Northumbria Healthcare
NHS Foundation Trust

Title: Standard versus accelerated weaning from non-invasive ventilation (NIV) in chronic obstructive pulmonary disease directed by the NIV outcomes score: a randomised controlled trial

Short running title (acronym): Non-Invasive Ventilation Outcomes score-directed Weaning (NIVOW) v1.2

Key Trial Information

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This protocol has regard for the HRA guidance and order of content.

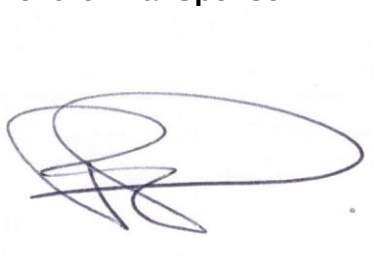
Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature:  Date: 05/08/2022

Name: (please print): PETA HESLOP

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Signature:  Date: 05/08/22

Name: (please print): PROFESSOR STEPHEN BOURKE

Position: Consultant Respiratory Physician

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Data Monitoring Committee Chair	Dr Michael Davies Consultant Respiratory Physician Tel: 01223 638000 Email: michael.davies10@nhs.net

i. List of Contents

ii. List of Abbreviations

ABG	Arterial blood gas
AE	Adverse Event
AF	Atrial Fibrillation
AHRF	Acute hypercapnic respiratory failure
APACHE II	Acute Physiology and Chronic Health Evaluation II
CCI	Charlson Comorbidity Index
CI	Chief investigator
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
DECAF	Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation prognostic score
DMC	Data Monitoring Committee
ECOPD	Exacerbation of Chronic Obstructive Pulmonary Disease
eMRCD	Extended Medical Research Council Dyspnoea
EPAP	Expiratory positive airway pressure
HADS	Hospital anxiety and depression scale
HCO_3-	Bicarbonate
HRA	Health Research Authority
IPAP	Inspiratory positive airway pressure
kPa	Kilopascal
NHS	National Health Service
NIHR	National Institute for Health and Care Research
NIV	Non-Invasive Ventilation
NIVO	Non-Invasive Ventilation Outcomes
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PEARL	Previous admissions, eMRCD score, Age, Right-sided heart failure and Left sided heart failure
PEEP	Positive end-expiratory pressure
PI	Principle investigator
PPI	Patient and public involvement
PS	Pressure support
$PtcCO_2$	Transcutaneous carbon dioxide
RCT	Randomised controlled trial
REC	Research Ethics Committee
RfPB	Research for Patient Benefit
SAE	Serious Adverse Event
SGRQ-C	St Georges Respiratory Questionnaire for COPD
SpO_2	Oxygen saturation
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
VAS	Visual analogue scale

iii. Trial Summary

Trial Title	Standard versus accelerated weaning from non-invasive ventilation (NIV) in chronic obstructive pulmonary disease directed by the NIV outcomes score: a randomised controlled trial	
Short Title	Non-Invasive Ventilation Outcomes score-directed Weaning (NIVOW)	
Trial Design	A multi-centre, open-label, parallel, randomised controlled trial.	
Trial Participants	Clinical diagnosis of ECOPD complicated by AHRF (pH<7.35 and $PaCO_2$>6.5kPa), with low or medium risk NIV Outcomes score, and meeting criteria for weaning.	
Planned Sample Size	164 participants randomised.	
Treatment Duration	24 months of recruitment.	
Follow Up Duration	90-days follow up post-randomisation.	
Planned Trial Period	Recruitment 01/09/2022 to 31/08/2024.	
	Objectives	Outcome Measures
Primary	To compare time to successful weaning from NIV in ECOPD using an accelerated versus a standard weaning protocol.	Time to successful weaning.
Secondary	To compare relapse requiring NIV (defined as recurrent AHRF>48 hours after removal of the ventilator), complications of NIV, respiratory symptoms (breathlessness and sputum clearance), sleep quality, health-related quality of life, readmissions, mortality, and NHS cost and cost-effectiveness between both weaning strategies.	Relapse requiring NIV; Total duration of ventilation; Length of hospital stay; NIV complications; Patient reported outcome measures; Mortality; Readmissions; Health economic analysis; Responder analysis (accelerated weaning group).
Control Arm	Standard weaning protocol: Progressively longer periods off NIV, determined by arterial blood gas (or capillary blood gas).	
Intervention Arm	Accelerated weaning protocol: Daily 4-hour weaning trial, success confirmed by arterial blood gas, with additional transcutaneous carbon dioxide monitoring.	

iv. Funding

Funder	Financial Support Given
NIHR Central Commissioning Facility Research for Patient Benefit Programme Grange House 15 Church Street Twickenham TW1 3NL Tel: 020 3692 7936 Email: Manager@ccfrms.org.uk	Funding to deliver the trial with per patient costs, and provide statistical and health economic analysis.

v. Role of Trial Sponsor and Funder

Sponsor	The Sponsor, Northumbria Healthcare Foundation Trust, assumes overall responsibility for the initiation and management of the trial.
Funder	The trial funder, NIHR (RfPB), undertook independent peer review of the trial proposal. They will not be directly involved in the trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

vi. Roles and Responsibilities of Trial Management Committees, Groups and Individuals

Trial Steering Committee	A Trial Steering Committee will be formed with an independent Chair, and will meet at least every six months, and send timely reports to the Sponsor. The independent Chair is: Dr Patrick Murphy Consultant Respiratory Physician Tel: 020 7188 7727 Email: Patrick.Murphy@gstt.nhs.uk
Data Monitoring and Ethics Committee	A Data Monitoring and Ethics Committee will be formed with an independent Chair, and will meet at least every six months, and report to the Trial Steering Committee. The Committee members will be completely uninvolved in the running of the trial. The independent chair is: Dr Michael Davies Consultant Respiratory Physician Tel: 01223 638000 Email: michael.davies10@nhs.net
Trial Management Group	The Trial Management Group will meet regularly to ensure all practical details of the trial are progressing and working well, and everyone within the trial understands them. The Chair will be the Chief Investigator who assumes primary responsibility for the design, conduct and reporting of the trial. Chief Investigator: Professor Stephen Bourke Consultant Respiratory Physician Tel: 0191 293 4026 Email: Stephen.Bourke@northumbria-healthcare.nhs.uk

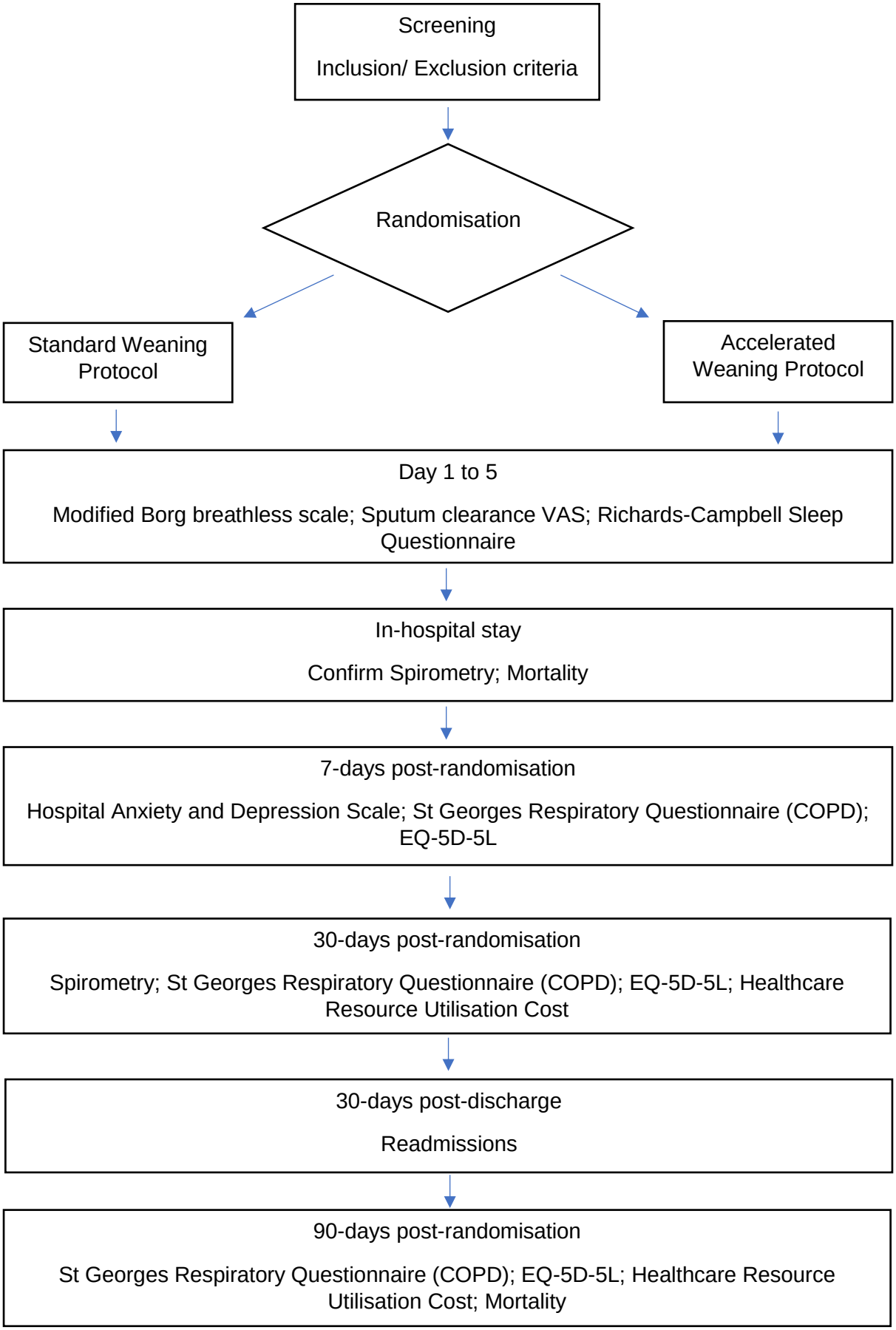
vii. Protocol Contributors

Professor Stephen Bourke	Co-developer of the NIV Outcomes score. Conceived the trial and has led the development of the accelerated weaning protocol, trial design and protocol, and will ensure appropriate governance is in place. Professor Bourke will assist Karen Brewin with all other key research activities ensuring mentorship and development, and strongly support dissemination and implementation of trial results.
Karen Brewin	Involved in all stages of this trial, from application (trial design) to final dissemination of results, including: developing key trial documents and modifiable trial assessments; seeking representative patient feedback for input into trial design and participant assessments; writing protocol; developing the source document worksheet; setting up the electronic database and randomisation service; working with other recruiting sites; performing baseline assessments; participant recruitment; randomisation and data collection at the lead site; performing data validation (all sites); involved in trial management meetings; applying statistical analysis; and involved in preparing publication of results for dissemination.
Professor Joanne Gray	Health Economic Analysis overseeing the economic evaluation (collecting and analysing data).
Dr Eduwin Pakpahan	Statistician responsible for development of the statistical analysis plan, providing support to the TMG, DMC and TSC, performing data analysis, and assisting with reports and publications.
Dr Nicholas Lane	Co-developer of the NIV Outcomes score, provided data required for the primary outcome power calculation, prepared the GP letter and Site Principle Investigator.
Patient and Public Involvement (PPI)	Representative patients requiring acute NIV and the Northumbria Lung Research PPI group have been involved in the trial design, including the design and burden of modifiable patient reported outcome measures, and design and terminology of patient facing documents e.g. consent form and patient information sheet.

viii. Key Words

Non-Invasive Ventilation (NIV)	Ventilation delivered via a face mask connected to a ventilator to help patients to breathe out a build-up of the waste gas carbon dioxide.
Chronic Obstructive Pulmonary Disease (COPD)	A lung disease causing breathlessness, sputum production and frequent flare-ups (exacerbations).
Acute Hypercapnic Respiratory Failure (AHRF)	Respiratory acidaemia diagnosed via arterial blood gas (quantified by pH<7.35 and $PaCO_2$ (carbon dioxide) >6.0kPa.
NIV Outcomes Score (NIVO score)	A clinical risk stratification tool to predict mortality in patients with exacerbation of COPD complicated by AHRF and requiring NIV treatment.
Standard weaning versus accelerated weaning	Patients will be randomised between these two weaning protocols, standard weaning and accelerated weaning.
Time to successful weaning	Duration from the baseline arterial blood gas confirming selection criteria is met, to final removal of the ventilator.

ix. Trial Flow Chart



1. Background

One quarter of patients admitted to hospital with exacerbation of Chronic Obstructive Pulmonary Disease (ECOPD) are complicated by life-threatening respiratory acidaemia/acute hypercapnic respiratory failure (AHRF).[1]

AHRF results from the inability of the respiratory system to maintain sufficient alveolar ventilation to keep arterial carbon dioxide ($PaCO_2$) and pH within normal limits. If respiratory acidaemia persists despite initial medical therapy, non-invasive ventilation (NIV) is the treatment of choice.

Weaning refers to how ventilation is discontinued once a patient has improved on treatment. Current British Thoracic Society (BTS) guidelines recommend withdrawal of NIV over 4 days,[2] but this is not based on randomised controlled trials (RCTs) comparing different weaning strategies. Reducing the duration of NIV, i.e. faster weaning, should reduce side-effects and complications for patients, as well as costs to the National Health Service (NHS). However, shorter treatment may be less effective, and respiratory failure (carbon dioxide build-up) may recur. The most effective way to wean NIV is unclear, and patients and clinicians have identified this as a research priority.[3]

There have been 4 RCTs comparing different strategies to wean patients with ECOPD from NIV. There are no planned or current registered trials similar to our proposed RCT.

Duan et al (2012)[4] compared protocol-directed (n=37) and physician-directed (n=36) weaning from NIV. Protocol directed weaning included once daily unsupported breathing trials once specific clinical criteria were met, repeated until successful. This was associated with a shorter mean duration of NIV, 2.6 versus 4.4 days ($p<0.001$), and duration of ICU stay, 5.8 versus 8.1 days ($p=0.02$). This trial supports protocol-directed weaning, but was small and included patients with a range of conditions (COPD=47/73).

Two small RCTs[5,6] compared a single attempt at immediate NIV withdrawal to a stepwise approach, but they were underpowered to detect a meaningful clinically significant difference. Success, defined as the absence of recurrent AHRF within 48 hrs, was not statistically different. Lun:[5] immediate=14/25, stepwise=26/35; Venkatnarayan:[6] immediate=23/30, stepwise reduction in pressures=27/30, stepwise reduction in duration=26/30. More importantly, failure of a first daily trial of unsupported breathing does not mean that the patient has failed to wean from NIV; repeated weaning trials should be performed on subsequent days.

Sellares[7] compared direct discontinuation of NIV (if initially unsuccessful, further attempts were performed) to nocturnal NIV for three additional nights once AHRF had resolved. Relapse with recurrent AHRF within 8 days of weaning occurred in: direct discontinuation group=10/59; nocturnal NIV group=8/61. Length of stay on the respiratory critical care unit was shorter with direct discontinuation. There were no significant differences in other outcomes. There was an unexplained 3.5-year hiatus during recruitment. In comparison to this study, recent large UK cohorts show more severe AHRF.[8,9] Across UK national audits, patients with progressively more severe AHRF were managed with NIV.[10]

ECOPD is the most common condition treated with NIV. Current guidelines on NIV weaning are not based on robust evidence, and are inconsistently followed. The NCEPOD report[8] into NIV outcomes highlights serious concerns that this research will help to address.

We recently developed the NIV Outcomes Score, that uses risk-stratification to accurately predict in-hospital mortality in patients with ECOPD requiring NIV.[9] Previous randomised controlled trials (RCTs) assessing accelerated NIV weaning protocols did not use objective prognostic tools to select patients.

This trial will clarify whether risk stratification can facilitate quicker weaning from acute NIV in patients with low and medium mortality risk. It will assess outcomes important to patients, and help address the marked variation in clinical practice.

2. Rationale

Despite NIV being one of the most effective interventions for ECOPD complicated by AHRF,[11] it can cause complications and unpleasant side-effects for patients, including pressure areas from the face mask, and gastric distension and hypotension from the pressure delivered. A shorter duration of weaning from the ventilator should provide benefits to patients and reduce costs to the NHS.

In addition, consecutive national audits raised concerns about UK NIV services, triggering a National Confidential Enquiry into Patient Outcome and Death (NCEPOD).[8] Mortality in patients with ECOPD was 25.1%, compared to around 10% in clinical trials.[12] NIV provision, including weaning strategies, varied considerably across hospitals.

Previous randomised controlled trials (RCTs) assessing accelerated NIV weaning protocols did not use objective prognostic tools to select patients. In the absence of a robust prognostic tool, they excluded patients with various features thought to confer high risk of poor outcome, notably co-existent consolidation.

We recently developed the NIV Outcomes (NIVO) score, to accurately predict in-hospital mortality in patients with ECOPD requiring NIV.[9] There was marked variation in duration of ventilation (31.5 to 95.5 hours) and relapse (4.5 to 15%) across the 10 centres involved, highlighting the need for objective guidance.

Using the NIVO score, 75% of patients have a low or medium mortality-risk and therefore may be suitable for accelerated weaning. The score is calculated using readily available clinical indices:

NIVO Score	**Points**
Chest radiograph consolidation	1
Glasgow Coma Scale (GCS) <15	1
Atrial Fibrillation (AF) including persistent, new or paroxysmal AF)	1
pH <7.25	1
Time to respiratory acidaemia >12 hours	2
Extended Medical Research Council Dyspnoea Scale (eMRCD) score 5a*	2
Extended Medical Research Council Dyspnoea Scale (eMRCD) score 5b*	3
Total	/ 9

*The extended MRC Dyspnoea Score (eMRCD) is based on performance on a good day within the last 3 months.

5a = unable to leave their home unassisted, independent in washing and/or dressing.

5b = unable to leave their home unassisted and requires help washing and dressing.

Patients are scored as either eMRCD 5a or 5b.

Use of the NIVO score to select patients will broaden inclusion compared to previous weaning trials, whilst also ensuring optimal risk-assessment. The British Thoracic Society is including the NIVO score in the next national NIV audit, which will help to embed use of the NIVO score into routine practice across the UK.

This interventional randomised controlled trial will compare 2 weaning strategies, standard weaning and accelerated weaning, for patients with low and medium risk NIVO score.

Our standard weaning protocol reflects the current national guideline,[2] advising that time on NIV should be maximised in the first 24 hours and tapered over the following 2 to 3 days, depending on pCO_2 self-ventilating, before being discontinued overnight. We acknowledge that few clinical trials have been performed comparing weaning strategies/protocols in acute NIV, and whilst in some centres there is a very consistent approach to NIV weaning, this is not the case in all. Professor Bourke led the 10-centre validation study for the NIV Outcome score.[9] Duration of NIV treatment was captured; we are therefore uniquely placed to ensure we select centres with a consistent approach (this was true of most, but not all, participating centres).

In regard to the accelerated weaning protocol, the Sellares[7] study trialled 4 hours of unassisted breathing before discontinuation of NIV, and allowed most patients to be successfully weaned. We have considered the strengths and weaknesses of this small RCT, but it provides a published evidence base to support a more robust evaluation of this approach. In our clinical practice, we encounter some patients who strongly dislike acute NIV and ask to discontinue treatment early. We have anecdotally found that in those who are able to manage for at least 4-hours off NIV, an accelerated wean was more likely to succeed. The accelerated weaning protocol, including the 4-hour trial off NIV, was developed informed by both the available trial evidence and our clinical experience. We highlight that our overall outcomes are very favourable: inpatient mortality for COPD requiring NIV = 9.2%[4] compared to 25.1% in the contemporaneous National Confidential Enquiry into Patient Outcome and Death.[8]

It is essential that participating centres confirm that their service will support adherence to the assigned protocol. This reassurance is in place for the recruiting centres, having been confirmed by the respective PI's.

Our recent Patient and Public Involvement (PPI) engagement confirms that patients would welcome a shorter period of NIV treatment, provided this remains safe and effective. This trial design has been developed with support from the Northumbria Lung Research PPI group and representative patients with low and medium risk NIVO score who have received acute NIV treatment. Separately, both patients and clinicians have identified NIV weaning as a research priority.[3] A shorter stay on Critical Care or Respiratory Support Units would reduce NHS costs, with additional savings if overall length of hospital stay is shorter.

The hypothesis is that daily four-hour unsupported breathing trials, with removal of NIV if the patient remains clinically and physiologically stable, will shorten the time to successful wean from NIV, compared to the standard protocol in ECOPD with a low or medium mortality risk.

3. Objectives and Outcome Measures/Endpoints

3.1 Primary aim

To compare time to successful weaning from NIV in ECOPD using an accelerated versus a standard weaning protocol.

3.2 Secondary aims

To compare relapse requiring NIV (defined as recurrent AHRF>48 hours after removal of the ventilator), complications of NIV, respiratory symptoms (breathlessness and sputum clearance), sleep quality, health-related quality of life, readmissions, mortality, and NHS cost and cost-effectiveness between both weaning strategies.

3.3 Primary outcome

Time to successful weaning: duration from the baseline ABG confirming selection criteria are met, to final removal of the ventilator. Weaning will be considered successful when there has been no recurrence of AHRF requiring replacement of NIV within 48 hours of discontinuation of NIV. Recurrent AHRF more than 48 hours after removal of the ventilator will be considered relapse. Death precludes weaning and will be captured in a competing risk analysis.

3.4 Secondary outcomes

1. Relapse requiring NIV (defined as recurrent AHRF>48 hours after removal of ventilator).
2. Total duration of ventilation.
3. Length of hospital stay.
4. NIV complications (incidence and severity).
5. Patient reported outcome measures: Modified Borg dyspnoea scale*; Sputum clearance via visual analogue scale*; Richards-Campbell sleep questionnaire*; Hospital Anxiety and Depression Scale (HADS) pre-discharge; St Georges Respiratory Questionnaire for COPD (SGRQ-C) and EQ-5D-5L days 7, 30 and 90 post-randomisations.
6. Mortality in-hospital and 90-days post-randomisation.
7. Readmissions 30-days post-discharge.
8. Health economic analysis:
    - Costs to the NHS in terms of provision of the interventions (both on a respiratory support unit and a critical care unit) and cost implications of subsequent resource utilisation up to 90 days follow up;
    - Cost utility analysis using EQ-5D-5L quality adjusted life years (QALYs).
9. Responder analysis within the accelerated weaning group to identify predictors of success/failure.

*Day 1 to 5.

4. Trial Design

A multi-centre, open-label, parallel, randomised controlled trial.

Our position is one of equipoise. The randomised controlled trial design will provide a definitive result as to the better outcome for patients: a) a standard wean may provide a longer duration of NIV wean, with lower $PaCO_2$ at discharge, with less relapse and readmissions; or b) an accelerated wean may mean a shorter duration of NIV wean, but with more relapse requiring NIV, and more readmissions.

5. Trial Setting

Patients will be recruited from at least seven secondary care centres across the UK, with different structures of care, to ensure that the results are applicable across the NHS. The centres have been carefully selected, based on current standard weaning time from acute NIV, and with PIs for each site confirming their commitment to adhere to the weaning protocols.

Confirmed recruiting sites are: 1) Northumbria Healthcare NHS Foundation Trust; 2) Newcastle Upon Tyne NHS Foundation Trust; 3) North Tees and Hartlepool NHS Foundation Trust; 4) The Leeds Teaching Hospitals NHS Trust; 5) Royal United Hospitals Bath NHS Foundation Trust; 6) University Hospitals Plymouth NHS Trust; 7) Nottingham University Hospitals NHS Trust; and 8) University Hospitals of Leicester NHS Trust.

Patients requiring NIV are managed on critical care or respiratory support units, and will be identified by daily screening by the usual care team.

6. Participant Eligibility Criteria

The selection criteria identify patients who have received more than 24 hours NIV and have improved sufficiently to consider weaning.

6.1 Inclusion criteria

1. Clinical diagnosis of Exacerbation of Chronic Obstructive Pulmonary Disease*, complicated by acute hypercapnic respiratory failure (pH<7.35 and $PaCO_2$>6.5kPa).

2. Age 35 years or over.

3. Smoking history of 10+ pack years.

4. Low or medium risk Non-Invasive Ventilation (NIV) Outcomes score.

5. Provision of acute NIV for 24 hours or longer.

6. Correction of respiratory acidaemia.

7. Able to tolerate 60 minutes of unsupported breathing, confirmed by arterial blood gas† (ABG). This is the qualifying ABG.

8. PaCO2 <8kPa, or PaCO2 8-9kPa with at least a 20% fall in PaCO2 from pre-NIV baseline value, with pH ≥7.35 on the qualifying blood gas.

9. Participants must be randomised within 24 hours of meeting the weaning criteria (based on the time of the qualifying ABG).

*Confirmation of airflow obstruction is not required (often unavailable on admission). Patients should have 1-year plus history of breathlessness, with or without cough and sputum production, consistent with a diagnosis of COPD.

†Capillary blood gas will be accepted.

6.2 Exclusion criteria

1. Poor tolerance of NIV likely to limit adherence to protocol.
2. Receiving home ventilation on admission, or planned referral for home ventilation on discharge.
3. Inability to provide informed consent.
4. Failure of another organ requiring level 2 or 3 organ support.
5. Clinically significant pulmonary fibrosis.
6. Metastatic Cancer, advanced haematological malignancy, or other serious comorbidities, which may influence survival or decisions about ventilation within the time-frame of the trial (3 months).

We will exclude few patients, and only on objective criteria compromising the validity of the research.

We will assist recruitment and retention of any patients with language or communication barriers. A video covering the full patient information sheet details will aid recruitment and the consent process.

7. Trial Procedures

A schedule of activities is included in this application (appendix 1). All inpatient assessments will be completed on the scheduled day. Assessments within 30 days post-discharge from hospital will be completed within 10 days of the scheduled visit, in the patient's home, outpatient setting, or via telephone. Assessments within 90 days post-randomisation will be completed within 14 days of the scheduled visit, in the patient's home, outpatient setting, or via telephone.

7.1 Recruitment

Patients who will potentially be eligible for the trial (ECOPD with AHRF requiring NIV who have low or medium risk NIVO score), will be provided with a summary patient information sheet (PIS) at initiation of NIV. This basic information about the trial will be available (one side of A4, large font) to support initial discussions between the usual care team and potentially eligible patients. However, patients will not be asked for consent or randomised at the time of acute presentation and initiation of NIV.

At all participating sites, patients who require acute NIV are managed on dedicated units (critical care or respiratory support units).

Recruitment and any facilitators or barriers identified across all sites will be discussed at the monthly trial management group meetings to share best practice. Feedback from trial participants will also be captured, reviewed by our PPI group, and shared with the trial management group and steering committee.

Will we be recording the details of patients who are not eligible for the trial in a screening log: patients with ECOPD requiring acute NIV, who have low or medium risk NIVO score, but are not recruited.

7.1.1 Participant Identification

Patients admitted to critical care and respiratory support units will be identified using the eligibility criteria and approached to discuss the trial by the usual care team at all sites.

Eligibility will be confirmed by the research team, on a source document worksheet, from historic and current, electronic and paper based clinical information.

7.1.2 Screening

Patients will be identified by daily screening on critical care and respiratory support units. We will be seeking consent when patients will still be receiving ventilation for an exacerbation of COPD, and may have only short breaks off the ventilator. The timing of randomisation and allocation to the weaning protocols under investigation is time critical. Patients must be randomised within 24 hours of meeting eligibility criteria. To meet eligibility criteria, patients will be required to have an arterial blood gas taken off NIV (part of usual care), and the blood gas result to be satisfactory to meet eligibility criteria. We will provide education and training to the usual care NIV teams at all centres, and encourage early discussions about the trial with those who are potentially eligible. Once patients meet the physiological and clinical criteria that define the start of the weaning process, and eligibility for randomisation, we will provide full trial information.

7.2 Consent

We have conducted two face to face group meetings with the Northumbria Lung Research PPI group. At the meetings, the consent process, and the content and terminology used in the Patient Information Sheet (PIS) was discussed. As a result, depending on patient preference, the patient can choose:

a) to read the full PIS themselves;
b) listen to the PIS being read to them; or
c) watch a video recording of the full PIS being read.

Only members of the usual care team will approach patients in the first instance to provide the patient information and answer any initial questions from the potential participants. With the patient's agreement, the research team will be available to discuss the trial and answer any additional questions or concerns arising. Written consent will be taken by members of the research team. Interpreters will also be available when possible if required. Consent will only be taken by individuals who have the appropriate GCP training, before any trial procedures or assessments are undertaken. There is a named Principle Investigator for each site who retains overall responsibility for the conduct of research at their site, including taking informed consent from participants.

Informed consent will be taken and then randomisation performed, only once patients have improved sufficiently to meet criteria for weaning from NIV (defined in the inclusion criteria). Only a minority of patients experience carbon dioxide narcosis or delirium with hypercapnic respiratory failure; such patients would only be given information once this had resolved.

We have allocated an average of 60 minutes for the consent process, in recognition that patients will still be receiving acute NIV. All participants will be aged 35 years or older.

7.3 The Randomisation Scheme

Randomisation will be on a 1:1 basis between the two treatment strategies, performed independently using minimisation to ensure groups are balanced for:

a) NIV Outcomes score: low or medium risk
b) Site
c) HCO_3-: <28 or ≥28

d) pH: <7.18 or ≥7.18
e) previous NIV: yes or no

7.3.1 Method of implementing the randomisation/allocation sequence

An independent electronic randomisation service will be set up (sealedenvelope.com). Each site will have access to the randomisation service, the system will provide an immediate allocation, and the sponsor site (Northumbria Healthcare) will receive new randomisation alerts (including randomisation number and site) via email. Access to the randomisation service will be 24 hours a day, 365 days a year for the duration of recruitment.

7.4 Blinding

As this is an interventional RCT comparing two weaning strategies, usual care clinicians and participants cannot be blinded to the trial. However, patient identifiable data will not be visible to the lead site (Northumbria Healthcare). All data collected will be anonymised to the statistician and health economist for the purpose of analysis.

7.5 Emergency unblinding

Not applicable.

7.6 Baseline Data

A separate source document worksheet (collecting the following data) and manual will be provided to all participating sites. The case report form is electronic (REDCap). Key data are shown in Table 1.

Table 1. Key data for source document worksheet.

Category	**Data**
Patient demographics	Name; NHS number. Hospital number; Gender; Age; Ethnicity; Multiple index of deprivation decile; Recruiting Site, Participant identifier generated at randomisation.
COPD diagnosis	Previous spirometry; Discharge spirometry (if required); Exacerbation history; NIV history; LTOT prescription; Covid-19 history; Previous lung surgery.
Admission indices	Date and time of arrival at hospital; Date and time clinician contacted to start NIV; Date and time NIV mask applied; Where NIV started and continued; Date and time patient moved to dedicated NIV area; Observations on arrival; Chest x-ray changes; ECG; Date and time of discharge from hospital; Mortality.
Risk stratification	NIV Outcomes score; eMRCD; DECAF; Apache II score; Charlson index.
Blood results	Full blood count indices.
Past Medical History	Various cardiovascular, respiratory and immunodeficiency variables.
Medication history	Bronchodilators, cardiovascular and antibiotic medications.
Social history	Home circumstances; smoking history; employment; Rockwood clinical frailty score; baseline function.
Blood gases	pH; $PaCO_2$; PaO_2; HCO_3-; BE; SaO_2.
NIV data	IPAP; EPAP/PEEP/CPAP; PS; Back up rate; Respiratory rate; Tidal volumes; Minute ventilation; Patient trigger, Interface used, Weaning plan; Complications; Date and time NIV removed; Relapse.

Observations	SpO2; Blood pressure; Heart rate; Temperature.
Randomisation allocation	Standard weaning protocol; accelerated weaning protocol.
Patient reported outcome measures	Borg breathless scale; Phlegm visual analogue scale; Richards-Campbell sleep questionnaire; Hospital Anxiety and Depression scale; St Georges Respiratory Questionnaire (COPD); EQ-5D-5L.
Trial outcomes	Readmissions; Mortality; Health economics (GP attendances; Emergency Department attendances; Readmission to hospital).

Respiratory Rate: **count** the number of breaths observed in 1 minute.

7.7 Trial Assessments

The following assessments will be completed during the acute phase of the trial.

Following confirmation of inclusion/exclusion criteria and informed consent, patients will undergo baseline assessment and randomisation. Baseline assessment will include sociodemographic details, full medical history, COPD history (confirmation of diagnosis and severity), details of index admission and NIV management.

On days 1 to 5, patients will be asked to complete the following assessments:

1) score their level of breathlessness on the Modified Borg breathless scale (score 0 not breathless at all to 10 maximal breathlessness);

2) their ease of sputum clearance on a visual analogue scale (score 0 very easy to 10 very difficult); and

3) their level of sleep quality via the Richards-Campbell questionnaire.

NIV status and weaning data will be recorded daily during admission.

Healthcare resource utilisation costs and mortality will be monitored during the in-hospital stay.

Spirometry will be performed pre-discharge if no previous spirometry confirming airflow obstruction is available.

7.8 Long-term Follow-up Assessments

The following assessments will be completed at set timepoints during the follow up phase of the trial.

- 7 days post-randomisation (within 10 days of the scheduled assessment): Hospital Anxiety and Depression Scale (HADS); St George's Respiratory Questionnaire for COPD (SGRQ-C); and EQ-5D-5L.

- 30 days post randomisation: Healthcare resource utilisation costs; SGRQ-C; EQ-5D-5L (within 10 days of the scheduled assessment); spirometry (30 days since last intercurrent exacerbation).

- 30 days post discharge: Readmissions.

- 90 days post randomisation: Healthcare resource utilisation costs; Mortality.
- 90 days post randomisation (within 14 days of the scheduled assessments): SGRQ-C and EQ-5D-5L

Informed consent will be reconfirmed at each assessment with participants pre-discharge from hospital, and at 30 and 90-days post-randomisation.

7.9 Qualitative Assessments

Not applicable.

7.10 Withdrawal Criteria

Participants are free to withdraw from the trial at any time without giving explanation. Date and time of withdrawal will be recorded on the source document worksheet by the usual care team. In this instance, there will be no further collection of patient reported outcome measures or spirometry testing, but we will continue to collect healthcare utilisation data and mortality until 90 days post randomisation (unless the participant states otherwise). Participants who have withdrawn from the trial after meeting the primary outcome (fully weaned from NIV including no relapse within 48 hours of removal of NIV) will not be replaced.

7.11 Storage and Analysis of Clinical Samples.

There is no requirement to store any clinical samples.

Blood gas samples will be analysed and disposed of as per local Trust guidelines.

7.12 End of the Trial

The end of the recruitment phase will be when 164 patients are recruited. The follow up phase will end 90 days after the last patient is randomised.

8. Trial Treatments

8.1 Control Arm: Standard weaning

During weaning, arterial blood gases are performed at the end of a period off NIV to help direct the duration of subsequent breaks from NIV. ABG's can be performed at each stage of the standard (stepwise) weaning protocol, and if satisfactory, the participant can receive progressively longer intervals without NIV. Typically, at least one ABG is performed daily to determine the amount of time off NIV each day. An ABG may be omitted, if a justified clinical improvement is observed that allows progress to the next weaning step. More than one weaning step may happen in a day. Once the patient has managed a full day without support, they receive a final night on NIV. When NIV is discontinued the following morning, $PtcCO_2$ monitoring is applied to the patient for 12 hours. Provided the patient remains stable, NIV will not be replaced.

The weaning time endpoint is the date and time that the NIV mask is removed from the patient's face for the last time (provided NIV does not need to be recommenced within 48 hours). Perform an ABG within 4 to 24 hours after the NIV mask is removed for the final time.

Some centres include a period of standby NIV after weaning, when the ventilator is kept at the bedside, with a subsequent ABG after 24 hours off NIV to confirm safe removal of the ventilator. This is entirely acceptable, but is not included in the weaning time.

Medical treatment will be optimised before and during NIV treatment. NIV will be delivered in spontaneous/timed pressure support mode. Supplementary oxygen will be strictly titrated to maintain SpO_2 88-92% when on and off NIV (ideally controlled oxygen off NIV).

Standard Weaning

USUAL CARE	**Pre-NIV**: arterial or capillary blood gas required showing pH<7.35, $PaCO_2$>6.5kPa ("NIV-decision blood gas" for NIVO score and minimisation criteria). Provide brief participant information sheet. **Confirm ready to wean**: After 24+ hours of NIV, 60-minute trial of unsupported breathing with arterial or capillary blood gas at the end ("qualifying blood gas" for inclusion criteria & randomisation). **Recommence NIV** at the end of 60-minute unsupported breathing trial.

Recruit: confirm all eligibility criteria met, provide full participant information and obtain consent.

Randomisation

↓

Step 1

Depending on clinical response, continue 30 to 60 minutes breaks off NIV or progress directly to step 2

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Step 2

If arterial blood gas* satisfactory, extend breaks off NIV to 2 to 4 hours

↓

Step 3

If arterial blood gas* satisfactory, extend breaks off NIV to 4 to 6 hours

↓

Step 4

If arterial blood gas* satisfactory, remain off NIV all day, on NIV overnight

↓

Step 5

NIV discontinued in the morning, with $PtcCO_2$ monitoring for 12 hours. Provided the patient remains stable, NIV is not replaced.

Perform blood gas at end of standard weaning (4 to 24 hours after removal of NIV mask).

Some centres include a period of standby NIV after weaning, when the ventilator is kept at the bedside. This is entirely acceptable, but is not included in the weaning time.

*During weaning, arterial blood gases are performed at the end of a period off NIV to help direct the duration of subsequent breaks from NIV. Typically, at least one ABG is performed daily. An ABG may be omitted, if a justified clinical improvement is observed that allows progress to the next weaning step.

More than one step may happen in a day. Target SpO_2 88-92% at all times when on and off NIV.

8.2 Intervention Arm: Accelerated weaning

The accelerated weaning protocol involves a daily 4-hour unsupported breathing trial with transcutaneous carbon dioxide tension ($PtcCO_2$) monitoring throughout, and an ABG taken at the end of the 4-hour period.

Following randomisation, $PtcCO_2$ monitoring is applied to the patient and sufficient time allowed to stabilise the trend of carbon dioxide (up to 20 minutes). Physiological measurements are recorded (RR, SpO_2, FiO_2, $PtcCO_2$). The NIV mask is then removed from the patient (start of the 4-hour weaning trial), and once the patient is stable off NIV with oxygen titrated to SpO_2 88-92%, the physiological measurements are repeated (10 to 30 minutes off NIV). If there are no signs of substantial clinical deterioration, and the $PtcCO_2$ does not rise by >1kPa, then the physiological measurements will be repeated at 4 hours after NIV removal, and an ABG taken (end of the 4-hour weaning trial).

For the outcome of the ABG:

pH≥7.35, leave the patient off NIV, continue $PtcCO_2$ monitoring for a further 8 hours. If there are no signs of substantial clinical deterioration, and the $PtcCO_2$ does not rise by >1kPa, then the ventilator and $PtcCO_2$ monitoring can be removed from the bed space.

pH<7.35, replace the NIV mask on the patient and recommence ventilation, and repeat a 4-hour weaning trial the next day. 4-hour weaning trials are completed daily until successful.

An ABG should be performed during the 4-hour trial after NIV removal or during the 8-hour monitoring after a successful ABG if: 1) $PtcCO_2$ rises by >1kPa, or 2) there is clinical concern, but any transient reasons for deterioration (e.g. coughing, mucus plugging) should be addressed first.

The weaning time endpoint is the date and time that the ABG is taken that confirms the first successful 4 hour weaning trial (provided NIV does not need to be recommenced within 48 hours).

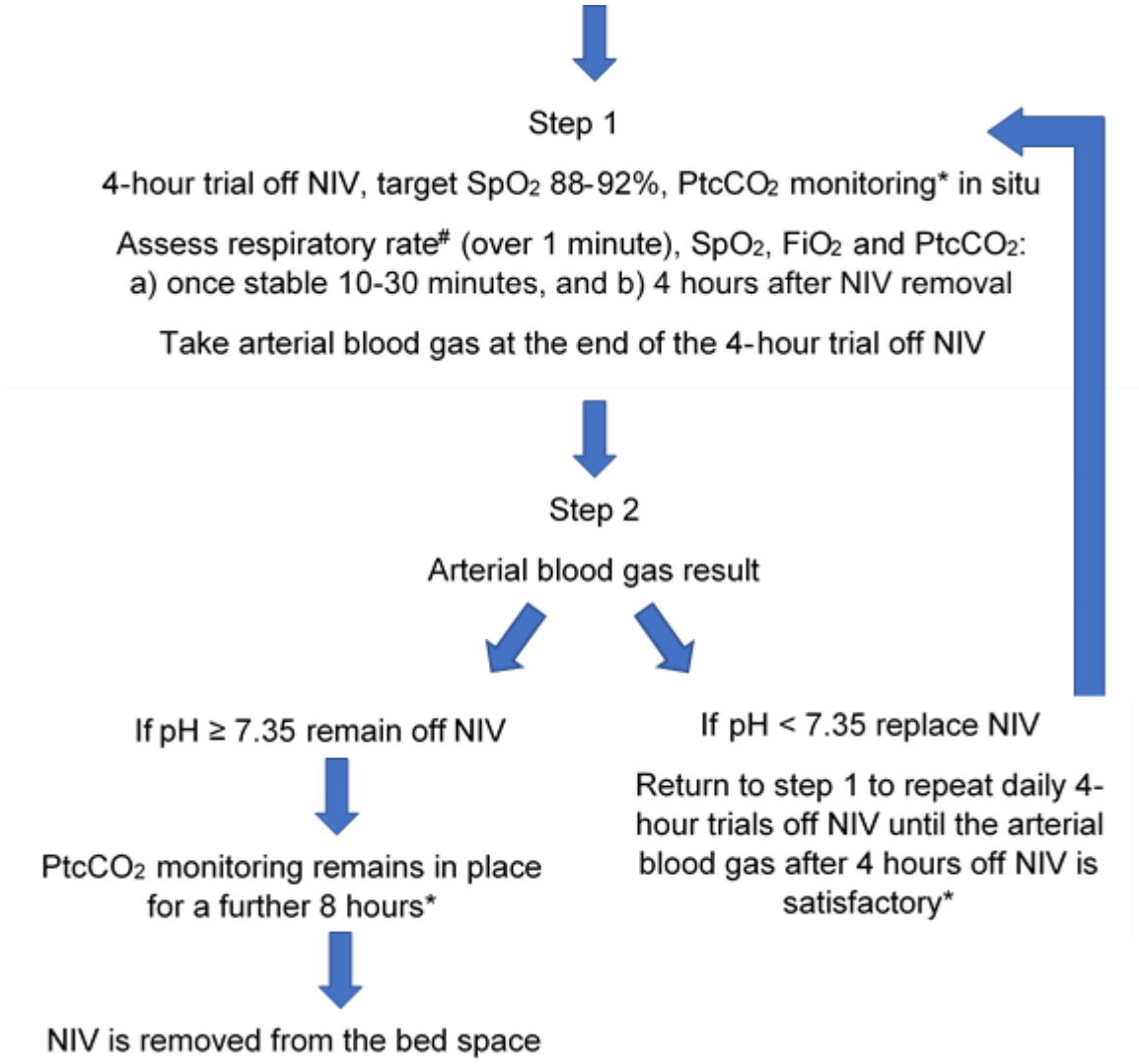
Medical treatment will be optimised before and during NIV treatment. NIV will be delivered in spontaneous/timed pressure support mode. Supplementary oxygen will be strictly titrated to maintain SpO_2 88-92% when on and off NIV (ideally controlled oxygen off NIV).

Accelerated Weaning

USUAL CARE	**Pre-NIV**: arterial or capillary blood gas required showing pH<7.35, $PaCO_2$>6.5kPa ("NIV-decision blood gas" for NIVO score and minimisation criteria). Provide brief participant information sheet. **Confirm ready to wean**: After 24+ hours of NIV, 60-minute trial of unsupported breathing with arterial or capillary blood gas at the end ("qualifying blood gas" for inclusion criteria & randomisation). **Recommence NIV** at the end of 60-minute unsupported breathing trial.

Recruit: confirm all eligibility criteria met, provide full participant information and obtain consent.

Randomisation



*Repeat ABG if there is a substantial clinical deterioration or an increase in $PtcCO_2$>1 kPa from the start of each period (4 hr trial post NIV removal, 8 hr monitoring post NIV discontinuation), that persists despite correction of any transient reasons for deterioration (e.g. coughing, mucus plugging). The presence or absence of other clinical features that would independently trigger a repeat ABG must be documented (oxygen desaturation, raised respiratory rate, symptoms etc).

#Respiratory rate should be observed and counted over 1 minute.

Step 1 and 2 happens same day. Target SpO_2 88-92% at all times when on and off NIV.

9. Adverse Event and Serious Adverse Event Reporting

Adverse events and serious advert event report forms have been developed specifically for the Trial. All serious adverse events will be reported to the Chief Investigator and investigated within 1 week of their occurrence.

The following definitions will be used:

Adverse event (AE)

An AE is any untoward medical occurrence in a participant whilst taking part in the trial; which does not necessarily have to have a causal relationship with the assessment being undertaken.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the assessment, whether or not considered related to the diagnosis and treatment.

Serious adverse event (SAE)

An SAE is an adverse event that:

- Results in death
- Is life-threatening, or places the participant at immediate risk of death from the events as it occurred
- Requires or prolongs hospitalisation
- Causes persistent or significant disability or incapacity
- Is another condition which investigators judge to represent significant hazards

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Resulted in a permanent impairment of a body structure or a body function
- Required in-patient hospitalisation or prolongation of existing hospitalisation
- Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Exacerbation of COPD (ECOPD)
ECOPD is a clinical diagnosis made when a patient with COPD experiences a sustained (e.g. 48 h+) increase in cough, sputum production, and/or dyspnoea. It commonly occurs in the cohort of patients under investigation in this study, who are at high risk of developing an ECOPD and indeed 20% will be readmitted to hospital within 28 days of being discharged (when the primary reason for admission was ECOPD). The Chief Investigator and Principal Investigator therefore deem ECOPD to be an expected AE and SAE. In the event of a participant developing an ECOPD, this will be captured as an outcome, but not reported as an AE.

In the NIVO study, of the patients who survived to discharge 51.2% were readmitted within 90 days from discharge. This timeframe is very close to the follow up period of this trial. The Chief Investigator, with the support of the Sponsor, therefore deems that ECOPD leading to readmission or death are expected events and will be reported to the DMC, TSC and sponsor, but not regarded as SAE's to be reported to REC or HRA.

Death during the index admission will be reported as a SAE to the DMC, TSC, sponsor, REC and HRA.

Reporting of AEs

All AE's occurring during the study observed by the investigator or reported by the participant, whether or not attributed to the assessments being made will be recorded on the source document worksheet as specified in the protocol. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to assessments and/or intervention, action taken and information should be provided as necessary.

Reporting procedure for all SAEs

All SAEs need to be reported to the Chief Investigator and Host Organisation (Northumbria Healthcare) within one working day of the investigator team becoming aware of them. Reports of related and unexpected SAEs will be submitted to Research Ethics within 15 days of the Chief Investigator becoming aware of the event, using the Northumbria Healthcare SAE report form.

All reporting to Northumbria Healthcare R&D will be by email (ResearchAndDevelopment@northumbria-healthcare.nhs.uk) giving as much information about the incident as possible, and should be signed by the PI or Co-investigator.

Risks and discomforts

It will be necessary to perform arterial blood gas analysis, as would be part of routine clinical care. This may be temporarily uncomfortable for the patient for the duration of the procedure. All staff performing arterial blood gases will be trained to do so according to local policy.

10. Statistics and Data Analysis

10.1 Sample size calculation

The sample size has been estimated using patient-level data from the 10-centre validation cohort within our NIV Outcomes study.

We selected patients meeting the inclusion criteria for the proposed RCT, and derived weaning time as defined in the protocol. Two sites were evidently not adhering to the standard weaning protocol and therefore were excluded. This provides the best available data on weaning time within standard care in the proposed RCT (median t=2.71 days).

The total study duration from first subject first visit to last subject last visit is 27 months. The cumulative incidence rate for the competing risk of death is the same for both treatment strategies, which is 5.4% at the time of interest, t=2.71 days or 65 hours. This chosen time corresponds to the cumulative incidence rate of the 50% for the event of interest (successful weaning) in standard care. We assume that weaning time might be achieved 1 day (24

hours) earlier in the accelerated weaning arm, thus, to reduce the median weaning time from 2.71 to 1.71 days the incidence rate in the new treatment must be equal to 0.667.

The other important statistical indices we use here are the critical alpha 5%, power 80%, two-sided, and we assume the sample size in both groups are the same. The sample size we obtained was 164 (82 for each group with expected number of events in the new treatment is 69 and in the standard treatment is 67). All calculations were done in nQuery 8.7. The total sample size reported includes 10% attrition or drop out.

10.2 Planned Recruitment Rate

Participating sites have estimated recruitment based on prior activity levels. Anticipated rate of recruitment: 8 patients per month (across 7 centres). Anticipated duration of recruitment: 24 months.

The physical measures to limit spread of COVID-19 were also associated with a reduction in admissions for ECOPD, primarily due to a reduction in spread of other respiratory pathogens and consequent exacerbations, rather than fear of attending hospital. It is unclear whether exacerbations will fully return to previous levels; some people with severe COPD may continue to take precautions. We will assess admission rates for ECOPD requiring NIV in the run up to and during the trial. Individual site recruitment to target will be closely monitored. If there are concerns we will seek to expand sites at an early stage. We will be recruiting patients whilst acutely unwell. Fortunately, our PPI work showed most would consider participation. We have detailed additional measures to support recruitment (including early identification, multiple methods of providing information, and support to overcome communication barriers, including poor health literacy).

10.3 Statistical Analysis Plan

The statistical plan has been designed by the Research Design Service and the co-applicant Statistician.

10.3.1 Summary of baseline data and flow of patients

We will assess baseline comparability of the randomised groups, including but not limited to the variables listed in Table 2.

Table 2. Baseline variables and reporting methods.

Variable	**Form of data**	**Reporting method**
Age (years)	Continuous	Mean (SD)
Sex (male/female)	Nominal	%
Smoking burden (pack years)	Continuous	Median (IQR)
FEV1 (% predicted)	Continuous	Mean (SD)
eMRCD	Ordinal	Median (IQR)
Long-term oxygen therapy (yes/no)	Nominal	%
Previous ECOPD requiring admission (yes/no)	Nominal	%
Previous admission requiring NIV (yes/no)	Nominal	%
Pre-NIV pH	Continuous	Median (IQR)
Pre-NIV $PaCO_2$	Continuous	Median (IQR)
Pre-NIV HCO_3-	Continuous	Mean (SD)
Pre-randomisation pH	Continuous	Median (IQR)
Pre-randomisation $PaCO_2$	Continuous	Median (IQR)
Pre-randomisation HCO_3-	Continuous	Mean (SD)
PEARL	Ordinal	Median (IQR)

We will produce a consort flow diagram to detail patients not eligible for the trial.

10.3.2 Primary outcomes analysis

Primary outcome: the competing risks (CR) approach will be used to compute cumulative incidence of successful weaning as the first event of interest, and death as a competing risk. The Fine-Gray subdistribution hazard model will be fitted to compare both groups while adjusting for covariates (hospital site; NIV Outcomes score; and independent predictors of weaning time identified in a post-hoc analysis of the equivalent subpopulation within the NIV Outcomes study).

10.3.3 Secondary outcome analysis

For all outcomes (both primary and secondary) we will present the characteristics, including those stratified by the weaning strategies. We will describe all baseline characteristics, follow-up measurements using suitable measures of tendencies: means and median with the associated standard deviation, 95% confidence interval and interquartile ranges for continuous variables and frequency and proportions for categorical variables (including binary variables). We will use Chi-Square test (or Fisher's Exact test in case of small number of observations) if the variable is categorical and will use t-test if the variable is continuous. For variables that are not parametric we will use Mann-Whitney U test. We will use the critical alpha 5% (thus p -value < 0.05 will be considered statistically significant) and we will also present the 95% confidence interval. Analyses will be performed by intention to treat, with secondary analyses of primary and secondary outcome based on protocol adherence. All analyses will be done in R[15] and SPSS.[16]

All baseline patient characteristics and outcomes will be included in the imputation mode. Mean change in quality of life over 90 days (SGRQ-C, EQ5D5L) from baseline will be calculated. In-hospital and 90-day mortality, and readmission within 30-days: time from discharge to death and time to readmission will be analysed using a Cox proportional hazards regression model, adjusted for covariates. For this analysis, no interaction between interventions will be assumed. Analysis will be two-sided at 5% level. We will also report the model performance by C-statistic. A sensitivity analysis will be performed with the log-rank test stratified by the centre. As we are only capturing readmission within 30 days, we will compare the proportion adjusted for the covariates (In-hospital mortality=NIVO; Readmission=PEARL: previous admission, extended MRC Dyspnoea scale, age, left and right heart failure).

10.4 Subgroup analyses

Any subgroup analyses will be post-hoc. Based on specified hypothesis the participants will be sub grouped with respect to its baseline characteristics.

10.5 Adjusted analysis

We intend to perform a responder analysis within the accelerated weaning group to identify predictors of weaning success/failure.

10.6 Interim analysis and criteria for premature termination of the trial

No routine interim analysis is planned. However, if a substantial difference in survival arises, the DMC will consider performing an interim survival analysis. Decisions on premature termination of the trial will be taken in accordance with the Haybittle-Peto boundary,

considering a p-value of less than 0.001 as "significant" and the likely impact on future practice. The DMC are not solely bound by this recommendation in regard to survival alone, but will undertake an holistic assessment of the trial and report to the TSC.

10.7 Participant population

Participants will be aged 35 years and over, admitted to hospital with exacerbation of COPD. They will have been treated with NIV for AHRF, have a low or medium risk NIV Outcomes score, and have met the eligibility criteria to be randomised and wean from ventilation. Patients will not be excluded for any equality and diversity reasons, (e.g. ethnic background, socioeconomic status), and we will support recruitment of people from diverse backgrounds (e.g. those with language barriers). We will monitor recruitment at individual sites, and discuss any problems with recruitment at Trial Management Group meetings.

10.8 Procedure(s) to account for loss to follow-up or missing

We consider the tolerable level of loss to follow-up or missing is less than 10%. Every effort will be made to minimise missing baseline and outcome data (data verification and validation). Standard approaches will be used to detect patterns in missing data. The level and pattern of the missing data in the baseline variables and outcomes will be established by forming appropriate tables and the likely causes of any missing data will be investigated. This information will be used to determine whether the level and type of missing data has the potential to introduce bias into the analysis results for the proposed statistical methods, or substantially reduce the precision of estimates related to treatment effects. Data quality will be closely monitored and we will perform on site data verification and validation for all outcome measures and expect missing data rates to be low. In case of substantive proportion of missing data, a multiple imputation will be performed, with missing data assumed to be missing at random, to create at least five data sets (depending on missing data per sites) using the chained equation (MICE Algorithm). In addition, we will conduct sensitivity analysis to examine the robustness of the findings (hypothesis testing or estimates).

10.9 Economic evaluation

An embedded economic evaluation will estimate the cost effectiveness (CE) and cost utility (CU) of the accelerated weaning protocol in comparison with standard care for NIV weaning from an NHS perspective. Costs of the protocols, resource use and associated costs will be estimated during the index admission for ECOPD up until discharge from electronic hospital records, and will include critical care, respiratory support unit and general ward length of stay (LOS). In addition, NHS resource use (primary, secondary and community care) and associated costs will be captured up until 90 days post-randomisation, triangulated from a number of sources. At discharge, participants will be given a heath resource diary to record events related to any COPD and non-COPD associated treatment they receive during the study. The diary is divided into four sections: (i) GP resources; (ii) hospital outpatient resources; (iii) accident and emergency (A&E) resources; and (iv) hospital admission resource used. Entries will include who they saw, where they saw them, whether it was emergency or routine, the reason for any A&E visit and length of any hospital stay.

Participants will be contacted via telephone by a researcher at 30 and 90 days post randomisation to complete a proforma which captures use of NHS services detailed in patient diaries from discharge. These estimates will be triangulated with electronic NHS records to check for accuracy. Appropriate unit costs will be applied to the NHS resources used by each trial participant. Similarly, the costs of the intervention will be estimated by

calculating the average cost of providing the intervention to patients. EQ-5D -5L QALYs will be estimated using the area under the curve approach and will be adjusted by time. Cost and effectiveness (utility) will be analysed as intention to treat and missing data will be imputed using multiple imputation. In the deterministic analysis, mean values of cost and effectiveness (utility), derived from generalized linear model adjusting for potential confounders, will be used as a representative value for calculating ICER (incremental cost-effectiveness ratio).

Uncertainty around estimates of CE and CU will be explored using cost effectiveness/utility acceptability curves (CEACs), which express uncertainty of outcome as a function of willingness to pay for a unit of outcome.

We will utilise findings from the economic evaluation and the evidence-base to provide a return on investment tool that organisations can utilise to assess value for money within local contexts; ultimately strengthening the alignment between data analysis and decision-making processes. The return on investment is the benefit minus the cost expressed as a proportion of the cost. This spreadsheet-based toolkit will estimate the costs and consequences of accelerated weaning according to local characteristics and assumptions, such as prevalence of disease and anticipated demand for the intervention.

11. Data Management

11.1 Data collection tools and source document identification

Data for each participant will be collected on a source document worksheet designed for the trial.

11.2 Data handling and record keeping

All study data will be entered onto a secure (N3 network with encryption) online database (REDCap) with integral data validation functionality. Trial participants will be identified by a unique trial specific participant code in the database, so that name and identifying data will be blinded to the statistician and health economist. On site data validation will be performed for all outcome indices for each participant. The database will have a security system to protect against unauthorised access and levels of access for sites, and scheduled weekly data back up, so that data is protected. We will maintain an audit trail of all data changes, to ensure that no data is deleted.

All study documents will be stored safely in confidential conditions at site. Personal data will be securely destroyed on completion of all data queries and database lock. Research data generated by the trial and its process evaluation will be stored for 3 years.

Data will be handled and stored in accordance with the 2018 General Data Protection Regulation (GDPR).

Professor Stephen Bourke and Karen Brewin are responsible for data collection, recording and quality.

11.3 Access to Data

Direct access will be granted to the CI and PI at the host institution (Northumbria Healthcare) for monitoring and/or audit of the study to ensure compliance with regulations.

11.4 Archiving

Each site will be responsible for storing and archiving their own study data. Archiving will be maintained for a minimum of 3 years after completion of the trial.

12. Monitoring, Audit and Inspection

The Data Monitoring Committee (DMC) will report to the Trial Steering Committee (TSC). The TSC will include a patient representative. Meetings will occur 6-12 monthly, with independent Chairs and membership in line with NIHR guidance. The Trial Management Group, chaired by the CI, will meet monthly.

Remote and on-site data verification and validation, including participant eligibility and all primary and secondary outcome data, will be performed. The CI reserves the right to review all processes at all sites. Processes reviewed can relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection.

Sites will be expected to assist the sponsor in monitoring the trial. This will include hosting site visits, providing information for remote monitoring or data validation or verification, or putting procedures in place to monitor the trial internally.

Site monitoring visits will include an early initial visit after participant recruitment, and subsequently scheduled every 6 – 12 months using a risk-based approach that focuses, for example, on sites that have the highest enrolment rates, large numbers of withdrawals, or atypical (low or high) numbers of reported adverse events.

13. Ethical and Regulatory Considerations

13.1 Research Ethics Committee (REC) Review and Reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. GP information letters.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (note that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites).

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

It is the Chief Investigator’s responsibility to produce the annual reports as required.

The Chief Investigator will notify the REC of the end of the trial.

If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

13.2 Peer Review

The protocol has been reviewed by 2 independent experts who will chair the TSC and DMC. The trial design has also been through an RfPB application process, during which it has been reviewed by a number of experts assessing research proposals.

13.3 Patient and Public Involvement

We have sought the views of patients with COPD requiring NIV on the planned research, including: a) the importance of the clinical question; b) the trial design and burden of the assessments; and c) willingness to participate. Patients have found the assessments manageable, and have contributed to layout design, instructions and terminology used on the assessments.

The Northumbria Lung Research PPI COPD Group (NLRPG) have met twice in person to review this trial, the assessments required and all patient-facing documents. They will continue to meet regularly to discuss this trial, supported by our PPI lead, who will attend and feedback to the TMG, and assist the PPI group with dissemination of results. In response to feedback from the NLRPG, we will produce a video of a clinician reading the full patient information sheet as an alternative option of providing information about the study prior to consent. The NLRPG have also provided input into layout of modifiable assessments used in the trial design and have supported the importance of including the assessments asked during the acute phase. In particular, assessing quality of sleep as an outcome was highly important to the group.

In addition, real-time patient experience capture (following primary outcome) will inform our research. PPI activities will include: a) co-design of a PPI impact log to capture and evaluate the impact of PPI activities; b) ensuring study materials are appropriate for all potential participants by removing any equality, diversity and inclusion barriers; c) measurement of patient experience and thematic analysis of results for integration into trial results; and d) co-creation of a dissemination plan, and dissemination of results and PPI impact results to trial participants and people with COPD. Our patient research experience surveys to inform future PPI and trial conduct.

13.4 Regulatory Compliance

The trial will not commence until a favourable REC opinion and HRA approval have been obtained. The anticipated start date for recruitment is 1st September 2022.

13.5 Protocol Compliance

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be reported to the CI, documented in a protocol deviation form, and filed in the study master file.

13.6 Notification of Serious Breaches to GCP and/or the Protocol

The CI will be notified immediately of any case where the above definition applies during the trial conduct phase.

13.7 Data Protection and Patient Confidentiality

Participant's personal identifying information will be replaced with an unrelated sequence of characters, with the data and the linking code secured in separate locations. Access to data will be limited to a need only basis. All electronic data will be transferred via the secure database, stored for at least 3 years after the end of the trial, and owned by the CI and R&D department (Northumbria Healthcare).

13.8 Financial and other competing interests for the Chief Investigator, PIs at each Site and Committee members for the overall Trial Management

Funding has been provided independently by NIHR (RfPB).

13.9 Indemnity

Northumbria Healthcare NHS Trust has liability for clinical negligence. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts for potential liability in respect of negligent harm arising from the conduct of the trial.
As Sponsor, Northumbria Healthcare NHS Foundation Trust will provide indemnity in respect of potential liability and negligent harm arising from trial management.
Indemnity in respect of potential liability arising from negligent harm related to trial design is provided by Northumbria Healthcare NHS Foundation Trust.
This is a non-commercial trial and therefore there are no arrangements for non-negligent compensation.

13.10 Amendments

Following Sponsor approval, the protocol, informed consent form, and participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

All amendments must be discussed with the Chief Investigator, and an amendment history will be recorded. The most up to date protocol version will be available to all sites.

13.11 Post Trial Care

The CI will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice, and with the principles of the Declaration of Helsinki.

13.12 Access to the Final Trial Dataset

The CI, Host Organisation, Statistician and Health Economist will have access to the full dataset, for the duration of the trial.

14. Dissemination Policy

14.1 Dissemination Policy

At trial completion, and with the PPI representatives, we will facilitate dissemination of the results to people with COPD. Results will be fully anonymised and shared with participants at all participating hospitals, and presented at conferences, and published in medical journals. We will engage the relevant British Thoracic Society Specialist Advisory Groups, British Lung Foundation (reaching people with COPD) and the National Institute for Health and Care Excellence to share the impact of the study.

This trial is comparing two weaning protocols, 'standard' weaning and 'accelerated' weaning using the NIVO score for risk stratification. We have developed the NIVO score and have already made it freely available for clinicians to use without restriction. The weaning protocols will also be made free to use for all clinicians without restriction.
We will accept and review requests for data sharing. Data ownership remains with Northumbria Healthcare NHS Foundation Trust. Data sharing will be considered from 6 months after publication of the final project, and data will be shared in a fully anonymised form. Any concerns about data sharing would be discussed with the Trial Steering Committee.

14.2 Authorship Eligibility Guidelines and any intended use of professional writers

The CI and Host Organisation (Northumbria Healthcare) will be writing manuscripts, abstracts, press releases and any other publications arising from the study. Study investigators will acknowledge that the study was funded by NIHR RfPB in any publications or presentations arising from this study. Authorship will be determined in accordance with the International Committee of Medical Journal Editors guidelines and other contributors will be acknowledged.

15. References

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16. Appendices

Appendix 1: Schedule of Activities

Appendix 1: Schedule of Activities

Schedule of Activities	Screening	Day 1*	Day 2 to 5	Pre-discharge	In-hospital stay	7 days post-randomisation	30 days post-randomisation	30 days post-discharge	90 days post-randomisation
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Demographic data	X								
Past Medical History	X								
COPD: diagnosis and severity	X								
Index admission and NIV details	X								
Modified Borg dyspnoea (breathlessness) scale		X	X						
Sputum clearance		X	X						
Richards-Campbell sleep questionnaire		X	X						
NIV status and weaning data		X	X		X				
Randomisation		X							
Spirometry				X[#]			X		
Re-confirm consent				X			X		X
Hospital anxiety and depression scale						X			
St Georges respiratory questionnaire (COPD)						X	X		X
EQ-5D-5L (health-related quality of life)						X	X		X
Healthcare utilisation cost							X		X
Mortality					X				X
Readmissions								X	