-enrolment agreement. Co-enrolment status will be collected using the eCRF.

3. METHODS AND ASSESSMENTS

Data collection will be restricted to variables required to define patient characteristics at enrolment, to monitor interventions received, to monitor adverse effects, to determine quality of life, and to capture the use of hospital healthcare resource. To ensure accurate, complete and reliable data are collected, the research team will provide training to site staff during investigator meetings and site initiation visits. The CTU will provide the PI and research staff with training on the protocol, CRF completion and trial procedures including standard operating procedures (SOPs).

3.1 Schedule of delivery of intervention and data collection

The following baseline, clinical, and outcome data will be collected by the local research delivery team from the electronic medical record. In brief the dataset will include:

	Baseline	Day 3	Day 7	Up to Day 10	Up to CCU discharge	Up to hospital discharge	Post-hospital discharge	
							2 months	6 months
Eligibility assessment	X							
Consultee agreement	X							
Baseline data collection	X							
Randomisation	X							
Ventilator settings, sedation use, organ failure, use of rescue therapies				X				
Serious Adverse Events						X		
Primary outcome					X			
Mortality (secondary outcome)					X	X	X	X
HrQoL (secondary outcome)							X	X
Healthcare utilisation after dx							X	X
Optional blood and urine samples	X	X	X					

3.2 Optional blood and urine samples

Optional consent may be provided for the collection of participant blood and urine samples for use in future ethically approved research. Consent will be collected as per section 2.7 of the RELEASE domain protocol and section 4.2.3 of the CoReCCT master protocol.

20mL of blood and 5mL of urine will be taken at baseline, day 3 and day 7. Samples will be obtained for each trial arm. The baseline samples will be collected prior to intervention commencement (either pre- or post-randomisation). Where this is not possible, samples should not be obtained at any

timepoint. Failure to collect optional blood or urine samples is not considered non-compliant with the trial protocol.

The collected samples will be labelled with the participant's trial number and a site identification code. Blood and urine samples will be collected and stored at the hospital site as per the RELEASE Sample Handling Guidelines document. Samples will be transported in batches to the Queen's University Belfast, at a time of mutual convenience, and stored beyond completion of the study. This activity will be coordinated by the WCTU trial team. Any samples not used will be disposed of in accordance with local policy and applicable regulations. Full details will be outlined in the RELEASE Sample Handling Guidelines document.

3.3 Follow-up Procedures

Follow-up questionnaires at 2 months and 6 months will capture health-related quality of life and healthcare resource use [22]. Follow up time points and management of follow up questionnaires are aligned over all CoReCCT domains and managed by WCTU. Refer to section 6 of the CoReCCT Master Protocol for further details.

4. ADVERSE EVENT MANAGEMENT

In order to accurately assess and report SAEs relevant to RELEASE, the CoReCCT Master Protocol must be read in conjunction with section 4.1 below.

Section 7 of the CoReCCT Master Protocol describes the CoReCCT Safety Reporting Flowchart and provides details on these adverse event management topics:

- Definitions of SAEs
- Assessing and reporting SAEs
- Causality Assessment of SAEs
- Expectedness Assessment of Related SAEs
- Expedited Reporting of Related and Unexpected SAEs to REC

4.1 Pre Specified Complications

As per the CoReCCT Safety Reporting Flowchart, adverse events that 1) occur at sites between randomisation and hospital discharge and 2) are not present on the CoReCCT Exemption List, must be reviewed for their presence on the RELEASE Pre-Specified Complications List as given below.

Pre-Specified Complications List (that occur up to Day 10 post randomisation)
Barotrauma (including pneumothorax, pneumomediastinum, subcutaneous emphysema)
Hypotension requiring new vasopressors or increase in vasopressors of more than 0.2 microgram/kg/min

As per the CoReCCT Safety Reporting Flowchart, if the event is present on the Pre-Specified Complications List and occurred up to Day 10 post-randomisation, the event must be recorded on the appropriate CRF as an outcome and does not need to be reported on an SAE form. Pre specified complications which occur beyond Day 10 post-randomisation will not be recorded. If the event is not

on the list, it must be assessed for seriousness and the remainder of the flowchart should be followed to determine next steps.

4.2 Expected Events

SAEs which are considered possibly related, probably related or definitely related to the study intervention will be assessed for expectedness by the Sponsor. This expectedness assessment may be supported by items such as, but not limited to associated domain working instructions and published literature.

5. DATA MANAGEMENT

Full details on data management are provided in sections 6 and 10 of the CoReCCT master protocol.

5.1 Data collection and management

Full details are listed in section 10 of the CoReCCT Master Protocol.

5.2 Data Shared with Third Parties

Full details are listed in section 12 of the CoReCCT Master Protocol.

5.3 Archiving

Full details are listed in section 13 of the CoReCCT Master Protocol.

6. STATISTICAL ANALYSIS

6.1 Power and sample size

The RELEASE trial will recruit a total of 710 (355 per arm) participants (using 90% power and 5% significance level).

The parameter estimates for this trial have been derived as follows:

(a) Effect size of 2-days reduction: Given our (Figure 1) and previous meta-analyses[8-11] showed a reduction of invasive mechanical ventilation duration with APRV of 3.3-5.4 days, an effect size of 2 days is conservative and can be realistically achieved.

(b) Median duration of ventilation on the control arm: the duration of ventilation varies in the UK from 7 to 14 days in reported studies (i.e., 7 days- BREATHE trial [23]; 14.1 days -OSCAR trial[24]. National reporting from the Intensive Care National Audit & Research Centre (ICNARC) Case Mix Programme Database 2019 indicates a duration of 6 days. Taking our trial population and comparing this to that reported in previous studies, we anticipate that the duration of ventilation in the control arm would be approximately 9 days.

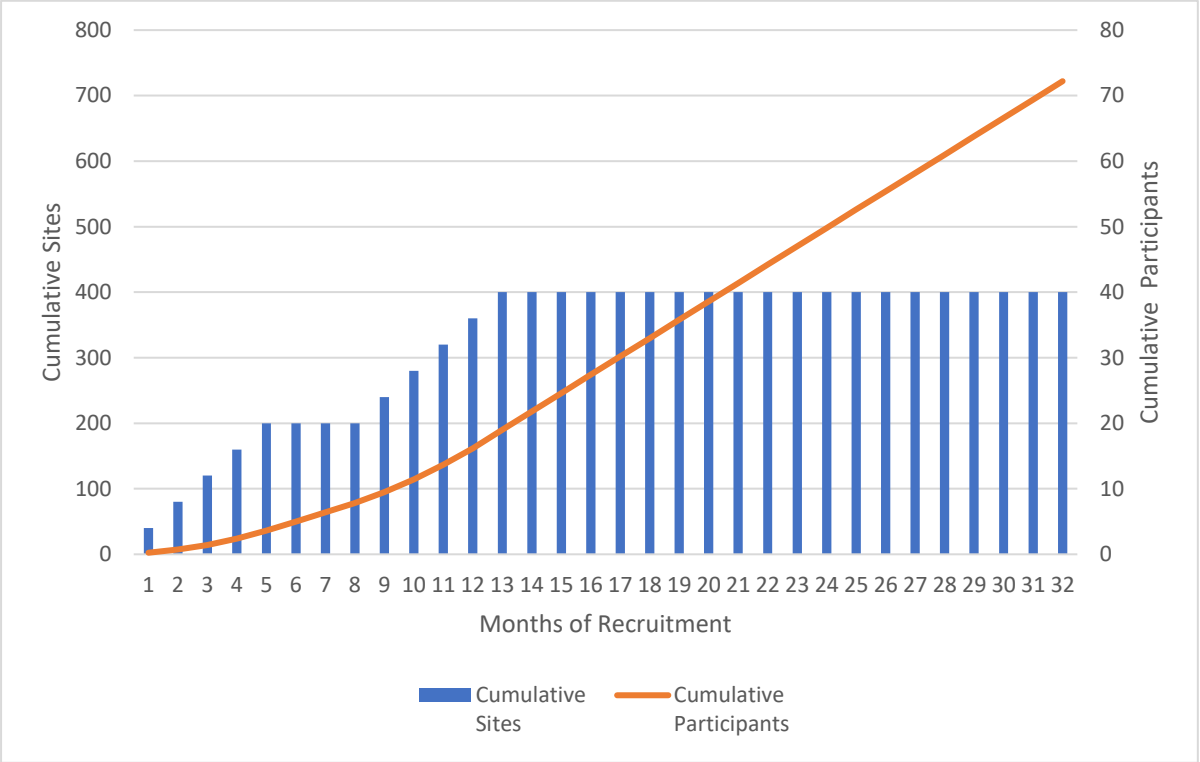
(c) Loss to follow-up: In the previous CCU studies, loss to follow-up ranges from 0% to 3% (1.1% -BREATHE trial [23]; 0% - OSCAR trial[24] 0.4%- HARP-2 trial[25]; 0.5% - HARP trial; 3% - REST trial[26]). We have assumed a worst-case scenario here and used 5% as our loss to follow-up rate.

6.2 Statistical analysis of efficacy and harms

6.2.1 Planned recruitment rate

We will conduct an 8-month internal pilot opening 20 sites over 5 months (4 sites/month). We estimate a conservative 0.7 patients/ICU/month recruitment rate based on previous clinical trials (0.6 patients/ICU/month in first 5 months of recruitment. A realistic staggered set-up of the remaining 20 sites will follow. Total recruitment duration including the internal pilot is 32 months.

Figure 3: Recruitment and site set up projections



6.2.2 Statistical analysis plan

A full and detailed Statistical Analysis Plan (SAP) will be agreed with the Data Monitoring Committee (DMC) prior to any analysis taking place. Data will be analysed and reported according to the CONSORT statement.

6.2.3.1 Summary of baseline data and flow of patients

Screening log data will be collected for each site on a regular basis, and this will be scrutinised by the trial team to assess patient recruitment.

At randomisation, patient demographic data will be recorded. This will include: age, sex, body mass index.

Continuous baseline data will be summarised with descriptive statistics, including number of observation (n), mean, standard deviation, median, interquartile range and number of missing data. Categorical baseline data will be summarised with frequency counts and percentages.

6.2.3.2 Primary outcome analysis

Primary outcome and the Estimand Framework

In addition to the objectives, interventions and the population already stated above, the following define the Estimand framework that will be used for the RELEASE trial, in line with the ICH E9 (R1) addendum on Estimand and sensitivity analyses in clinical trials[23].

Variable (outcome): Our main variable (outcome) of interest is ventilation duration, from the time of randomisation to successful unassisted breathing or death. 'Successful unassisted breathing' will be defined using the core outcome set[21] definition i.e., the time point a patient is free of ventilatory (invasive or non-invasive) support for >48 hours as per section 2.4.3.

Summary measure and the primary Estimand: Ventilation duration will be determined as the time of successful unassisted breathing/death minus the time from the point of randomisation (in hours/mins). The statistical analysis for this outcome will be performed using the treatment policy strategy (i.e., intention-to -treat). Statistical summaries of ventilation duration will be made using median and interquartile range (IQR). We will use a Cox proportional hazard regression model to estimate the treatment difference reporting hazards ratios and their 95% confidence intervals (CIs), using both unadjusted and adjusted estimates. We will report the mean difference with 95% CIs using linear regression.

Intercurrent events (ICEs) and strategies for handling ICEs: post-randomisation events that may affect the interpretation of the primary outcome include: (a) crossover; (ii) non-adherence (including discontinuation of treatment); and (iii) death. Rates of crossover and non-adherence will be added using the principal stratum strategy. We will use the inverse probability weighted analysis method[24] to assess the treatment effect, having taken account of these events. The composite strategy will be used to assess the effect of death, with ventilation duration. We will use the Pocock's win-ratio method[25] and also assess the interaction of ventilation duration with mortality status, bearing in mind the interaction term may not be powered to detect differences.

6.2.3.3 Secondary outcome analysis

In general, continuous baseline and outcome data will be summarised with descriptive statistics, including n, mean, standard deviation, median, IQR and n of missing data. We will use mixed-effects linear regression models to estimate mean treatment differences (95% CI). Categorical baseline and outcome data will be summarised with frequency counts and percentages. We will use mixed-effects logistic regression models to estimate the difference in binary outcomes between treatment groups, with odds ratios and 95% CIs reported. Survival based outcomes will be analyzed using the Cox proportional hazards model with data displayed using the Kaplan-Meier plots.

6.3 Subgroup analyses

We will examine the following subgroups:

- baseline oxygenation status (moderate PaO_2/FiO_2 <20 but >13kPa, and severe ≤13kPa)
- Illness severity on admission
- previous site experience with APRV (APRV naïve vs previous APRV experience)

These subgroup analyses will be performed using intention to treat. We will use the primary outcome as the dependent variable and interaction with treatment and sub-group. We will use linear regression models to assess the subgroup effect, using interaction terms. As these analyses are post-hoc analyses not powered for any effect size, emphasis will not be based on the statistical testing, rather the point estimates and 95% CIs.

6.4 Interim analysis

We will not carry out a formal interim analysis.

6.5 Health Economic Evaluation

We will conduct a prospectively planned within-trial cost-utility analysis with a six-month time horizon from an NHS hospital care perspective (primary economic analysis).

Costs will be analysed for the period from randomisation to 6 months post randomisation. Initial hospitalisation resources (randomisation to initial discharge) will be identified from Core case report forms (CRFs) and potentially enriched using data obtained through linkage to routine datasets (e.g., Hospital Episode Statistics (HES), Intensive Care National Audit & Research Centre (ICNARC)). The data of interest here include information on critical care (e.g. CCU length of stay and organs supported), inpatient care (e.g. length of stay -where applicable including transfer to another unit for ongoing treatment- and reason for admission), and emergency care.
Post-discharge hospital resource use at 2- and 6-months post randomisation will be identified from data obtained from participant completed resource use questionnaires (RUQs) and if available enriched using data obtained through CRFs/linkage. These data will comprise of information on critical care, inpatient care, outpatient care, and emergency care.

Our approach with regard to resource utilisation is to focus on the relevant resource items for patients who are receiving invasive mechanical ventilation, recognising that their underlying reasons for admission and other care needs are complex and heterogeneous. This means we have selected a hospital care perspective as our primary analysis. Our experience in this field suggests that primary, other community and social care are not likely to be as relevant to the intervention given that economic evaluation is an incremental analysis. Additionally, our PPI consultation has repeatedly stressed the need to avoid the burden of questionnaire completion during recovery. However, to align with other studies in the CORRECT confederation, we propose to use a brief resource use questionnaire to allow us to collect post-discharge NHS Community and Social care resource use. These data will allow us to conduct a secondary analysis from an NHS and personal social services perspective. Data on resource items usage will be converted into costs using up-to-date sources of NHS and PSS reference costs [26, 27].

Generic health-related quality of life will be assessed at 2- and 6-months using the EQ-5D-5L questionnaire. EQ-5D-5L scores will be converted to health status scores using the UK value set recommended by NICE guidance at the time of analysis[28]. We will calculate patient-level Quality adjusted life year (QALY) estimates using the trapezoidal rule using utilities generated via the EQ-5D-5L in surviving patients, with baseline utility (which cannot be self-reported be critically ill patients) estimated following a method used in other CCU studies conducted by our group[29, 30].

Selected statistical methods will deal with skew, baseline imbalance, and sampling uncertainty as appropriate. Every effort will be made to minimise missingness. If missingness of patient-level costs or QALYs is ≤ 5%, the primary analysis will use complete case data[31]. If missingness exceeds 5%, mechanisms of missingness will be explored and multiple imputation methods will be applied to impute missing data.

We will use bootstrapped bivariate analyses of costs and QALYs to generate within trial incremental cost per QALY estimates and confidence intervals. Findings will be analysed and visualised as cost-effectiveness acceptability curves [32] and net monetary benefit approach which will show the probability that APRV is the optimal choice over a range of possible values of the ceiling ratio.

If findings are non-convergent at six months, we will explore the sensitivity of cost-effectiveness to extrapolation of costs and benefits beyond the trial time horizon, via a suitable decision model or parametric survival analysis model in a secondary analysis.

Details of the prospective plan and analysis will be described in the Health Economics Analysis Plan (HEAP) written by the trial health economists in line with guidance from Warwick CTU SOP 21. Reporting will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement[33].

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

The University of Warwick will act as trial sponsor. Full details are listed in section 9.1 of the CoReCCT Master Protocol.

7.2 Ethical approval

Full details are listed in section 9 of the CoReCCT Master Protocol.

7.3 Trial Registration

We will prospectively register the trial with an appropriate trial registry.

7.4 Notification of non-compliances to GCP and/or trial protocol

Full details are listed in section 9.5 of the CoReCCT Master Protocol.

7.5 Indemnity

Full details are listed in section 9.6 of the CoReCCT Master Protocol.

7.6 Trial timetable and milestones

The total planned project duration is 52 months. A summary of key trial milestones is shown below.

Table 4: Project Milestones

	Month	Recruitment
Set-up	1-7	N/A
Internal Pilot	8-15	78
Recruitment	16-39	710
Follow up	40-45	N/A
Analysis, reporting & dissemination	46-52	N/A

7.7 Administration

The trial co-ordination will be based at WCTU, University of Warwick. Full details are listed in section 9.7 of the CoReCCT Master Protocol.

7.8 Trial Management Group (TMG)

Full details are listed in section 9.9 of the CoReCCT Master Protocol.

7.9 Trial Steering Committee (TSC)

Full details are listed in section 9.11 of the CoReCCT Master Protocol.

7.10 Data Monitoring Committee (DMC)

Full details are listed in section 9.10 of the CoReCCT Master Protocol.

7.11 Essential Documentation

Full details are listed in section 9.14 of the CoReCCT Master Protocol.

7.12 Financial Support

The trial has been funded by a grant from the National Institute of Health and Care Research Health Technology Assessment programme (NIHR154501). Full details are listed in section 9.13 of the CoReCCT Master Protocol.

7.13 Safeguarding Researchers and Research Participants

Full details are listed in section 9.15 of the CoReCCT Master Protocol.

8. MONITORING, AUDIT AND INSPECTION

A Trial Monitoring Plan will be developed by the trial team and a member of the WCTU Quality Assurance team and approved by the domain chief investigator. A risk-based proportionate approach will be outlined in the monitoring plan to facilitate remote and off-site monitoring, except where on-site monitoring is deemed to be required. Further details on monitoring, audit an inspection is detailed in the CoReCCT master protocol.

8.1 Training

Principal investigators, research team members involved in approaching patients/ consultees for consent, and members of the WCTU team will be required to undergo GCP training. PIs will be required to provide a copy of their GCP certificate and a signed and dated CV to WCTU. Site staff listed on the delegation log should ensure their CVs and, where appropriate, evidence of GCP training is available to WCTU on request.

Training materials on trial procedures, including eligibility assessment and consent processes, will be developed by WCTU to standardise trial processes for site research staff. The training will take a modular approach, such that individuals will only need to undertake training relevant to their training role. Training may be delivered face-to-face (in-person or via video call) or through completion of the web-based training package. In-person training is required to be delivered by a member of WCTU staff or a member of the site team approved by the PI. Completion of training for individuals listed on the delegation log will be recorded in the site file.

WCTU staff that are new to the trial will follow a thorough induction plan developed by the Trial Manager.

8.2 Data Quality

Full details are listed in section 10.4 of the CoReCCT Master Protocol.

8.3 Visits to Sites

Full details are listed in section 10.1 of the CoReCCT Master Protocol.

9. PATIENT AND PUBLIC INVOLVEMENT (PPI)

Our two PPI co-applicants will advise on all trial aspects and will participate in TMG and PPI advisory group meetings.

We will continue to embed meaningful patient and public involvement throughout the project. We will convene a PPI group of approximately 6-members with a membership that reflects the diversity of people at risk of acute hypoxaemic respiratory failure. The PPI group will meet regularly throughout the trial to provide advice and support to the trial management group. PPI advisory group meetings will seek input on: final trial protocol, participant facing documents, ongoing trial awareness and dissemination activities.

We will identify at least two PPI members to become independent members of the Trial Steering Committee. This group will be responsible for the oversight of the trial and advising the Sponsor and Funder in accordance with the NIHR terms of reference for steering committees.

10. DISSEMINATION AND PUBLICATION

The trial investigators named in this document will have access to data and be involved in drafting of manuscripts, abstracts, press releases and any other publications arising from the trial. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

Results will be reported as papers in peer reviewed journals and presentations at academic conferences. A lay results summary will be available via the trial website. Executive summaries will be sent to relevant professional societies, charities and uploaded to ISRCTN.

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