Statistical Analysis
and
Health Economics Analysis Plan
for the NIVOW RCT

Non-**I**nvasive **V**entilation **O**utcomes
score-directed **W**eaning
(**NIVOW**)

Contents

Abbreviations

NIVOW – Non-Invasive Ventilation Outcomes score-directed Weaning

NIV – Non-invasive ventilation

ECOPD – Exacerbations of Chronic Obstructive Pulmonary Disease

NHS – National Health Service

AHRF – Acute Hypercapnic respiratory failure

ABG – Arterial Blood Gas

HADS – Hospital Anxiety and Depression Scale

SGRQ-C – St Georges Respiratory Questionnaire for COPD

RCT – Randomised Control Trial

CRF – Case Report Form

DMC – Data Monitoring Committee

TSC – Trial Steering Committee

CI – Chief Investigator

CONSORT – Consolidated Standards of Reporting Trials

ITT – Intention to treat

IQR – Interquartile range

SD – Standard Deviation

CR – Competing risks

MRC – Medical Research Council

QALY – Quality adjusted life year

ICER – Incremental Cost Effectiveness Ratio

NICE – National Institute for Health and Care Excellence

CEAC – Cost-Effectiveness Acceptability Curve

PSSRU – Personal Social Services Research Unit

COPD – Chronic Obstructive Pulmonary Disease

MICE – Multiple imputation chain equations

SE – Standard Error

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1 Introduction

This document details the proposed presentation and analysis for the main paper reporting the results from the multicentre randomised control trial of Non-Invasive Ventilation Outcomes score-directed Weaning (NIVOW). NIVOW aims to investigate standard versus accelerated weaning from non-invasive ventilation (NIV) in exacerbations of chronic obstructive pulmonary disease with a low or medium risk NIV outcomes score.

The results reported in this paper will follow the strategy set out here, which adheres to the guidelines for the content of a statistical analysis plan. Any subsequent analyses of a more exploratory nature will not be bound by this strategy and will be detailed in a separate analysis plan.

Suggestions for subsequent analyses by oversight committees, journal editors or referees will be considered carefully in line with the principles of this analysis plan.

Any deviations from the statistical analysis plan will be described and justified in the final report to the funder. The analysis will be carried out by identified, appropriately qualified, and experienced statisticians, who will ensure the integrity of the data during their processing.

This statistical analysis plan is based on the latest version of the protocol (Version 1.3, 16th September 2024).

2 Background Information

2.1 Rationale

In Exacerbations of Chronic Obstructive Pulmonary Disease (ECOPD) complicated by acute hypercapnic respiratory failure (AHRF), NIV reduces risk of death by 2–fold. However, it can be the cause of complications and unpleasant side-effects for patients. A shorter duration of weaning from the ventilator should provide benefits to patients and reduce costs to the National Health Service (NHS), provided AHRF is adequately controlled without an increased risk of relapse and readmission. The NIV Outcomes (NIVO) score is the best predictor of a patient's chance of survival. The aim of this trial is to compare the time to successful weaning from NIV using an accelerated weaning protocol to a standard weaning protocol in patients with ECOPD and a low or medium risk NIVO score.

2.2 Objectives of the trial

2.2.1 Primary Objectives

To compare time to successful weaning from NIV in ECOPD using an accelerated versus a standard weaning protocol. Failure to wean from NIV and death prior to weaning from NIV are competing risks.

2.2.2 Secondary Objectives

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.

2.3 Trial Design

This is multi centre, open-label, parallel, randomised control trial. Patients will be recruited from at least seven secondary care centres across the UK.

2.4 Eligibility

2.4.1 Inclusion criteria

1. Clinical diagnosis of Exacerbation of Chronic Obstructive Pulmonary Disease*, complicated by acute hypercapnic respiratory failure (pH<7.35 and PaCO2>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. PaCO2 <8kPa, or PaCO2 8-9kPa with at least a 20% fall in PaCO2 from pre-NIV baseline value.
8. Able to tolerate 60 minutes of unsupported breathing, confirmed by arterial blood gas† (ABG).
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 a 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.

2.4.2 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 timeframe of the trial (3 months).

The aim will be to exclude few patients, and only on objective criteria compromising the validity of the research.

2.5 Treatments

Weaning from acute NIV will be attempted in all patients by the protocol assigned following randomisation: either the Accelerated Weaning Protocol or the Standard (stepwise) Weaning Protocol.

2.5.1 Randomisation

Patients will be randomised 1:1 to receive weaning via either the accelerated protocol or the standard protocol using minimisation with 25% by simple randomisation.

2.6 Definitions of primary and secondary outcomes

Outcomes will be assessed 90 days after randomisation.

2.6.1 Primary outcome

Time to successful weaning: duration from the baseline ABG confirming selection criteria are met (the "qualifying ABG"), to final removal of the ventilator. In the accelerated arm, this includes the final successful 4-hour trial off ventilation. 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 on NIV or failure to wean from NIV preclude weaning and will be captured in a competing risk analysis.

2.6.2 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 will be captured from the date and time of the baseline ABG confirming selection criteria are met:
    - 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. In a sensitivity analysis, we will also report costs up to the point of hospital discharge.
    - 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.

2.7 Randomisation

Eligible patients will be randomised on a 1:1 basis between the two treatment strategies using minimisation, with a 25% chance of randomisation by random number sequence. Randomisation will be performed independently, and has been designed to ensure groups are balanced for the number of subjects allocated to each arm, and the following stratification (minimisation) variables:

a) NIV Outcomes score: low or medium risk

b) Site (please see appendix for full list)

c) HCO3-: <28 or ≥28 mmol/L

d) pH: <7.18 or ≥7.18

e) Previous NIV: yes or no

An independent electronic randomisation service has been 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.

2.8 Blinding

As this is an interventional randomised control trial (RCT) comparing two NIV weaning strategies; usual care clinicians and participants cannot be blinded to the allocated weaning protocol. However, patient identifiable data will not be visible to the lead site (Northumbria Healthcare). All confidential data (such as name and surname, and post code) will be anonymised in the analysis stage.

2.9 Data collection schedule

Baseline and outcome information will be collected on a trial-specific source document worksheet and entered onto a secure (N3 network with encryption) online electronic Case Record Form (eCRF)/ database (REDCap) with integral data validation functionality. Follow up information will be collected on all study participants via CRFs. Follow up will be collected at 7-, 30- and 90-days post randomisation. All randomised participants will be followed until death or 90 days post randomisation (whichever is sooner).

2.10 Data monitoring

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 chief investigator (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.

In case of missing data, assuming it is missing not at random (or error in the data entry process) then we will complete it by checking and confirming with the nurse or researcher in each site.

2.11 Trial Reporting

The trial will be reported according to the principles of the Consolidated Standards of Reporting Trials (CONSORT) statements.

3 Analysis Population

3.1 Population definitions

The intention to treat (ITT) population will be all participants meeting selection criteria who are randomised, irrespective of treatment received.

4 Descriptive analyses

4.1 Participant throughput

The flow of patients through the trial will be summarised for both arms using a CONSORT diagram. The flow diagram will describe the numbers of participants randomly allocated, who received allocation, withdrew consent, and included in the ITT population.

4.2 Baseline comparability of randomised groups

The following characteristics will be described separately for patients randomised to each weaning protocol.

Table 1. Baseline variables and reporting methods.

Variable	Form of data	Reporting method
Age (years)	Continuous	Mean (SD) and Range
Sex (male/female)	Nominal	Percentage
Smoking burden (pack years)	Continuous	Mean (SD) and Range
Current smoker (yes/no)	Nominal	Percentage
FEV1 (% predicted)	Continuous	Mean (SD)
eMRCD	Ordinal	Median (IQR)
Rockford Clinical Frailty Score	Ordinal	Median (IQR)
BMI	Continuous	Mean (SD) and Range
Long-term oxygen therapy (yes/no)	Nominal	Percentage
Number of community treated ECOPD last 12 months	Ordinal	Median (IQR)
Number of ECOPD requiring admission last 12 months	Ordinal	Median (IQR)
Previous admission requiring NIV (yes/no)	Nominal	Percentage
Charlson Comorbidity Index	Continuous	Mean (SD) and Range
Cardiovascular disease (yes/no)	Nominal	Percentage
Index of multiple deprivation decile	Ordinal	Median (IQR)
DECAF	Ordinal	Median (IQR)
APACHE II	Ordinal	Median (IQR)

NIVO Score	Ordinal	Median (IQR)
Duration of NIV prior to the start of weaning (qualifying ABG)	Continuous	Mean (SD)
Pre-NIV pH	Continuous	Mean (SD)
Pre-NIV PaCO2	Continuous	Mean (SD)
Pre-NIV PaO2	Continuous	Mean (SD)
Pre-NIV HCO3-	Continuous	Mean (SD)
Pre-randomisation pH	Continuous	Mean (SD)
Pre-randomisation PaCO2	Continuous	Mean (SD)
Pre-randomisation PaO2	Continuous	Mean (SD)
Pre-randomisation HCO3-	Continuous	Mean (SD)
Site (n of participant)	Nominal	Percentage
NIVO Risk (Low or Medium)	Nominal	Percentage

The analysis will be adjusted as appropriate depending on the distribution of the data.

4.3 Completeness of follow-up

All reasonable efforts will be taken to minimise loss to follow-up. The number of percentage of participants with follow-up information at day 7, 30 and 90 after randomisation will be reported.

4.4 Adherence to NIV weaning protocol

Adherence to the allocated weaning protocol will be assessed as follows:

a) Accelerated weaning protocol: all participants should have a daily attempt to wean from NIV (4hr trial off NIV) each day they remain on NIV after randomisation, until successfully weaned.

b) Standard weaning protocol: all participants should have a final night on NIV after a full day off ventilation.

The number of participants breaching the assigned weaning protocol will be reported.

5 Comparative Analysis

For all outcomes, primary analysis will be performed on the ITT population at 90 days post randomisation.

5.1 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 or failure to wean as a competing risks. The Fine-Gray sub distribution 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). Analysis on both all-cause mortality and respiratory mortality will be performed.

5.2 Secondary outcome

For all outcomes (both primary and secondary) the characteristics, including those stratified by the weaning strategies, will be presented. Descriptions of 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) will be given. To test for significance between the arms, a generalised linear model or mixed model will be used to account for baseline characteristics including the correlated measurement across time. Analyses will be performed by intention to treat, with secondary analyses of primary and secondary outcome based on protocol adherence.

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. Model performance will be evaluated by ROC and Harrell's C-statistic. Survival experience between Standard and Accelerated Weaning arms will be compared using the log rank test. As only readmission within 30 days is captured, including mortality cases, the proportion adjusted for the covariates will be reported (NIVO score, PEARL, Dyspnoea scale, age, left and right heart failure).

In case of missing data, assuming missing at random (MAR) and the proportion is greater than 10%, we will run two analyses: first with complete data only, and then following multiple imputation. In the case of different results, both analyses will be presented, with greater weight given to outcomes following multiple imputation.

5.3 Pre-specified 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.

5.4 Significance levels

The critical alpha 5% will be used (thus p-value < 0.05 will be considered statistically significant) and the 95% confidence interval will also be presented.

5.5 Statistical software employed

Analyses will be done in R (Version 4.4.2) and Stata (Version 18).

6 Health Economics Analysis plan

6.1 Aims

The aim is to provide definitive evidence of the cost-effectiveness of an accelerated weaning protocol compared to a standard weaning protocol for participants who are on non-invasive ventilation (NIV), using data from the NIVOW study. That is, to establish whether an accelerated weaning protocol is cost-effective for participants who are on NIV.

6.2 Objectives of the study

The economic evaluation will consist of:

- A within-trial cost effectiveness analysis using EQ-5D derived QALYs.
- A return-on-investment toolkit for accelerated weaning protocol compared to a standard weaning protocol.

6.3 Data Collection

See section 2.9.

6.4 Analysis

6.4.1 Costs

Costing (from the perspective of the NHS) will be based on the standard approach used in economic evaluations following the three-stage process: identification of resource use, measurement, and valuation. The costs will include the following:

- The cost of weaning the participant from NIV.
- The cost of transcutaneous carbon dioxide monitoring (if shown to improve safety and retained in the clinical model of care). This cost may not be applicable if, within the trial, there are no episodes of recurrent respiratory acidaemia detected only by transcutaneous monitoring.
- The cost of hospitalisation post-weaning (but pre-hospital discharge).
- The cost of any health-care resource-use, from hospital discharge to 90 days post randomisation.

Participant's hospital costs (both for weaning the participant from NIV and post-weaning but pre-discharge) will be costed using the NHS National Schedule of costs and will include both the costs of time spent on a Respiratory Support Unit, Critical Care and/or a general ward. These costs will be reported both separately and as a combined Total Hospital Cost.

Resource-use post-discharge (including any Pulmonary Rehabilitation) will be collected via a health resource diary given to participants. This diary will be used to record events related to any COPD and non-COPD associated treatments the participant has received post-discharge. Participants will be contacted, via the telephone, at 30 days and 90 days post-randomisation to complete a proforma which captures use of NHS resources detailed in the diaries. We will triangulate this data with secondary care systems and, where possible, primary care systems. This resource use will be converted into costs using the unit costs of health and social care [1] or the NHS National Schedule of costs [2], where appropriate.

6.4.2 Health-related quality of life

Based on NICE's position statement on the EQ-5D-5L valuation tariffs for England, QALYs will be calculated using data collected via the EQ-5D-5L questionnaire [3]. This data will then be mapped from EQ-5D-5L to the EQ-5D-3L tariffs using the mapping function developed by the Decision Support Unit [4], using the 'EEPRU dataset' [5]. QALYs will be calculated at an individual participant level and utility data will be collected at 7-, 30- and 90-days post-randomisation. QALYs will then be calculated using the area under the curve [6]. Specifically, the area under the curve equates to the total QALY value where QALYs are calculated by multiplying duration of time in a health state by the utility score (Eq. 1).

$$\text{Total QALYs} = \left(\frac{u1 + u2}{2} * p1\right) + \left(\frac{u2 + u3}{2} * p2\right) + \cdots \quad (1)$$

where u is the EQ-5D-5L utility value for each time period (1,2,3…) and p is the difference between the two time periods. Descriptive analysis of the utility scores at each time point will be provided.

6.4.3 Cost-effectiveness analysis

A cost-effectiveness analysis will be undertaken from the NHS perspective and recommended by the National Institute for Health and Care Excellence (NICE) [3]. The analysis will follow recommended methods and good practise guides [7]. Differences between costs and QALYs in the two groups will be described and a full incremental cost-utility analysis will be performed, comparing participants who were allocated to the accelerated weaning protocol to participants who were allocated to the standard weaning protocol. All health economic outcomes (resource use, costs, QALYs) will be described with the appropriate descriptive statistics. The continuous and count outcomes will be expressed as mean ± standard deviation or medians and inter-quartile range where appropriate and dichotomous and categorical outcomes will be presented as absolute numbers and percentages.

Total costs and total QALYs for each patient will be estimated using a generalised linear model or mixed model (see section 5.2) to account for baseline characteristics including the correlated measurement across time. Analyses will be performed using intention to treat. Analysis of costs and outcomes (QALYs) will estimate the mean differences (with a bootstrapped 95% confidence interval) between the accelerated weaning group and the standard weaning group. Uncertainty around estimates of cost-effectiveness and cost-utility 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.

6.5 Missing Data

All reasonable efforts will be taken to minimise loss to follow-up. The number of percentage of participants with follow-up information at day 7, 30 and 90 after randomisation will be reported (section 4.3). Ignoring small amounts of missing data (e.g., <5% of the observations) is acceptable if the amount and pattern of missing data are similar across treatment groups and a reasonable case can be made that doing so is unlikely to bias treatment group comparisons. As total cost is calculated as a sum of numerous components, if one component is missing then the total cost will be missing. Such complete case analysis may introduce bias if those with complete data differ from those with partial data. The method to handle missing data will be grounded in a plausible assumption regarding the missing data mechanism [8]. Rubin's framework will be utilised for classifying missing data in order to define assumptions and choose an appropriate analysis method for the base case [9].

6.6 Return-on-investment tool

The findings from the economic evaluation and the evidence-base will be used to provide a return-on-investment tool that organisations can utilise to assess value for money within local contexts. 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.

References

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[9] Little RJA RD. Statistical Analysis with Missing Data. New York: John Wiley & Sons 1987.

Appendix

List of sites

1. Northumbria Healthcare NHS Foundation Trust
2. Newcastle upon Tyne Hospitals NHS Foundation Trust
3. North Tees and Hartlepool NHS Foundation Trust
4. Royal United Hospitals Bath NHS Foundation Trust
5. The Leeds Teaching Hospitals NHS Trust
6. University Hospitals of Leicester NHS Trust
7. Nottingham University Hospitals NHS Trust