Study Protocol

Remote monitoring to improve low adherence in non-invasive ventilation: a protocol for a randomised controlled clinical trial (READ-NIV trial)

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Background: Obstructive sleep apnoea (OSA) is the most common sleep-related breathing disorder. Non-invasive ventilation (NIV) is essential for managing hypercapnic respiratory failure in patients with obesity hypoventilation syndrome (OHS) and those with co-existing OSA, where continuous positive airway pressure (CPAP) alone is insufficient. However, adherence to NIV can be challenging, with substantial non-compliance occurring due to factors such as discomfort and phobia. The objective of this protocol is to assess the improvement of adherence to NIV remotely monitored, as well as to record symptom control and long-term clinical outcomes, and to optimise healthcare resource usage.

Methods: This is a prospective, randomised, and controlled (usual care) trial with a two-arm parallel group design, testing remote monitoring of home NIV (T4P device, SRETT, Paris, France) for 3 months in patients with OSA/OHS who have previously had low NIV adherence (<4 hours/night). This project has been approved by the research ethics committee/Health Research Authority (HRA) [Integrated Research Application System (IRAS) ID: 270108], as well as by Guy's & St Thomas' NHS Foundation Trust R&D Department.

Discussion: Outcomes will be compared between the intervention and the control group (NIV with *vs.* without remote monitoring). The trial will also assess suitability of the outcome parameters, and test whether the data collection, symptom questionnaires, and used healthcare resources are suitable to describe the impact on patient-related outcomes.

Trial Registration: This study is registered at ClinicalTrials.gov (NCT04884165).

Keywords: Adherence; telemedicine; obstructive sleep apnoea (OSA); obesity hypoventilation syndrome (OHS); sleepiness

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Introduction

Sleep-disordered breathing is highly prevalent (1,2) as the obesity epidemic increasing the incidence of obstructive sleep apnoea (OSA) and obesity hypoventilation syndrome (OHS) (2,3). Positive airway pressure (PAP) therapies, including both continuous PAP (CPAP) for uncomplicated and moderate to severe OSA while non-invasive ventilation (NIV) may be required for the treatment of hypercapnic respiratory failure in OSA/OHS (4-6). Despite the clinical efficacy of NIV, adherence remains a significant challenge with non-compliance often correlating with adverse effects and leading to poorer outcomes (6). The main reasons for this non-compliance include discomfort, the presence of leaks, and the need for frequent setting adjustments to optimize therapy (7). Several studies have suggested that a minimum of 4 hours and perhaps 6 hours of therapy per night is needed in order to improve symptoms, quality of life, and cardiovascular outcomes associated with sleep-disordered breathing (8-10).

Developments in NIV telemonitoring have shown significant potential to enhance treatment adherence and patient outcomes (11). A remote monitoring technology allows for close supervision, real-time feedback, and adaptive adjustments, which is extremely important for improving compliance (12). Furthermore, home-based NIV setups have been demonstrated to improve patient outcomes, particularly in managing chronic respiratory failure associated with OSA/OHS (13). These setups encourage more consistent use of treatment, and better patient education on device usage (14). Successful use of NIV at home can reduce hospital visits and improve overall treatment efficiency (15).

Moreover, remote monitoring enables clinicians to adjust ventilator settings without the need for in-person visits, significantly reducing the burden on healthcare resources and improving patient comfort (16).

This lends further support to the integration of telemedicine in the management of sleep-disordered breathing (17). Addressing disease severity, psychological factors, and managing side effects may also be important for improving treatment adherence. We present this article in accordance with the SPIRIT reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-86/rc).

Methods

Objectives and hypotheses of the clinical investigation

General

The objective is to determine if remote monitoring of NIV will enhance adherence to therapy, as well as symptom control and healthcare usage. The proposed study will provide information about the average use of NIV. The study design will test the hypothesis 'NIV adherence will be improved by remote monitoring over a period of 3 months'.

The primary outcome parameter is the improvement in NIV adherence over a 3-month period, measured as the average nightly usage in hours compared to baseline.

Secondary outcome parameters will address symptomatic improvement and healthcare resource usage [general practitioner (GP), hospital contacts, readmissions].

Design of the clinical investigation

This is a prospective trial in a randomized controlled two-arm parallel group design testing remote monitoring of home NIV for a 3-month' period and comparing outcomes against usual care (NIV without remote monitoring). The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). This trial, registered on ClinicalTrials.gov (NCT04884165), has been approved by the research ethics committee/Health Research Authority (HRA) [Integrated Research Application System (IRAS) ID: 270108], as well as by Guy's & St Thomas' NHS Foundation Trust R&D Department. We will recruit patients who have been established on NIV for more than 3 months from the Lane Fox Unit/Sleep Disorders Centre at Guy's & St Thomas' NHS Foundation Trust. Following an initial analysis of their NIV usage (average use of <4 hours/night) patients will be randomized into two groups: one for remote monitoring using the T4P device at home and one for usual care treatment. The T4P device is a portable, battery-powered apparatus for remote monitoring of NIV. The device will be used in conjunction with NIV and remotely transmit data to the hospital (*Figure 1*). We will follow-up at 6-week (via phone call) and at 3 months during an outpatient clinic appointment (*Figure 2*).

Investigational device and comparators

Description of active treatment

The patients receiving remote monitoring will be shown the device and settings will be recorded. The device will be connected in the circuit to their regular non-invasive ventilator. The device is kept on and active during the entire follow-up period and transmits data via the telephone network (wireless) towards a server and monitored weekly by our team, patient data are anonymised and can only be

Figure 1 SRETT device, Paris, France. The device is placed between the HMV and the tube leading to the facemask. It measures flow and automatically transmits the data to the hospital. The patient does not need to be present for the attachment of the device to their ventilator. This can be organised with the annual service of the equipment (remotely via the use of a courier). HMV, home mechanical ventilation.

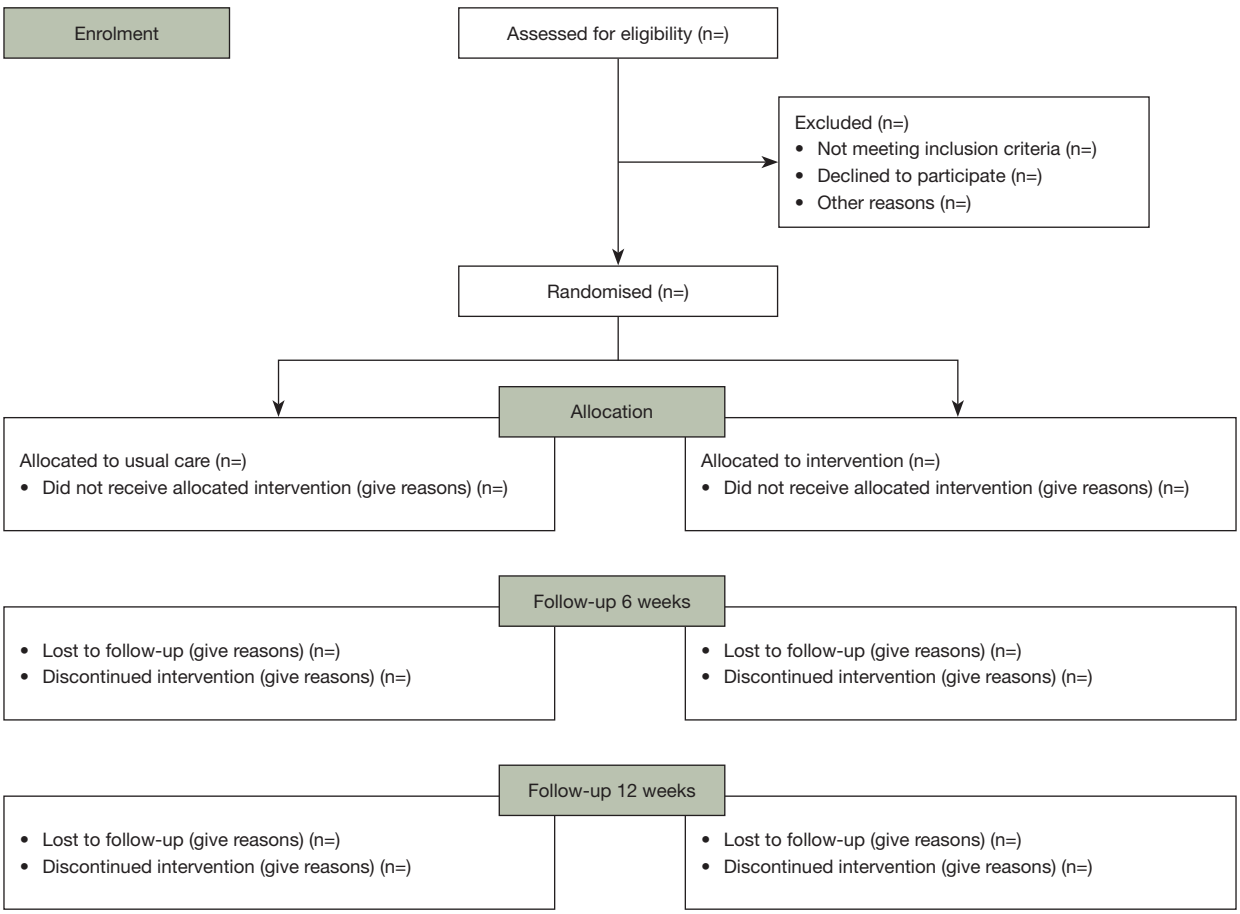

Figure 2 CONSORT flow diagram for the READ-NIV trial. CONSORT, Consolidated Standards of Reporting Trials; NIV, non-invasive ventilation.

linked to a subject with code sheets by the clinical care team.

Advice on sleep hygiene, posture in bed, and general lifestyle (including alcohol, sedatives) will be discussed. A phone call at 6-week and a follow-up visit at 12-week will be organized. At each visit, NIV usage, mask comfort, treatment compliance, and additional healthcare usage will be recorded.

Description of usual care

Patients who are randomised to the usual care group will be provided with their own NIV device, as the standard treatment per current clinical practice. Additionally, their mask fit will be reviewed, advice on sleep hygiene, posture in bed and general lifestyle factors will be discussed. The device will be fitted and explained as standard in the current

clinical service. A phone call at 6-week and a follow-up visit at 12-week will be arranged.

Inclusion criteria

Patients who have hypercapnic respiratory failure ($PaCO_2$ >6 kPa) at enrolment will be included in this study if they fail to use or have been withdrawn from standard care (NIV <4 hours/night) over a 3-month period. We will include patients with a body mass index (BMI) >18.5 kg/m^2, both genders, age 18–90 years.

Exclusion criteria

We will exclude patients without hypercapnic respiratory failure ($PaCO_2$ <6 kPa) or sleep-disordered breathing [apnoea-hypopnoea index (AHI) <5/hour], with exclusively OSA, isolated rapid-eye-movement (REM) sleep associated OSA and patients who are cachectic (BMI <18.5 kg/m^2). Patients should not have severe pulmonary hypertension, valvular heart disease, heart failure [New York Heart Association (NYHA) III–IV], myocardial infarction and significant cardiac arrhythmias, uncontrolled hypertension, active psychiatric disease, or co-existing non-respiratory sleep disorder.

Screening and eligibility assessment

Patients on NIV will be recruited from the Lane Fox Unit at Guy's & St Thomas' NHS Foundation Trust where they are assessed in clinics. The Lane Fox Unit runs daily outpatient clinics at the St Thomas' site. Currently, the Lane Fox Unit cares for >2,000 patients on home NIV.

The direct care team will approach patients after consultation with the consultant and hand out a patient information sheet to discuss the study with them. Informed written consent will be taken after sufficient time to allow for information and questioning. Once a potential participant agrees to participate in the trial they will be invited for further discussion and consent. Participants will be screened, and the remote monitoring period will commence. They will be informed about what the remote monitoring cannot monitor, e.g., physiological variables, and will be offered a clinic date to come to the hospital. If the patient fulfils all inclusion and no exclusion criteria, follow-up will be booked at 6-week (phone call) and at 12-week (clinic appointment) following randomisation.

Due to the coronavirus disease 2019 (COVID-19) pandemic, participants do not have to attend face-to-face appointments if they are shielding or do not feel comfortable to do so. In this case, the telephone consent script will be used and the ventilator equipment will be prepared using couriers to install the medical device (a replacement ventilator is sent prior to the patient's ventilator being brought to the hospital).

Procedures

Informed consent

A member of the direct clinical care team [Good Clinical Practice (GCP)-trained] will take informed consent once the patients have had the opportunity to read and discuss the Patient Information Sheet with sufficient time. It will be clearly stated that the participant is free to withdraw from the study at any time without this affecting any future care and with no obligation to give the reason for withdrawal.

Following sufficient time and the opportunity to question the (co-)investigator or other independent parties to decide whether they will participate in the study, written informed consent will then be obtained. A copy of the signed informed consent will be given to the participants. The original signed form will be kept at the study site and a copy will be inserted in the medical notes.

In times of the COVID-19 pandemic this step may be considered/offered remotely via virtual contact to minimise risk of exposure.

Baseline assessments

At the initial assessment which typically coincides with the regular clinical follow-up (at least annual service of the machine), the medical device will be attached to the home NIV.

The initial assessment will include an outpatient clinic appointment. Patients will be assessed using the following parameters:

(I) Demographics:
  (i) Age;
  (ii) Gender;
  (iii) Height, weight, BMI;
  (iv) Neck circumference;
  (v) Waist:hip (W:H) ratio;
  (vi) Basic lung function [spirometry: forced expiratory volume at 1 second (FEV_1), forced vital capacity (FVC)];
  (vii) Blood pressure and heart rate;
  (viii) Medication use;

(ix) GP appointments/accident and emergency (A&E) contacts/hospitalisations (previous 3 months);

(II) Upper airway:
  (i) Mallampati and Friedman score;

(III) Blood tests:
  (i) Arterial or earlobe blood gas analysis as part of regular clinical care (including pH, pO_2, pCO_2, HCO_3^-);

(IV) Previous sleep study parameters, as measured when NIV was set up:
  (i) AHI/4% oxygen desaturation index (ODI);
  (ii) Average SpO_2 (%);
  (iii) Total recording time;
  (iv) Diagnosis;

(V) Symptom and quality of life scores:
  (i) Epworth Sleepiness Scale (ESS);
  (ii) Stanford Sleepiness Scale (SSS);
  (iii) European Quality of Life Survey-5 Dimensions (EQ-5D) tool;
  (iv) Hospital Anxiety and Depression Scale (HADS);

(VI) NIV adherence:
  (i) Total hours used;
  (ii) Average usage per night (hours): the mean usage per night, calculated as the total hours used divided by the number of nights in the monitoring period, inclusive of both used and unused nights.

During the COVID-19 pandemic, the face-to-face exposure will be minimised as points (I)–(VI) can largely be recorded via remote interaction [except for point (I)-(vii), (I)-(viii), and (III), which may be recorded retrospectively from the last clinic appointment].

Randomization

Randomisation and home treatment

Following the baseline assessment, if eligible, patients will be randomized into active treatment (remote monitoring of NIV) or usual care (NIV). In the active treatment group, patients will receive remote monitoring while using NIV, while in the usual care group participants will receive ongoing NIV therapy (usual care) without remote monitoring.

Randomisation will involve assigning a unique patient number in sequential, ascending chronological order. This number will be a two-digit number prefixed by "R" (e.g., R01, R02, etc.) and will be used to identify the treatment the patient was randomised to. Treatment assignment will be determined according to a computer-generated randomisation list prepared by an individual not directly involved in subject assessments.

Subsequent assessments

Six-week telephone contacts

The patient will receive a telephone call at 6-week to encourage the use of NIV and address any problems with the treatment. Patients will be asked about comfort and adverse events (AEs). The following parameters will be assessed:

(I) ESS;
(II) SSS;
(III) Subjective NIV usage (hours).

At this stage, the patients will be educated on the device/NIV again and encouraged to continue with the usage. This is a remote appointment.

Follow-up at 12-week

At 12-week follow-up the patients will be invited to attend outpatient clinics at the Lane Fox Unit. The assessment will repeat the following measurements (for more details see above):

(I) Demographics;
(II) Upper airway;
(III) Blood tests;
(IV) Symptom and quality of life scores;
(V) NIV usage.

During the COVID-19 pandemic, the face-to-face exposure will be minimised as points (I)–(V) can largely be recorded via remote interaction [except for point (III), which may be recorded retrospectively from the last clinic appointment].

Patients will be given a debriefing by the study team and individual study reports can be requested at this stage, and they will be provided once the entire analysis has been completed.

Definition of end of trial

The trial finishes with the 12-week follow-up assessment. The patients will then be referred back to standard care to be followed up in the outpatient setting at the Lane Fox Unit.

Discontinuation/withdrawal of participants from study treatment

Each participant has the right to withdraw from the study at any time without providing a reason. In addition, the

investigator may discontinue the study at any time if considered necessary for one of the following reasons:

- Ineligibility (either arising during the study or retrospectively);
- Disease progression which requires discontinuation of the study or inability to continue to comply with study procedures;
- Consent withdrawn;
- Lost to follow-up;
- The reason for withdrawal will be recorded, including 'no reason given', in the case report forms (CRFs).

Source data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication and sleep apnoea treatment may be summarised into the CRF).

All documents will be stored safely on password-protected systems in locked rooms at the Lane Fox Unit Clinical Research Facility. Only the research team will have access to the data. Rooms are locked and computers are password protected. 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. Data are stored for the duration of the study (2 years) and then archived (for at least 5 years).

Statistical considerations

Sample size

We performed a sample size analysis based on the previous in-house data on NIV adherence (18). A total of 28 patients is required to enter this two-treatment parallel-design study. The probability is 81 percent that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 4.5 hours of usage. This is based on the assumption that the standard deviation of the response variable is 4. To adjust for the unknown distribution of the primary outcome and based on the lower bound for the asymptotic relative efficiency of the Mann-Whitney *U* test, we have increased the sample size by a further 10% to 32 patients. Considering our experience with previous studies over this time period, we need to account for dropouts and loss-to-follow-up of between 10% and 15%. We therefore propose to study a total sample size of 36 patients, 18 in each group, for this study.

Statistical methods

Statistical analysis will compare the respective outcome parameters (compliance in hours usage/night, comfort) between active stimulation and the control group. Full statistical description will be provided and for each of the variables analyzed, univariate descriptive statistics will present an overview of the data. Continuous variables will be presented as median and interquartile range (IQR), unless otherwise stated. For categorical variables, frequency counts and percentages will be presented as summary statistics for the subgroups of interest. To compare study groups, we will use the Wilcoxon and paired *t*-test for continuous paired variables, and the χ^2 test for categorical variables. The primary outcome parameters (compliance) will be analyzed using the Mann-Whitney *U* test between treatment groups (active treatment) and control group (NIV). Similar analyses will be conducted for secondary outcomes. The trial follows up each patient for at least 12 weeks and some patients will be inevitably lost to follow-up. Sample size estimation assumed 20% of patients would not provide end of study information that could be evaluated. If this rate is observed, data for many patients will be only partially observed. For patients who withdraw or drop out before the end of the study, the "no change assumption" will be used to impute the missing subsequent values. This may introduce a bias if the main reason for drop-out was deterioration. To examine this possibility, sensitivity analysis, including intention-to-treat (ITT) analysis, will be performed to assess the primary efficacy outcome using different imputation methods including "best-case scenario" and "worst-case scenario" possible scores for the missing data as well as Markov Chain Monte Carlo Multiple Imputation. A second per-protocol analysis, including only those subjects with complete follow-up data will also be performed. All analyses will be performed using Stata™ version 12. Differences will be considered significant at $P<0.05$.

Data management

Data handling and record keeping

The participants will be identified by a study specific participants number and/or code in any database. The name and any other identifying detail will not be included in any study data electronic file. The research team will be adhering to Data Protection Act 2018. The data will be collected by the clinical research fellow and controlled by the chief investigator (CI)/principal investigator (PI) on site, as well as in the quarterly data management meetings with the trial

statistician. Records will be kept and archived for 10 years in the Lane Fox Unit CRF. Protocols for data handling are provided by the Trust R&D Department as part of each employee annual mandatory training (data protection/ information governance; online education platform GSTi).

Monitoring

There will be quarterly meetings of the trial steering committee (CI, PI, and clinical research fellow) as well as Data Monitoring meetings every 6-month (CI, statisticians, clinical research fellow).

Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998. The CRFs will not bear the subject's name or other personal identifiable data. The subject's initials, date of birth and trial identification number, will be used for identification. Subjects will be assigned a trial identification number by the study site sequentially starting with one upon enrolment into the study. The study site will maintain a master Subject Identification Log.

Definitions of medical device-related terms

AE

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

- Includes events related to the investigational medical device or comparator;
- This includes events related to the procedures involved;
- For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse device effect (ADE)

An ADE is an AE specifically related to the use of an investigational medical device.

- Includes AEs resulting from inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the device;
- Includes events from use errors or intentional misuse of the investigational medical device.

Serious AE (SAE)

A SAE is any AE that:

- Led to death;
- Led to serious deterioration in the health of the subject, that either resulted in:
  - A life-threatening illness or injury;
  - A permanent impairment of a body structure or a body function;
  - In-patient or prolonged hospitalisation;
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function;
- Planned hospitalisation for a pre-existing condition, or a procedure required by the Clinical Investigation Plan (CIP), without serious deterioration in health is not considered a SAE.

Serious ADE (SADE)

An ADE that has resulted in any of the consequences characteristic of a SAE.

Unanticipated SADE (USADE)

A SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Device deficiency (DD)

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

- This includes malfunctions, use errors, and inadequate labelling.

An AE does not include:

- Medical or surgical procedures; the condition that leads to the procedure is an AE;
- Pre-existing diseases, conditions, or laboratory abnormalities present at the start of the study that do not worsen in frequency or intensity;
- The disease being studied or signs/symptoms associated with the disease unless more severe than expected for the subject's condition.

Assessment of AE

Each AE will be assessed based on the following severity criteria:

- Mild:
  - The AE does not interfere with the subjects' daily routine, and does not require intervention; it causes slight discomfort;
- Moderate:
  - The AE interferes with some aspects of the subjects' routine, or requires intervention, but is not

damaging to health; it causes moderate discomfort;
- Severe:
  - The AE results in alteration, discomfort or disability which is clearly damaging to health;
  - A severity rating of severe does not necessarily categorise the event as an SAE.

Procedures for recording and reporting AEs and DDs

All AEs and SAEs will be recorded in the medical records and CRF following consent.

All SAEs will need to be reported to the sponsor on a SAE form unless stated in the CIP that some expected SAEs will not be reported to the sponsor, with a justification as to why they will not be reported.

For patients on the control arm of a trial, SAEs may not have to be reported to the sponsor but will be recorded in the CRF and medical records.

The CI or PI will complete the sponsor's SAE form and the form will be emailed to the sponsor immediately (or within 24 hours but certainly no later than 24 hours) of his/her becoming aware of the event. The CI or PI will respond to any SAE queries raised by the sponsor as soon as possible.

Discussion

Justification for the design of the clinical investigation

Sleep-disordered breathing is a widespread problem (1,2) and has been increasing over the last two decades as obesity has become more prevalent (3), leaving some cohorts of patients with limited access to sleep services (2). The absence of treatment for hypercapnic respiratory failure can result in adverse health outcomes over the long term, including cardiovascular complications (19), stroke, and excessive daytime sleepiness (20). The most effective treatment for chronic hypercapnic respiratory failure remains NIV. However, the requirement to sleep with a mask can result in poor long-term adherence to treatment (21) leaving few alternatives.

In conclusion, the proposed study will provide us with information about the efficacy of remote monitoring of NIV. We will determine if the selected outcome measures and the data collection timeline are acceptable and feasible for the patients and the study team, and whether this approach could help to streamline an increasingly frequented service in future. The benefit of remote monitoring, particularly in times of a global pandemic, is to deliver healthcare in a timely manner and without face-to-face attendance.

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Footnote

Provenance and Peer Review: This article was a standard submission to the series "Sleep Section" published in the *Journal of Thoracic Disease*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-86/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-86/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-86/coif). The series "Sleep Section" was commissioned by the editorial office without any funding or sponsorship. J.S. serves as an unpaid editorial board member of *Journal of Thoracic Disease*. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). This project has been approved by the research ethics committee/Health Research Authority (HRA) [version 1.0, Integrated Research Application System (IRAS) ID: 270108], as well as by Guy's & St Thomas' NHS Foundation Trust R&D Department. Written informed consent will be signed by the participants.

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