1. Protocol details

1.1 PROTOCOL TITLE:

Pilot feasibility study to determine the clinical effectiveness of neural respiratory drive (NRD) to predict COPD exacerbations at home.

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1.3 Protocol details

Version number 1.6
Final/draft
Date 4th September 2017

2 Signature Page

The Chief Investigator and the R&D (sponsor office) have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP, the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

Professor Nicholas Hart

Signature Date

Sponsor Representative

R&D to Add
GSTFT

Signature Date

This Protocol template is intended for use with UK sites only.

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3 List of Abbreviations and Definitions

AE	Adverse Event
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Record File
ICF	Informed Consent Form
NHS R&D	National Health Service Research & Development
NRD	Neural Respiratory Drive
NIV	Non-invasive ventilation
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
REC	Research Ethics Committee
RMS	Root Mean Square
SAE	Serious Adverse Event

Glossary of Definitions and Terms

AECOPD: Acute Exacerbation of Chronic Obstructive Pulmonary Disease is a clinical diagnosis made when a patient with COPD experiences a sustained (e.g. 24–48 h) increase in cough, sputum production, and/or dyspnoea.

(M)EWS: (Modified) Early Warning Score is a guide used by medical services to quickly determine the degree of illness of a patient. It is based on data derived from four physiological readings (systolic blood pressure, heart rate, respiratory rate, body temperature) and one observation (level of consciousness, AVPU).

EMG: Electromyography is a diagnostic procedure to assess the health of muscles and the nerve cells that control them (motor neurons).

$EMG_{di\%max}$: Peak inspiratory Root Mean Square EMG normalized to the sniff manoeuvre is a measurement found of the Neural Respiratory Drive using diaphragmatic EMG.

$EMG_{para\%max}$: Peak inspiratory Root Mean Square EMG normalized to the sniff manoeuvre is a measurement found of the Neural Respiratory drive using parasternal muscle EMG.

FEV_1: Forced Expiratory Volume in one second – the volume of air exhaled in the first second of the **FVC** (Forced Vital Capacity) manoeuvre and is the most reproducible measurement of airway obstruction.

IC: Inspiratory Capacity – the volume of air that can be inspired after tidal expiration.

Myotrace device: Measures parasternal EMG signal by means of electrode leads and differential amplification, respiratory signal by means of a nasal cannula and an additional differential pressure sensor and acceleration signal by means of a 3D-accelerometer.

NIV: Non Invasive Ventilation is ventilator support that is not invasive, thus no endotracheal tube or tracheostomy tube is needed to ventilate the patient.

NRD: Neural Respiratory Drive is a measure derived from the electrical activation of the respiratory muscles that is often measured by diaphragmatic EMG. NRD is an indirect measure of the balance between the load placed on the respiratory muscle pump and the capacity of the respiratory muscle pump.

PAP: Positive Airway Pressure

4 Summary/Synopsis

Title	Pilot feasibility study to determine the clinical effectiveness of neural respiratory drive (NRD) to predict COPD exacerbations at home
Protocol Short Title/Acronym	NRD to predict COPD exacerbations at home
Protocol Version number and Date	Version 1.6 4th September 2017
Study Phase if not mentioned in title	Pilot study
IRAS Number	232381
REC Reference	
Study Duration	12 months
Sponsor name	Guy's & St Thomas' NHS Foundation Trust
Chief Investigator	Professor Nicholas Hart
Funder	National Institute for Health Research Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust. Equipment (NRD measurement equipment and physical activity monitors) provided by Philips and Affiliates.
Medical condition or disease under investigation	Chronic Obstructive Pulmonary Disease
Purpose of research	To identify whether NRD measurements at home following admission to hospital with exacerbation of COPD can detect an exacerbation within 30 days of discharge.
Primary objective	To investigate whether home measurement of NRD can detect a re-exacerbation of COPD within a 30-day post hospital discharge period.
Secondary objective (s)	**Clinical:** To validate NRD as an advanced physiological biomarker of clinical respiratory deterioration and re-exacerbation of COPD. To analyse NRD trajectory as it relates to standardly subjective measurements of respiratory symptoms e.g. COPD Assessment Test or the EXACT-PRO questionnaire. To determine positive and negative predictive value of NRD to predict re-exacerbation of COPD. To investigate composite clinical features to detect re-exacerbation of COPD To assess correlation of change in NRD, physical activity and symptom resolution. **Feasibility:** To investigate quality of the parasternal EMG measurements. **Technical:** To use the data collected during the study to tune, refine, optimise the automated NRD calculation algorithm.
Number of Subjects/Patients	30
Study Type	Observational pilot feasibility study
Endpoints	**Primary end-point**: Change in NRD from baseline to day prior to an acute exacerbation of COPD. **Secondary end-points:** Change in NRD from peak exacerbation (hospital) to recovery baseline (home) Correlation of time to recovery as measured by NRD and EXACT-PRO

	Correlation of NRD, EXACT-PRO and daytime activity from hospital discharge to recovery Physician-assessed exacerbation within 30-day post-discharge Self-treated exacerbation within 30-day post-discharge All cause hospital readmission within 30-day post-discharge Mortality within 30-day post-discharge Recovery as defined by the EXACT-PRO within 30-day post-discharge Medication change within 30-day post-discharge Unplanned healthcare contacts Attendance of emergency department (without admission)
Main Inclusion Criteria	Age 40-80 years Patients hospitalized with a primary diagnosis of an acute exacerbation of COPD Body mass index (BMI) ≤ 35 kg/m^2 Cognitively and linguistically able to follow instructions given in English and provide informed consent To be discharged to home following the hospitalization Patient lives in the catchment area served by the Lane Fox Unit at Guy's and St Thomas' NHS Foundation Trust in a home environment deemed safe by the investigators to perform home assessments
Statistical Methodology and Analysis	NRD measurements will be analysed after assessments to obtain EMG data. Independent or paired t-test and ANOVA for normally distributed data, non-parametric tests for non-normally distributed data. Measures of association between the defined indices of NRD, the monitored endpoints and routinely used metrics. Univariate and multivariate logistic regression may be used to evaluate predictive value of investigated features using Receiver operating Characteristic Methodology.
Human Tissue Samples (if applicable)	Results of arterial and venous blood tests taken as part of routine clinical care will be recorded: • Arterial blood gas • Venous blood tests: haemoglobin, white cell count including differential, platelet count, urea, creatinine, C-reactive protein
Data collected/storage (if applicable)	Patient data will be de-identified. • All de-identified data will be stored on a password-protected computer stored in a locked seminar room on the Lane Fox Respiratory Unit, St Thomas' Hospital. • All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Kings Health Partners Clinical Trials Office Archiving SOP.

5 Introduction

Chronic obstructive pulmonary disease (COPD) is the fifth biggest cause of death in the United Kingdom (UK) and second most common cause of hospital admissions. The UK population prevalence is 1.5% (5.1% in the United States of America, USA). As per the UK Office for National Statistics, COPD was the underlying cause of death in 30,858 cases in England and Wales in 2015[1]. The direct cost of treating COPD is £1.9 billion annually[2]. Innovative improvements in healthcare delivery, including strategies to prevent hospital readmission are essential.

In the USA, across a selection of 15 states in 2008, there were 190,700 index admissions with a principal diagnosis of COPD[3]. The 30-day readmission rate for an acute exacerbation of COPD (AECOPD) was 7.1% and the rate of 30-day readmissions for other primary diagnoses but with COPD as an additional diagnosis was 17.3 percent[3,4]. Indeed, these data indicate that COPD accounts indirectly and directly for one out of five readmissions to hospital within 30 days[3,4]. Healthcare costs were consistently higher for readmissions than for initial stays[4]. Cost for the 30-day readmission, with COPD as principal diagnosis, was 18% higher than for the index stay. Costs were more than 50% greater for the readmission with COPD as any diagnosis or for all-cause readmissions. Currently in the UK, several European countries and the USA, healthcare providers and institutions face financial penalties for patients who are readmitted within 30 days. The additional healthcare costs could be reduced by innovative approaches directed to reduce hospital readmission.

Monitoring the trajectory of recovery is essential for COPD patients recovering from an exacerbation and potentially this will determine the need for escalation of care as well as the requirement for delayed or supported discharge at the end of their hospital stay. Physiological deterioration leading to critical care admission often goes undetected[5] and early identification by measuring advanced physiological biomarkers, such as neural respiratory drive (NRD), could improve outcome as well as reduce health care costs by reducing late intervention and admissions to hospital and critical care[6]. Early detection of treatment failure is recommended by the Royal College of Physicians of the UK and the National Institute for Health and Clinical Excellence (NICE)[7]. Early warning scores (EWS) have therefore been developed in the UK using standard physiological variables to derive an aggregate score. Higher scores are associated with worse outcomes. However the scores are not always employed and their effectiveness, particularly in the COPD cohort, is controversial[8-13].

NRD, or drive to breathe, directly reflects the balance between respiratory muscle load and respiratory muscle capacity. Diaphragmatic electromyography (EMG), performed using an array of electrodes inserted into the oesophagus, has been demonstrated to be a robust technique for assessing NRD[18,19]. The magnitude of the EMG signal is expressed as the root mean square (RMS) of the EMG voltage trace. The NRD is then derived from the RMS of the diaphragmatic EMG signal expressed as a percentage of the maximal EMG ($EMG_{di\%max}$). However, this technique is of limited use in the acutely unwell COPD patient, as it required the insertion of an oesophageal multi-pair electrode catheter.

Second intercostal space parasternal EMG, acquired using electrodes placed on the chest wall on either side of the sternum, avoids this technical difficulty[20]. The parasternal muscles are obligate muscles of respiration with minimal post-inspiratory activity[14-17]. Furthermore, the parasternal muscles make a relatively greater contribution to ventilation during periods of increased hyperinflation, such as during an acute exacerbation of COPD (AECOPD), as the resting length of the parasternal muscles is less affected than diaphragm[21]. The activity of these muscles would be expected to be high at the beginning of an AECOPD[12] and decrease with subsequent unloading of the parasternal muscles through treatment with bronchodilators, corticosteroids and antibiotics.

In a pilot feasibility study of this technique, Murphy *et. al.*[22] demonstrated that the change in NRD during hospital admission was a marker of physician-defined clinical deterioration and, furthermore,

change in NRD from admission to discharge identified patients with COPD who were readmitted within 14 days. This study was in a small group of selected patients with AECOPD, with the majority of patients having only a single pair of NRD measurements made during their hospital admission. The NRD was derived from the RMS of the parasternal EMG expressed as a percentage of maximal parasternal EMG obtained during a sniff manoeuvre ($EMG_{para\%max}$). An additional clinically useful measure was the NRD index (NRDI), which was calculated as the product of $EMG_{para\%max}$ and respiratory rate.

A subsequent study from the same group by Suh *et. al.*[23] at a UK teaching hospital enrolled patients with a physician diagnosis of AECOPD within 12 hours of admission. Spirometry, inspiratory capacity (IC), EMG_{para}, routine physiological parameters, MEWS, modified Borg scale for dyspnoea and physician defined episodes of deterioration were recorded daily until discharge. Readmissions at 14 and 28 days post discharge were also recorded. 120 patients were recruited (age 70±9 years, forced expiratory volume in 1s (FEV_1) of 30.5±11.2 as percentage of predicted). Subjective worsening of dyspnoea, defined as at least one-point increase in Borg scale, was associated with increases in $EMG_{para\%max}$ and MEWS, whereas physician-defined inpatient clinical deterioration was associated with an increase in $EMG_{para\%max}$ alone. Admission-to-discharge change (Δ) in the normalized value of EMG_{para} ($\Delta EMG_{para\%max}$) was inversely correlated with ΔFEV_1 ($r=-0.38$, $p<0.001$) and ΔIC ($r=-0.44$, $p<0.001$). $\Delta EMG_{para\%max}$ predicted 14-day readmission (OR 1.13, 95% 1.03 to 1.23) in the whole cohort and 28-day readmission in patients under 85 years (OR 1.09, 95% CI 1.01 to 1.18)

Two further studies were conducted to ascertain if participants could perform self-measurement of NRD following training by a nurse coordinator. This study enrolled 10 healthy controls and 10 stable COPD patients attending outpatient clinic and performing self-measurement steps to obtain NRD measurements over two visits. The second study was conducted with 10 stable COPD participants who self-measured NRD in their home for 7 consecutive days. The measurement steps for both studies were the same as the ones performed during the UK studies[22, 23], including skin preparation, placement of two electrodes at the 2nd intercostal space and one ground electrode on the clavicle, positioning of nasal cannula and breathing at rest for 6 minutes, followed by a sniff manoeuvre. For both of these studies, equipment measuring parasternal EMG signal using electrode leads and differential amplification (termed Myotrace device), respiratory signal using nasal cannulae and a differential pressure sensor, and acceleration signal by means of an accelerometer was used. The data acquisition system (Porti7 from the company TMSi) was powered by a medical grade external power supply. The acquired data were sent to a notebook via optical fibre, where the signals could be further processed, stored, and visualized.

The results from the first study indicated that most participants could perform self-measurement using the Myotrace device after being trained by a coordinator and following picture instructions. The second study demonstrated that:

- The measure was acceptable to patients. When interviewed at the end of the study, 9 out of 10 found the measurement easy to very easy to perform. All felt confident to very confident to perform the measurement, and 8 felt that they would be likely to very likely to conduct the measurement at home, 6 of those for one month.
- All 10 patients managed the different measurement steps (skin preparation, electrode placement, nasal cannula placement). Although not perceived by the patients as the most difficult step, it was observed during the measurements that adopting a consistent and relaxed posture and behaviour during breathing at rest could represent a challenge for some patients.
- The majority of the 10 patients (7/10) could perform self-measurements with acceptable reproducibility and accuracy, as assessed by inter-occasion reliability and inter-observer reliability (note that in that study the coordinator also performed a measurement every day, which allowed to compare measurements between the coordinator and each patient). Some

promising directions for improvement were also identified at different levels (algorithm, form factor, user experience and instructions for use).

Overall, further data (larger sample size and higher COPD severity) are required to validate the level of reproducibility of the NRD measurement, also in conjunction with the ability to detect clinically relevant change in NRD due to deterioration in the home.

This study will be a single arm, pilot feasibility prospective observational study to assess whether NRD when utilized as an objective monitoring signal, is able to detect a clinical respiratory deterioration (re-exacerbations or failure to respond to treatment) in COPD patients within 30 days of discharge from hospital, following index hospitalization for AECOPD. The goal of using this advanced physiological biomarker is to facilitate early intervention and prevent hospital readmission and/or reduce the impact of relapse. As a pilot feasibility study, the aims are to assess the practical limitations to acquiring NRD in the home setting. Furthermore, data will be collected to assess the potential for NRD to detect and predict re-exacerbations allowing potential sensitivity and specificity to be calculated. If this pilot study confirms that NRD measurements are practical to acquire at home and successfully detect and predict future exacerbations of COPD, this will facilitate a study to validate the use of the Myotrace device by patients themselves in detecting and predicting AECOPD at home following index hospital hospitalization for AECOPD.

Physical activity is a key feature of stable and acute COPD, with inactivity being associated with poorer outcomes including reduced health related quality of life scores, hospital admissions and increased mortality. This study will include a quantification of physical activity using wrist-worn physical activity monitors, which will be compared to NRD measurements. Using an accelerometer, the physical activity monitor will collect data on total sleep time, time spent awake after sleep onset, sleep onset latency, sleep efficiency, average activity (counts/minute), maximum activity (counts/minute), mobile time, average mobile bout, immobile time and total wake and sleep times. In this way, physical activity will be evaluated as an additional advanced physiological biomarker to identify further re-exacerbations of COPD and predict readmission.

COPD exacerbations will be pre-defined according to the following criteria in a hierarchical fashion[1, 2].

- COPD-related hospital admission - worsening respiratory symptoms (cough, wheeze, increased sputum production, increased volume of sputum and/or increased breathlessness) with senior physician (registrar or consultant) assessment and treatment for acute COPD exacerbation started on admission to hospital.
- Physician-assessed exacerbation - worsening respiratory symptoms (cough, wheeze, increased sputum production, increased volume of sputum and/or increased breathlessness) with physician assessment and COPD treatment escalated (increased beta-agonist use as inhaled or nebulized therapy and/or oral corticosteroids and/or oral antibiotics) by physician WITHOUT admission to hospital.
- Self-treated exacerbation - worsening respiratory symptoms (cough, wheeze, increased sputum production, increased volume of sputum and/or increased breathlessness) WITHOUT physician assessment but patient self-initiated AECOPD treatment (use of rescue pack of oral corticosteroids and/or oral antibiotics, depending on standard of care at clinical site).

Exacerbations will also be categorized by according to the GOLD definition:

- Mild (treated with short acting bronchodilators only, SABDs)
- Moderate (treated with SABDs plus antibiotics and/or oral corticosteroids) or
- Severe (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure.

Note that the EXACT questionnaire will be used throughout the study in an attempt to monitor symptom-based changes in patient status. The EXAcerbations of Chronic Pulmonary Disease Tool is a Patient-Reported Outcome measure (EXACT-PRO) designed to standardize the method for evaluating the frequency, severity and duration of both reported and unreported AECOPD in studies[26]. The EXACT-PRO total score is computed across the 14 items and has a theoretical range of 0 to 100, with higher values indicating a more severe condition. Specifically, changes in the total score may be used to define recovery from the primary exacerbation event.

6 Trial objectives and purpose

Primary objective:

To investigate whether home measurement of NRD can detect a re-exacerbation of COPD (symptom based definition) within a 30-day post hospital discharge period.

Secondary objectives:

Clinical:

- To validate NRD as an advanced physiological biomarker of clinical respiratory deterioration and re-exacerbation of COPD.
- To analyse NRD trajectory as it relates to standardly subjective measurements of respiratory symptoms e.g. COPD Assessment Test or the EXACT-PRO questionnaire.
- To determine positive and negative predictive value of NRD to predict re-exacerbation of COPD.
- To investigate composite clinical features to detect re-exacerbation of COPD.
- To assess correlation of change in NRD, physical activity and symptom resolution.

Feasibility:

- To investigate quality of parasternal EMG measurements performed in the home environment

Technical:

- To use the data collected during the study to tune, refine, optimise the automated NRD calculation algorithm

7 Study design & Flowchart

7.1 Study Design

Primary end-point:

Change in NRD from baseline to day prior to an acute exacerbation of COPD.

Secondary end-points:

Change in NRD from peak exacerbation (hospital) to recovery baseline (home)
Correlation of time to recovery as measured by NRD and EXACT-PRO
Correlation of NRD, EXACT-PRO and daytime activity from hospital discharge to recovery
Physician-assessed exacerbation within 30-day post-discharge
Self-treated exacerbation within 30-day post-discharge
All cause hospital readmission within 30-day post-discharge
Mortality within 30-day post-discharge
Recovery as defined by the EXACT-PRO within 30-day post-discharge
Medication change within 30-day post-discharge
Unplanned healthcare contacts
Attendance of emergency department (without admission)

Trial design
This study will be an observational cohort design.

7.2 Flowchart

	Screen Visit	Day 1	Hospital measurements	Pre-discharge	Home measurements
Patient information and informed consent	X				
Medical history Comorbidities Smoking history Premorbid data		X		X	
Medications		X		X	
Blood tests		X		X	
Chest x-ray		X			
Demographics: Age, height, weight, FFM		X			
Vital observations		X	X	X	
Questionnaires: EXACT-PRO CAT (weekly)		X	X	X	X
Spirometry: FEV_1, FVC, IC		X		X	X (weekly)
Neural respiratory drive		X	X	X	X
Physical activity watch issued				X	

8 Subject selection

Target population
Patients admitted to hospital with a primary diagnosis of an acute exacerbation of COPD.

Screening and eligibility assessment
Patients will be identified by the clinical team and enrolled in the study within 16 hours of hospital admission to St Thomas' Hospital as study participants. All efforts will be made to reduce disruption of care and respect patient privacy. Interruption of patient care will be minimized by making sure that study staff only approach potential participants after their initial triage and decision to admit. Study related procedures will commence only after the informed consent form is signed by the subject. The study will be explained to the potential participant and sufficient time provided to the subject to ask questions regarding the study (minimum 1 hour). Before signing the consent form, the participant will also be shown the Patient Information Sheet that details the steps of the study procedure to them.

If the participants develop any of the exclusion criteria listed below between enrolment and as the study proceeds, they will be asked to discontinue from the study.

Approximately 300 patients are admitted with COPD per year. Based on previous research conducted by the group in this area there would be expected to be 4-5 eligible patients per week with 2 patients recruited each week.

8.1 Subject inclusion criteria

Inclusion criteria

- Age 40-80 years
- Patients hospitalized with a primary diagnosis of an acute exacerbation of COPD
- Body mass index (BMI) ≤ 35 kg/m^2
- Cognitively and linguistically able to follow instructions given in English and provide informed consent
- To be discharged to home following the hospitalization
- Patient lives in the catchment area served by the Lane Fox Unit at Guy's and St Thomas' NHS Foundation Trust in a home environment deemed safe by the investigators to perform home assessments

8.2 Subject exclusion criteria

Exclusion criteria

- Previous home PAP (CPAP or NIV) therapy use within the past year, or post-discharge
- Allergies to latex, metals or local anaesthetic agents
- Wound or inflamed skin at parasternal location (2nd intercostal space)
- History of skin allergies or sensitivity to cosmetics and lotions
- Psychological and social factors that would impair compliance with study protocol and schedule
- Any major non-COPD chronic disease or condition, such as severe heart failure (LVEF<30%), malignancy (active treatment or palliation), end stage renal failure/dialysis, significant neuromuscular disease (e.g. Motor Neuron Disease, Muscular Dystrophy) determined by review of medical history and / or patient reported medical history that may contribute significantly to risk of readmission, as determined by PI
- Length of stay ≤ 24 hours
- Planned travel away from home within the 30 day post discharge period

9 Study procedures

9.1 Subject recruitment

Eligible participants will be identified by the clinical team. The investigator will subsequently approach these patients to discuss recruitment to the study and will be responsible for obtaining informed consent. Recruitment will be achieved through discussion of the project and providing the patient with a comprehensive information leaflet. The patient will be given the opportunity to ask questions concerning the project and their care.

Participants will be provided with at least one hour to decide upon their participation in the study. A longer period can be provided however patients must be recruited within 16 hours of presentation to the Accident and Emergency department of St Thomas' Hospital. Participants will sign a consent form to confirm enrolment into the study.

Participants will not receive payments for study participation.

9.2 Screening Procedures

Screening for eligible patients will be undertaken by the clinical team.

9.3 Schedule of assessments for each visit

Baseline assessments

Enrolled patients will have clinical review and the following data collected at the 1st study assessment:

- The following data will be obtained from electronic patient records:
  - Age, height, weight,
  - Pack year history
  - Comorbidities
  - Medications (acute & chronic)
  - Premorbid data (exacerbation frequency, spirometry (FEV_1, FVC, IC), extended Medical Research Council Dyspnoea (eMRCD) score)
  - Chest radiograph
  - Admission venous blood results: Haemoglobin, white cell count (including differential), platelet count, urea, creatinine, C-reactive protein, venous blood gas
  - Arterial blood gas on admission
  - Vital observations (heart rate, blood pressure, respiratory rate, oxygen saturations and supplementary O_2 flow rate) at the time of the investigator assessment
- The following data will be obtained by measurements taken by the investigator:
  - eMRCD Score
  - EXACT-PRO questionnaire
  - COPD assessment test (CAT)
  - Body composition (Fat Free Mass)
  - Clinical examination for signs of right and/or left ventricular failure
  - Spirometry – FEV_1, FVC, IC
  - Neural respiratory drive (NRD) – resting and maximal manoeuvres to obtain RMS EMG_{para} (microvolts), RMS as percentage of maximum ($EMG_{para\%max}$) and Neural Respiratory Drive Index (NRDI). The procedure for NRD measurement is described below.

Hospital assessments

Patients will be seen as inpatients by the trial team for clinical review and further physiological characterisation. The following measurements will be performed by the investigator:

- EXACT-PRO questionnaire
- NRD
- Vital observations at the time of the investigator assessment will be obtained from electronic patient records

Pre-discharge measurements

The investigator will perform a final study visit on the day of discharge collecting the following data:

- Medications (acute & chronic)
- Up to date venous blood tests (haemoglobin, white cell count including differential, platelet count, urea, creatinine, C-reactive protein) and arterial blood gas if performed by the clinical team. These tests do not need to be performed by the research team.
- Vital observations
- COPD assessment test (CAT)
- EXACT-PRO questionnaire
- Spirometry – FEV_1, FVC, IC
- NRD
- Participants will be issued with a wrist-worn physical activity monitor which should be worn for the remaining duration of the study, apart from short periods for personal hygiene

Home measurements to be collected by the investigator:

- EXACT-PRO
- Neural respiratory drive (resting and maximal manoeuvres)
- Review of participants' symptom diaries
- COPD assessment test (CAT) (weekly)
- Spirometry – FEV_1, FVC, IC (weekly)
- Physical activity monitors will be collected at the final assessment

NRD measurement

The NRD measurement device consists of three surface electrodes, shielded cables and a base unit. This is connected to a laptop on which software which analyses raw EMG data to generate a measurement of NRD is installed. The system is used to measure and record 2nd intercostal space parasternal EMG signal, nasal cannula pressure and accelerometer data.

EMG_{para} will be collected by the investigator using standard medical grade equipment as previously described[3]. In brief, the 2nd intercostal space will be identified by bony landmarks and marked with an indelible marker. Skin preparation will be performed using EMG preparation gel (Nuprep skin prep gel, Weaver and Company, Colorado, USA) followed by detergent wipes (Clinell patient wipe, GAMA healthcare, London, UK) followed by to remove exfoliated skin. Two wet gel electrodes will be placed immediately adjacent to the sternal border in the 2nd intercostal space and one wet-gel electrode will be placed on the clavicle. All electrodes will be connected to the automated EMG analysis system. A nasal cannula will be placed in the nares to detect pressure changes during respiration in order to ensure accurate detection of the inspiratory cycle of respiration. In addition, an accelerometer will be attached to the thorax of the patient.

These 3 modalities (EMG_{para}, pressure-based respiratory signal and accelerometer) are connected to the automated EMG analysis system. This system is based on the Porti device from the TMSi company. The Porti system is CE certified (class 2A, type CF) and FDA 510k approved. The automated EMG analysis system extends the Porti device by providing bespoke software to capture, visualize and process the received data. The software runs on a laptop computer connected by USB cable to the fibre/USB interface of the Porti. Data is processed by the software to identify the inspiratory portion of the EMG signal and calculate an index of neural respiratory drive, as reported previously (EMG_{para} in microvolts (µV), $EMG_{para\%max}$ as the ratio to the maximum sniff EMG_{para} (by instructing the patient to undertake three maximal sniffs) and NRDI (product of $EMG_{para\%max}$ and respiratory rate). The processed data (i.e. the indices of NRD) are not displayed online and not provided to the investigator. It therefore cannot influence clinical judgment. The software as tested in the study does not deliver any diagnosis, prevention, monitoring, treatment or alleviation of disease.

Before starting any spot-check NRD measurement, it will be ensured that the participant is seated in a relaxed semi-recumbent position with posture to ensure minimal tonic activity of anterior chest wall muscles. This practically entails participants to be seated with arms supported by arm rests or a pillow on the lap. The process of measuring NRD indices is expected to take approximately 10 minutes. To obtain the measurements of NRD, raw EMG_{para}, RMS EMG_{para} and airflow will be obtained over a seven minute 'spot check' period. In the final minute, patients will be asked to perform a minimum of six maximal sniff manoeuvres in order to obtain maximal sniff measurements. This data will be analysed after data acquisition using an automated algorithm to obtain NRD and sniff measurements.

NRD measurements will be recorded by an investigator during participants' hospital stay following the procedure described above. Measurements will be taken twice daily, one pre-SABD and the second

20-minute post-SABD. The timing of NRD measurements should stay consistent throughout their hospital admission.

9.4 Follow up Procedures

Hospital Discharge and subsequent readings
On the day of discharge, vital observations, spirometry (FEV_1, FVC, IC) and NRD will be measured and the EXACT-PRO and CAT symptom questionnaires will be completed. The list of discharge medications will be documented. Patients will be issued with physical activity watches on the day of discharge and this should be worn for the remaining duration of the study, apart from short periods for personal hygiene.

The study staff will schedule a time to visit the participant the next day after their discharge. The timing of the visit will be scheduled at the participant's convenience however should remain the same time for the remaining duration of the study. At each visit, the EXACT-PRO questionnaire will be completed and EMG measurements performed. NRD will be analysed after the home visit is completed. A symptom dairy will be recorded along with record of additional medications used which will be reviewed by the investigator. The CAT questionnaire and spirometry (FEV_1, FVC, IC) will be performed weekly at home.

If, when during conducting the measurements in the home setting, the assessment of the investigator is that the patient has a significant exacerbation and requires emergency treatment they will use the following traffic light system to provide assistance:

- Green: The participant is clinically stable with an increase in their COPD symptoms – the investigator will signpost the participant to take the course of action they usually would (for example using their rescue pack and/or arranging an appointment with their General Practitioner).
- Amber: The participant is more unwell than category Green but less unwell than category Red – the investigator will signpost the participant to take the course of action they usually would and additionally provide an escalation plan to seek urgent medical attention should they deteriorate (GP appointment or attendance at their local Accident and Emergency department).
- Red: The participant is critically unwell – Investigator will urgently call 999 to request an ambulance.

If the patient requests a medical review the investigator will direct the patient to the usual health care provider for the patient.

The final study visit at day 30 will ensure completion of questionnaires, collection of physical activity monitors and confirmation of health status.

Medical record review
The study investigator will corroborate patient reported events with primary care physicians and local hospital electronic patient records to confirm nature and timings of visits.

9.5 Radiology Assessments

If participants' have had a chest radiograph on admission to hospital, this will be reviewed by the investigator at the baseline assessment for the presence of focal consolidation.

9.6 End of Study Definition

The trial will cease when the final patient has completed 30 days of home monitoring or has an exacerbation requiring hospital re-admission or 12 months from trial initiation, whichever is sooner.

10 Laboratories

10.1 Central/Local Laboratories

The research group is based at the Lane Fox Unit, St Thomas' Hospital. NRD will be analysed using bespoke computer software using data derived from EMG measurements.

10.2 Sample Collection/Labelling/Logging

All measurements are de-identified when entered into research software. Patient study identifiers will be used. The results of blood samples included in this study are taken as part of routine clinical care. No blood tests beyond routine care will be taken by investigators.

10.3 Sample Analysis Procedures

EMG measurements are analysed by research software to generate a measurement of NRD.

10.4 Sample Storage Procedures

Not applicable.

10.5 Data Recording/Reporting

Source documents are original documents, data, and records from which participants' CRF data are obtained. CRF entries will be considered source data. In this study the CRF will be used as the source document for all participants recruited into the study.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

10.6 Sample Receipt/Chain of Custody/Accountability

Not applicable

10.7 Sample Transfer to sites outside the Organisation

Not applicable

11 Assessment of Safety

Adverse event (AE)

An AE or adverse event is any untoward medical occurrence in a participant or other clinical investigation whilst participants are 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 study.

Serious adverse event (SAE)

SAE is an adverse event that

- Led to death
- Led to serious deterioration in the health of the subject that
- Resulted in a life-threatening illness or injury

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.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

In addition, a serious AE is one that is judged by the investigator to be an important or medically significant event. Causality assessments of AEs: For all AEs, the investigator will provide an assessment of causal relationship to study devices. Appropriate forms will be used for this purpose and filed in the case report forms and submitted to the IRB for review. They will be classified as related, possibly related, and not related. The severity will be adjudged as being mild, moderate, or severe. All significant adverse events will be reported to the Institutional Review Board within 24 hours.

AECOPD is a clinical diagnosis made when a patient with COPD experiences a sustained (e.g. 24–48 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 AECOPD and indeed 20% will be readmitted to hospital within 28 of being discharged (when the primary reason for admission was AECOPD). The Chief Investigator and Principal Investigator therefore deem AECOPD to be an expected AE and SAE and AECOPD will not be reported to the sponsor. In the event of a participant developing an AECOPD, this will be documented in the participant's medical notes and case record file.

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 CRF 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 sponsor/legal representative and GSTT **within one working day** of the investigator team becoming aware of them.
Reports of related and unexpected SAEs should be submitted to ethics within 15 days of the Chief Investigator becoming aware of the event, using the SAE report form for non-CTIMPs published on the NRES website.

All reporting to GSTT R&D should be by fax (0207 188 6116) giving as much information about the incident as possible, and should be signed by the PI or Co-investigator. The GSTFT SAE reporting form should be used for GSTT sponsored studies.
The GSTT R&D Department will undertake an initial review of the information and ensure it is reviewed by GSTT R&D. Events will be followed up until resolution, any appropriate further information will be sent by the research team in a timely manner.
Reporting to the MHRA will be done in liaison with the Chief Investigator.

Risks and discomforts
Placement of electrodes: In order for electrodes to be placed correctly the participant may be required to shave their chest. This may be uncomfortable. The adhesive electrode pads and the cream used to clean the skin before monitoring may cause minor irritation.
Sniff manoeuvre: Participants will be asked to perform a number of sniff manoeuvres with a nasal cannula. Participants may find this to be uncomfortable, but the procedures are safe. If participants start to feel lightheaded or short of breath they may begin to breathe normally.
Skin irritation: There may be a risk of skin irritation as a result of prolonged use of the physical activity monitor.

11.1 Ethics Reporting

The study will be performed in line with the declaration of Helsinki and local procedures including approval by the research ethics committee.
Whilst it is not expected that the trial measurements will be related to any SAE, patients hospitalised due to exacerbations of COPD have high rates of both rehospitalisation and death within 30 days of discharge.

11.2 Trial Steering Committee

This is an observational study, which has minimal risk to the study subjects. A Data Monitoring Committee (DMC) will not be utilized in this study. Site monitoring and oversight will be provided by the local R&D departments in line with local and national regulations on trial conduct.
The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

11.3 Ethics & Regulatory Approvals

This study will be submitted for NHS ethical review.

12 Compliance and withdrawal

12.1 1Subject compliance

Patients will undergo inpatient monitoring by an investigator who will also perform home assessments. Patients will also complete a daily symptom diary which will be reviewed at each assessment.

12.2 Withdrawal / dropout of subjects

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospective having been overlooked at screening)

- Disease progression which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Consent withdrawn
- Lost to follow up

The reason for withdrawal will be recorded in the CRF.

12.3 Protocol Compliance

No protocol compliance issues are anticipated. Any compliance issues that arise will be reported to the study sponsor.

13 Data

13.1 Data to be collected

All data will be collected by the research team.

Baseline assessment
Demographics (age, height, weight), co-morbidities, pack year history, medication (acute and chronic), chest radiograph, blood tests (haemoglobin, white cell count, platelets, urea, creatinine, CRP, venous blood gas), arterial blood gas and observations (heart rate, blood pressure, respiratory rate, oxygen saturations and supplementary oxygen flow rate) will be obtained from the electronic patient medical record system.
EXACT-PRO and COPD Assessment Tool (standardised questionnaires) will be completed by the participant.
Pre-morbid data on participants' exacerbation frequency, lung function tests and eMRCD score will be collected from conversation with the patient and medical records.
The investigator will measure participants' spirometry (FEV_1, FVC, IC) and NRD and clinical examination for signs of right and/or left ventricular failure.

Hospital assessments
Measurements of heart rate, blood pressure, respiratory rate, oxygen saturations and supplementary oxygen flow rate and NRD will be collected by the investigator. Participants will complete the EXACT-PRO questionnaire daily.

Pre-discharge measurements
On the day of discharge, medical records will be used to collect data on acute and chronic medications, most recent blood tests (haemoglobin, white cell count, platelets, urea, creatinine, CRP) and most recent arterial blood gas analysis.
Heart rate, blood pressure, respiratory rate, oxygen saturations and supplementary oxygen flow rate, spirometry (FEV_1, FVC, IC) and NRD will be measured by an investigator. Participants will complete the EXACT-PRO and CAT questionnaires. Patients will be issued with wrist-worn watch-like physical activity monitors which will be collected at the end of the study. These physical activity monitors measure activity by recording and analysing readings from the on-board accelerometer and are designed to be comfortable so they can be worn safely 24 hours a day and have battery lives exceeding 6 months. No patient information is contained in the monitors or in the encrypted data files. De-identified physical activity data will be downloaded which will be collected and analysed at the end of the study.

Hospital discharge and subsequent readings

Participants will receive home visits by an investigator who will perform NRD measurement, help the participant to complete the EXACT-PRO questionnaire and review participants' symptom diary. The CAT questionnaire and spirometry (FEV_1, FVC, IC) will be measured weekly.
The final study visit at day 30 will ensure completion of questionnaires and collection of physical activity monitors.

13.2 Data handling and record keeping

All documents will be stored safely in confidential conditions on the Lane Fox Unit, St Thomas' Hospital. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

Personal data will be stored for 6-12 months after the study has ended. Research data generated by the study will be stored for 5 years.

Data will be handled in accordance with the Data Protection Act 1998.

Professor Nicholas Hart is responsible for data collection, recording and quality.

14 Statistical considerations

14.1 Sample size calculation (some pilot/feasibility studies may not require a formal sample size calculation)

A sample size of 30 has been set. This study is a pilot feasibility study with no prior data to power the sample size. As such, the sample size was not determined based on power analysis but will provide sufficient data to inform a larger future study. Data collected during this study will be used for sample size calculation for validation of future work. Recruitment will continue until 30 patients have completed the study.

14.2 Statistical analysis

For all analyses, $p<0.05$ will be deemed statistically significant. Comparison of data with one or more factors will be analysed using independent or paired t-test and ANOVA with repeated measures (if needed) for normally distributed data, and non-parametric tests in cases of non-normally distributed data, whenever applicable. Measures of association between the defined indices of NRD, the monitored endpoints and routinely used metrics will be investigated (e.g. using regression analysis). At last, univariate and multi-variate logistic regression may be employed to evaluate the predictive value of a number of investigated features (using the Receiver Operating Characteristic Methodology).

Interim analysis will be performed after 5 patients have been readmitted.

Dr Abdel Douiri (King's College London) will be involved in statistical analysis for the study. The Lane Fox Research Unit has an existing contract with Dr Douiri for *ad hoc* statistical support.

15 Ethical considerations

The study will be performed in line with the declaration of Helsinki and local procedures including approval by the research ethics committee.

16 Financing and Insurance

This study is funded by Philips and its Affiliates who supply the NRD measurement equipment (laptop with bespoke NRD analysis software) and physical activity monitors (Philips Actiwatch Spectrum). Dr Rebecca D'Cruz has allocated funding from the NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust to work on this study.

17 Reporting and dissemination

The results of the study will be analysed with the aim to publish at an international respiratory conference and as a peer reviewed journal article in a high ranking respiratory journal. A lay summary of the trial outcomes will be provided by the trial group to the participants and to the Lane Fox Respiratory Unit Patient Association. The study results in lay form will also be uploaded to a trial registry and the research group website to provide visible access to patients and relevant members of the medical profession. The results will also be presented at local clinical and research meetings. The researchers will, where appropriate use social media to increase the visibility of the findings. We will seek patients' permission for unidentifiable de-identified information (without patients' name and personal details) to be transferred to Philips and its Affiliates for internal research and development purposes only following completion of the study.

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Appendix

EXACT-PRO

COPD Assessment Tool

CAT.pdf

Extended MRC Dyspnoea score

1	Breathlessness only with strenuous exercise
2	Breathless when hurrying on the level or walking up a slight hill
3	Walks slower than contemporaries, or stops after walking on the level at own pace
4	Stops for breath after walking 100 m, or for a few minutes, on the level
5	Too breathless to leave the house unassisted
5a	5 but independent in washing and/or dressing
5b	5 and dependent in washing and dressing