PennState

HRP-591 - Protocol for Human Subject Research

Protocol Title:

Remote pulmonary function testing in amyotrophic lateral sclerosis (ALS)

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Version Date:

March 7, 2021

Clinicaltrials.gov Registration #:

NCT03214224

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University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205 University Park, PA 16802-7014 Phone: 814-865-1775 Fax: 814-863-8699 Email: irb-orp@psu.edu	**College of Medicine and Hershey Medical Center:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855 Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687 Fax number: 717-531-3937 Email: irb-hspo@psu.edu

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1.0 Objectives

1.1 Study Objectives

The specific objective of this proposal is to utilize the practice of telemedicine via connected health devices to enable the guided performance of a remote pulmonary function test (rPFT) in the home. The rationale for this study is to determine whether telemonitoring of respiratory health can help exceed standards of ALS care.

Part 1: Demonstrate the reliability of remote pulmonary function testing, performed via telemedicine, for monitoring respiratory function in patients with amyotrophic lateral sclerosis (ALS)

Primary Hypothesis: There is no difference in the results of PFT and rPFT for respiratory assessment of FVC and MIP.

Secondary Hypothesis: The respiratory therapist, patient, and caregiver will express confidence in conducting the rPFT, as determined by surveys of procedure acceptance.

Part 2: Weekly remote pulmonary function testing (rPFT) and nurse respiratory health coaching (NRHC) in ALS telemedicine

This part randomizes subjects into two arms – both perform weekly rPFT testing and one receives monthly NRHC.

Aim 1: Clinically-meaningful benefit of weekly rPFT

Primary Hypothesis: Home respiratory assessment enables thresholds for non-invasive ventilation (NIV) recommendation to be met on average 30 days sooner when measured weekly compared to the standard 3-month interval.

Secondary Hypothesis: Determine the factors associated with adherence to weekly rPFT procedures.

Aim 2: The impact of NRHC on patient outcomes

Primary Hypothesis: Patient and caregiver teams in the NRHC arm report higher self-efficacy in the respiratory management of the disease at 6 months compared to those in the non-NRHC arm.

Secondary Hypotheses: Patients in the NRHC arm report higher self-efficacy at 12 months, experience less decline of respiratory-related quality of life and fewer respiratory complications compared to those in the non-NRHC arm.

1.2 Primary Study Endpoints

Part 1: The primary endpoint is completion of a standard PFT and an experimental rPFT during a single clinic appointment. At the endpoint, study outcomes will include:

1) The best forced vital capacity (FVC) and maximal inspiratory pressure (MIP) results from that visit's PFT
2) The best FVC and MIP results from that visit's rPFT
3) Survey responses from study participants.

Part 2: The primary endpoint for Aim 1 occurs at the clinic visit following initiation of NIV. At this time, participants will have had weekly measurements of FVC and MIP from self-administered rPFT procedures, as well as standard PFT assessments performed with the assistance of the respiratory therapist at approximately three-month intervals during standard in-person or telehealth clinic appointments. The primary endpoint for Aim 2 will be the change in self-efficacy scores from baseline. Changes will be compared across arms.

1.3 Secondary Study Endpoints

In Part 2: All participants will undergo a training period for rPFT procedures, which entails weekly rPFT coaching by a member of the research team for the first four weeks. To proceed with the remainder of the study, the participant team must demonstrate the ability to perform and transmit rPFT results to the research team during the 4th rPFT training session, and demonstrate FVC test results that are within 10% of the mean values achieved during the first three training sessions. Training sessions will occur at

weeks 8 and 12 to monitor aptitude. Changes in self-reported respiratory quality of life will be measured as part of procedures in Part 2. Participants completing the study may be offered the opportunity to participate in a focus group on their experience in the study, which will be conducted via Penn State Health Zoom videoconferencing and have audio recorded.

2.0 Background

2.1 Scientific Background and Gaps

Non-invasive ventilation (NIV) lengthens survival and improves QoL for patients with ALS.

According to the Quality Measurement Set put forth by the American Academy of Neurology (AAN), two parameters of high importance in ALS care are monitoring of respiratory function and management with NIV [Miller2013]. The practice parameter of the AAN regarding ALS care states that NIV is effective in prolonging survival and slowing the rate of respiratory decline [Miller2009]. NIV has been documented to have a positive effect on QoL in the areas of sleep quality, daytime sleepiness, physical fatigue, and depression [Butz2003]. NIV is recommended when a patient presents with either an FVC≤50% predicted or a MIP > -60 cm H_2O [Miller2009]. It is recommended that PFTs be done at least once every three months, and that doctors discuss options for NIV support regularly.

The multidisciplinary clinical model may not provide optimal management for patients with rapidly progressing respiratory symptoms.

Although disease course varies substantially, some patients experience rapid respiratory decline. In prospective study of 38 newly diagnosed patients, half presented with chronic hypoventilation after one year, necessitating the introduction of NIV [LoCoco2006]. The authors suggest that efforts should be made to evaluate pulmonary function in these patients at least once every month. Furthermore, it has been shown that early initiation of NIV at an FVC threshold of 65% predicted was associated with a significant increase in the median time from ALS diagnosis to death [Lechtzin2007]. The current practice of quarterly respiratory assessment may leave some individuals in danger of developing to untreated respiratory insufficiency or beginning treatment later than would be optimal or other more scientific wording.

Telemedicine has impacted other areas of neurology, but is understudied for efficacy in ALS.

The practice of telemedicine involves the delivery of medical care via long-distance and electronic communication between a health care professional and a patient or another health care professional. This type of intervention can expand medical coverage into underserved regions, while maintaining the high quality of care. Success with telemedicine in other areas of neurology, such as in the treatment of Parkinson's disease [Samii2006], epilepsy [Ahmed2008], and stroke [Demaerschalk2009], provide a framework for achieving positive outcomes.

It is largely unknown whether remotely-provided multidisciplinary care results in outcomes for ALS patients and their caregivers that are comparable to those achieved with traditional care. A review by Hobson et al. identified 32 publications addressing telemedicine in ALS [Hobson2016], which concluded that patients are comfortable using the videoconferencing interface to discuss most concerns, they appreciated the reduced travel time and costs, and the use of telemedicine extended the period for which they received multidisciplinary care. Some programs offered live interaction with providers as a way to delivered care to individuals in rural areas with no alternative treatment options [ALS-Maine2010, Bedlack2014]. Other models utilized a traveling nurse to perform the assessment in the patient's home, which is stored and forwarded to the appropriate providers at the multidisciplinary clinic [Pulley2015, McClellan2013]. Others have taken on a more passive role, with monitoring of oximetry and non-invasive ventilation (NIV) data by a nurse led to fewer hospital visits, and higher treatment adherence [Pinto2010, Vitacca2010, Ashcroft2016].

Despite these results, Hobson concludes "*There is limited evidence to recommend the use of telemedicine or telehealth in the case of patients with ALS. Using telehealth as an alternative to clinic visits appears technically feasible but further research needs to establish its safety and effectiveness*" [Hobson2016]. To address gaps in telemedicine care, randomized controlled clinical trials must be used to identify methods that can meet or surpass the standards of in-person assessment.

2.2 Previous Data

Preliminary work by our group as part of a pilot study assessing the benefits of ALS telemedicine has shown that the practice of live telemedicine is viewed favorably by ALS patients, caregivers, and multidisciplinary ALS team members, although less so by the latter group (Figure 1, [Morris2016, Geronimo2017]). Overall, the three rater groups were concerned that the lack of physical contact lessened the ability for providers to deliver equal care. This led us to identify and act upon one area of care that could be improved in telemedicine – assessment of breathing function.

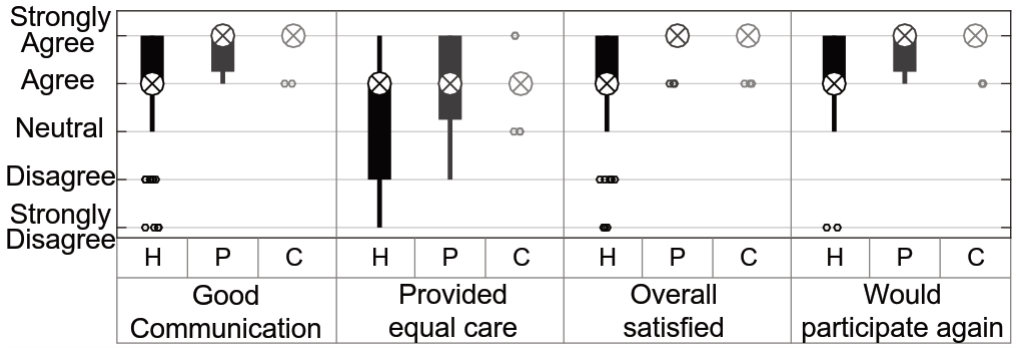

Figure 1: Patient (P), caregiver (C), and health care provider (H) ratings of the ALS telemedicine pilot in four domains [Geronimo2017]. Circles containing an X mark the medians, thick lines span the first to third quartile of data, with thin lines extending up to two times this range. Outliers are those small circles outside this range

From January to September 2018, the procedures for part 1 were completed in forty patients. The main result was that the simulated remote assessment produced similar values of FVC and MIP compared to standard assessments (Figure 2). In this sample, the specificity and sensitivity of FVC measurements were 100%, for MIP assessments was 89% and 82%, respectively [Geronimo2019]. The results of part 1 indicate that rPFTs are accurate and acceptable measures of respiratory health.

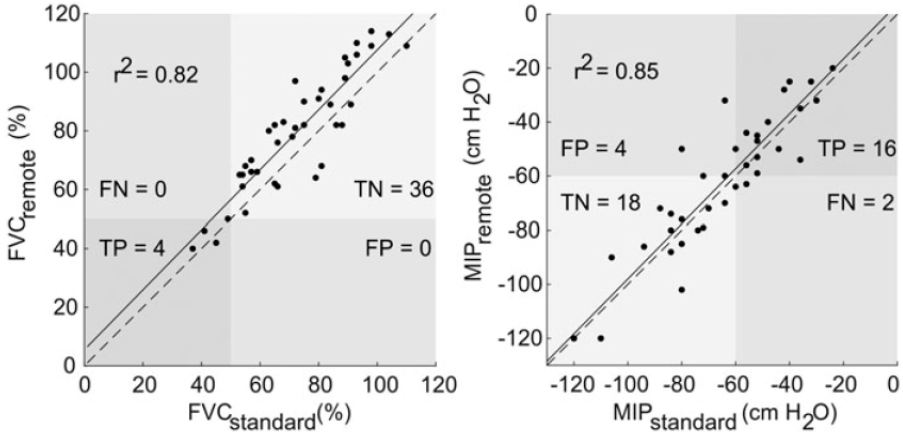

Figure 2: FVC (Left) and MIP (Right) data from 40 subjects of the rPFT pilot study, comparing standard PFT measures to therapist-guided remote assessments. Four shaded quadrants are created by segmenting standard and remote tests by predefined clinical thresholds.

2.3 Study Rationale

The rationale for this study is to determine whether telemonitoring of respiratory health can help exceed standards of ALS care.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

Part 1

Patients:

1) Possess a diagnosis of definite, probable, probable laboratory-supported, or possible ALS by revised El Escorial research criteria [Brooks2000], or a diagnosis of primary lateral sclerosis (PLS, upper motor neuron involvement only) or progressive muscular atrophy (PMA, lower motor neuron involvement only).
2) Be 18 years of age or older.
3) Have a caregiver available to participate in the study

Caregivers:

1) Be 18 years of age or older, of either gender.
2) Be able and willing to provide informed consent.

Controls:

1) Be 18 years of age or older, of either gender.
2) Be able and willing to provide informed consent.

Respiratory Therapist

1) Be a member of the Hershey Medical Center ALS multidisciplinary care team.
2) Be able and willing to provide verbal informed consent after receiving a summary explanation of research (SER).

Part 2:

Patients:

1) Possess a diagnosis of definite, probable, probable laboratory-supported, or possible ALS by revised El Escorial research criteria.
2) Be 18 years of age or older.
3) Have a caregiver available to assist with home PFTs or, in the opinion of the investigator, can perform home PFTs unassisted.
4) Symptom onset within the last three years.
5) Have a computer and home internet service sufficient for engaging in telemedicine sessions.
6) Have a second device capable of downloading the spirometer application from an app store (Android- or iOS-based smartphone or tablet).

Caregivers (not necessary to be enrolled if patient can perform home PFTs unassisted):

1) Be 18 years of age or older, of either gender.
2) Be able and willing to provide informed consent.

3.2 Exclusion Criteria

Part 1

Patients:
1) Cognitive impairment, as judged by the ALS clinic neurologist, that prevents participation in the study.
2) Unable to perform pulmonary function testing with mouthpiece or with mask, as determined by one of the study investigators.

Caregivers: None

Controls: None

Respiratory Therapists: None

Part 2 imposes additional exclusion criteria for patients only.

Patients:
3) Use of NIV or diaphragm pacer at time of obtaining informed consent.
4) FVC ≤50% predicted

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Participants may voluntarily withdraw from the study at any time. The research team may also terminate the study if the participant does not meet the inclusion criteria or exhibits one or more of the exclusion criteria during the course of the study. For part 2 of the study, participants may be removed if they exhibit non-compliance to study procedures. Non-compliance is defined as 30 days without submission of an rPFT report if still eligible for rPFT reporting, or 3 months without a nurse coaching session if in the nurse coaching arm.

3.3.2 Follow-up for withdrawn subjects

The research team will follow up with withdrawn subjects to collect the research equipment. If the participant agrees, they will be given the endpoint assessment to document their reason for withdrawal. They may be asked to participate in a future focus group on subject experience in the study. There will be no additional follow-up. The withdrawn subjects may be replaced by another patient and caregiver from the recruitment waitlist.

4.0 Recruitment Methods

4.1 Identification of subjects

Potential patient participants will be identified by study staff of the Penn State Hershey ALS center at the time they are seen for routine visits to the Penn State Hershey ALS Clinic, or based on their responses to recruitment letters (see below). Potential subjects may also learn of the study by a flyer posted in the ALS clinic area. Practice control participants will be recruited from clinical staff. Respiratory therapists sought for participation in the study will be those providing respiratory therapy services to ALS patients in the clinic on the date of the study. The study will be listed on StudyFinder.

4.2 Recruitment process

Potential patients and caregivers will be approached by study staff of the Penn State Hershey ALS center at the time they are seen for routine in-person or telehealth visits to the Penn State Hershey ALS Clinic. In addition, a letter will be sent via mail or email to patients of the Penn State Hershey Medical Center ALS clinic, as well as those who are registered with the Greater Philadelphia chapter of the ALS

Association. A flyer will be posted in the clinic area informing patients of the study. Study information and contact information will be posted on Studyfinder.

Interested individuals will respond to a member of the study team who will follow up as in Section 4.4.

Practice control participants will be recruited from clinical staff by members of the study team.

Respiratory therapists will be approached by study staff prior to their first rPFT administration so that they may be delivered the SER and give verbal consent.

4.3 Recruitment materials

Potential patient participants may be mailed (see "Recruitment Letter" in Recruitment Materials) or emailed (see "Email Recruitment Letter" in Recruitment Materials) a recruitment letter. There will also be a flyer for the study posted within the clinic area (see "Study Flyer" in Recruitment Materials).

4.4 Eligibility/screening of subjects

Before enrolling prospective participants, we will contact the potential them by phone, email, or in person. For those individuals who are Hershey Medical Center patients, we will ask for their consent to access their medical record to confirm certain inclusion and exclusion criteria. For potential participants who are not treated at the Hershey Medical Center, we will request that they release medical records to us from their doctor. These will be reviewed by the study physician to confirm the diagnosis of ALS and other inclusion/exclusion criteria.

We will confirm that they and their caregiver are aware of the study requirements and are willing to complete the study procedures according to the procedures described (see "Screening questionnaire" in recruitment materials). This form addresses the remaining inclusion and exclusion criteria. In it, we will ask the patient if they anticipate any issues relating to performing spirometry or lack or devices or adequate internet access to participate (in the case of Part 2). They will be directed to an online internet speed test to ensure sufficient connection speed. We also ask if the caregiver anticipates they will be able assist in administering the procedure. If a caregiver is not available, a patient may be enrolled in the study if the investigator judges that they have the capacity to perform home PFTs unassisted. If at any point in the study a patient enrolled without a caregiver is no longer able to perform the home tests without additional assistance, a caregiver must be enrolled to aid home PFT administration, or the patient will be exited from the rPFT portion of the study.

Eligibility of respiratory therapists will be determined by their role in the Hershey Medical Center ALS clinic as well as their verbal consent to participate in the study.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

A member of the study team will review the informed consent documents with the participants and receive their written consent to participate in the study. This consent procedure will take place only after initial screening procedures have been completed. This will take place either at the Hershey Medical Center ALS clinic, over the phone, or using the telemedicine interface between the clinic and the patient's home.

Prior to any phone consent, participants will be provided with a physical or electronic copy of the informed consent document. The researcher attesting to the appropriateness of the consent process will complete the **Phone Consent Signature Page**. The patient will mail back the signed consent forms, and the member of the research team who explained the research will attach the completed Phone Consent Signature Page to the consent forms with the original signatures of the patient and LAR. The study team will then send the patient and LAR a copy of their signed consent form and the Phone Consent Signature Page for their records. Once the original signed documents are received by the study team, the participant may begin research procedures.

A member of the study team will deliver the summary explanation of research (SER) to participating respiratory therapists before their first clinical interaction in this study. The SER will be delivered at the Hershey Medical Center ALS Clinic.

5.1.1.2 Coercion or Undue Influence during Consent

Patients will be informed that the treatment they receive for ALS will not be affected by their choice to participate in the study. Explanation of the study and obtaining consent will be performed by a member of the research team who is not part of the clinical care team.

5.1.2 Waiver or alteration of the informed consent requirement

Partial waiver of consent is requested for pre-screening purposes.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

We will verify that we are using the most current IRB-approved version of the study specific consent form and that the consent form is in language understandable to the subject. Whenever possible, the consent form will be provided to the subject in advance of the consent discussion.

A member of the research team will review the informed consent documents with the prospective participants and receive their written consent to participate in the study described in this protocol. If performed over the phone or telemedicine interfaces, participants will sign a physical copy of the form and mail/email it to the research team. The patient and the caregiver, if available, will sign their own consent forms. This consent procedure will take place either in the ALS Clinic or over the telemedicine interface between the clinic and the patient's home. Written documentation of consent will be delivered after participants have been given an overview of the study's goals, procedures, risks, and benefits. Participants will receive a copy of the consent after it has been signed and dated by the person explaining the study.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

Verbal consent will be obtained by the respiratory therapist participant before their first study session.

Verbal consent will also be obtained by participants via telephone to ask screening questions.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Non-English speaking subjects will not be enrolled.

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent

The physician investigator will determine whether an individual is capable of providing informed consent. Cognitively impaired patients will not be enrolled in this study.

Due to disease progression, some subjects may not be able to physically sign the consent form, regardless of cognitive status thereby requesting LAR signature.

5.3.2.2 Adults Unable To Consent

The procedure outlined in HRP 013, "SOP: Legally Authorized Representatives, Children, and Guardians" will be followed to determine the legally authorized representative capable of providing informed consent. Written informed consent from the subject's LAR will be obtained before any study procedures take place.

5.3.2.3 Assent of Adults Unable to Consent

Subjects who are unable to sign the consent will be asked to provide verbal assent, which may be provided using an assistive communication device.

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

N/A

5.3.3.2 Assent of subjects who are not yet adults

N/A

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☒ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

The identifiers collected in the study and stored on REDCap will be maintained until the completion of the study, including analysis, and dissemination of results. Email addresses and phone numbers may be retained for those participants who are interested in participating in future research studies.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Certain PHI is used to maintain contact with the research subject though phone, mail, or email. Other PHI are variables related to the analysis of the study, such as date of birth, diagnosis, and gender. Voice recordings of the subject during coaching sessions will be used to assess quality and consistency of NRHC procedures. Voice recording of post-study focus groups will allow for easy transcription for analysis.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

In order to be able to screen participants, we will need to access their medical record, either through the Hershey Medical Center EMR or through the release of records from an external care provider. We will access patients' medical records for the purpose of confirming the diagnosis of ALS before we admit them into the study and obtain consent. In order to contact patients, to describe the study and schedule the study visit, we will need access to phone numbers and email. Additionally, in the case of Study 2, we will need to know the patient's address to be able to ship the rPFT kit.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

Part 1: This is a self-controlled study where each participant will be administered a standard of care PFT for measurement of FVC and MIP, as well as an rPFT, separated by at least an hour, for measurement of

experimental FVC and MIP. The rPFT is guided by a respiratory therapist in another room, utilizing the telemedicine interface of the Hersey ALS clinic and devices for measuring FVC and MIP (**Error! Reference source not found.**).

Air Smart spirometer and mouthpiece	Pressure gauge and mouthpiece
	

Figure 3: Tools for remote pulmonary testing. Left: Air Smart Spirometer and turbine. Right: respiratory pressure meter and mouthpiece.

Part 2: This is a two-arm, randomized study to determine 1) whether weekly monitoring of respiratory function can lead to timelier initiation of NIV and 2) whether structured nurse coaching leads to improved self-efficacy for managing disease and better maintenance of respiratory health. For enrollees in both arms, standard FVC and MIP measurements obtained approximately every three months by the respiratory therapist during ALS Clinic are supplemented with self-administered rPFTs performed weekly. To train the participant in the performance of rPFTs, a member of the research team will be present either in person or virtually to guide the patient and caregiver in the appropriate use of the equipment during the first four weeks of the study. Enrollees in the NRHC arm will additionally receive monthly coaching with the study nurse via telehealth. Approximately 5% of NRHC sessions will include audio recordings that will be evaluated by a second clinician nurse for quality and consistency.

<u>rPFT protocol</u>

Two devices are used to measure respiratory function:

1) Air Smart Spirometer, NuvoAir AB

The following information is paraphrased from the user manual, which is included in the “devices” page of the protocol.

The Air Smart Spirometer measures the forced vital capacity (FVC) in a forced expiratory maneuver. The Air Smart Spirometer is intended to be used by:

- Healthcare professionals trained to perform spirometry tests on patients.
- Adults trained by healthcare professionals or through self-learning who understand how to perform a high quality spirometry test.

The Air Smart Spirometer works iOS and Android devices. The Air Smart Spirometer has a built-in battery designed to function for at least 2 years or 1 000 single tests. The Air Smart Spirometer is designed to work with disposable and single use FlowMir® turbines. When performing a spirometry test, the user exhales into the turbine. The airflow generated sets a rotor in motion. The Air Smart Spirometer

registers the speed of the spinning rotor, converts it and transfers the data to the smartphone with the Air Smart Spirometer app.

The study subject will conduct 3-5 spirometry maneuvers to generate a forced vital capacity using the spirometer and associated application. Subjects may use the "Home Monitoring" version of the app, which requires the user to enter their date of birth, height, gender, and ethnicity. Alternatively, the "Clinical Trial" version of the application may pair the subject's smartphone to a cloud database hosted by Nuvoair using a subject-specific code. The coordinator will enter date of birth, height, gender, and ethnicity into the database, to which all spirometry recordings made by the subject will be synced.

2) NIF Meter NS 120-TRR, Instrumentation Industries

The following information is paraphrased from the user manual, which is included in the “devices” page of the protocol.

“The Instrumentation Industries, Inc. Negative Inspiratory Force (NIF) Meters are devices used to measure and monitor patient inspiratory effort. During use the NIF Meter is attached to the patient airway at a point that provides optimal readings of patient respiratory effort.”

During each guided rPFT administration, a member of the research team and/or respiratory therapist will guide the patient and caregiver through three valid maneuvers of the FVC and MIP tests. The participants prepare the spirometer by connecting it to the tablet and opening the associated application. The patient is told to sit as upright as possible for the measurement of FVC. They will be told that to do this they will 1) inhale maximally, 2) exhale as hard and fast as possible, and 3) continue to exhale until indicated by the therapist. The researcher will also demonstrate this procedure to the patient. The caregiver applies nose clips to block airflow through the nose, holds the turbine of the spirometer to the patient’s mouth and performs three repetitions of this sequence, with periods of relaxation between testings. Testing is repeated until three valid maneuvers are achieved. The application on the tablet computes the FVC and percentage predicted value, the best of which is retained.

To perform the MIP test, the participant inserts the mouthpiece into the pressure meter. The patient is told they will be asked to draw breath in as quickly and powerfully as possible, for at least one second. The researcher tells the caregiver to place a finger over the valve outlet so that no air flows through the mouthpiece during inhalation. Nose clips will be used. The patient performs three repetitions of this task. The maximal negative pressure from a valid run is recorded.

Each piece of reusable equipment will be labeled with an identification number. A log of all loaned materials will be maintained by the researchers. This log, included in the supporting documents, will be maintained on REDCap. Before delivery of the system to the study participant, each piece of equipment will be inspected and tested. This study will not collect prior medical therapy relevant to the use of the device. There are no restrictions on medicines or therapies used by the participants in this study.

<u>Randomization (Part 2 only)</u>

An unblinded blocked minimization method will randomize participants based on demonstrated factors affecting prognosis [Chio2009]. These include: time since diagnosis, age at consent, most recent FVC, and FVC slope from up to the previous year, if available.

<u>NRHC protocol (Part 2 only)</u>

Nurse Respiratory Health Coaching - The NRHC intervention follows the "teamlet" model described by Bennett et al. [Bennett2010], made up of the research coordinator who performs respiratory testing, and the nurse practitioner using an ALS-tailored variant of the GROW model. 5 percent of NRHC sessions will undergo audio recording and be reviewed by a nurse-researcher on the study team.

- Goal setting - Discuss patient-driven goals for the session as well as for short and long term respiratory management for the patient/caregiver dyad.
- Reality Check - Explore current situation. Review PFT results and answers to the respiratory questionnaire. Share information and gently challenge assumptions that may present barriers to goal attainment.
- Options - Identify options and alternative strategies, including NIV, Cough Assist, Nebulizer, and Breath Stacking. Discuss patient and system barriers to pursuing these options.
- Wrap-up - Coach dyad towards implementing endorsed plan with a focus on trouble-shooting barriers and enhancing facilitators to successful implementation. Address what is to be done and by whom.

Those randomized to the coaching arm will receive brief coaching checkups from another nurse on the study team who is not the coach. These will occur during the 4th and 8th months after randomization, and at study exit. The nurse performing the checkup will guide the participant to reflect on the coaching process, using prompts provided in the Focus Group template. Coaching checkups will be by phone or via Penn State Health Zoom videoconferencing. Audio of these sessions may be recorded.

Focus groups (Part 2 only)

Focus groups may be convened comprised of subjects who have completed the study. Focus groups will ask subjects to reflect on their experiences in the study regarding the use of technology, nurse coaching, and any behavioral changes observed. Focus groups will be conducted either at the location of the Hershey ALS Clinic or via Penn State Health Zoom videoconferencing. Audio recordings of the focus groups will be captured.

7.2 Study Procedures

7.2.1 Part 1

On or before the date scheduled for Study 1, a member of the research team who is not part of the ALS clinical team will describe the procedures and receive written informed consent from the patient and caregiver dyad, as well as the respiratory therapist. The participant team undergoes the initial in-person pulmonary function testing, followed 2-3 hours later at the end of the clinical visit by the rPFT. rPFT administration is described in Section 7.4.2. For roughly half of the enrolled participants, the order of assessments is reversed. Following the study procedures, the therapist and patient/caregiver dyad will complete a survey concerning the ease of use and confidence in the rPFT assessment.

Part 1 includes the recruitment of up to 20 practice control participants for validation of the study procedures. They will perform the same procedures as the patient and caregiver, in conjunction with the respiratory therapist.

7.2.2 Part 2

Following consent, the researcher will collect demographic and clinical information: date of birth, gender, time since symptom onset, ALSF Functional Rating Scale - Revised, PFT history, and region of symptom onset. The researcher will guide the subject through completion of the respiratory health questionnaire and self-efficacy assessment.

Subjects consented on the day of their in-person clinic visit will be sent home with an rPFT kit and scheduled for weekly training appointments with a member of the research team. For patients consented remotely, the research team will ship a kit and schedule them for weekly training appointments.

The weekly schedule following the first site visit at week 0 is shown in **Error! Reference source not found.**. Weekly training sessions will be guided through the telehealth interface by a member of the research team. If by the 4th training session the participant is able to complete rPFT procedures without guidance as determined by the researcher-completed aptitude assessment, and achieve an FVC result within 10% of the average value from the first three sessions, the participants will be randomized to one of the two study arms.

Patients may be enrolled without a caregiver available if the investigator determines that the patient is able to perform the home breathing tests without additional assistance. The patient's ability to perform these tests solo will be reviewed at a minimum interval of successive clinic visits. If they are no longer able to perform the home tests without additional assistance, a caregiver must be enrolled aid home PFT administration, or they will be exited from the rPFT portion of the study. Caregivers enrolled part-way into the study will receive training on administering rPFTs at that time.

rPFT arm: Subjects will continue to self-administer rPFTs every week. A research team member will schedule rPFT training appointments at weeks 8 and 12 order to re-assess aptitude. rPFT procedures are not performed during weeks in which a clinical appointment occurs. Subjects will complete the following patient-reported outcomes:

- Respiratory health questionnaire (monthly) - The questionnaire contains three Patient-Reported Outcomes Measurement Information System (PROMIS) sub-scales on Dyspnea Characteristics (5 items, [PROdc2016]), Dyspnea Functional Limitations (10 items, [PROdfl2016]), and Sleep Related Impairment (8 items, [PROsri2016]). The PROMIS sub-scales, all of which utilize Likert-type scaling, will be summed as composite scores, with higher numbers indicating poorer quality of life. Also included are seven questions regarding respiratory complications experienced in the previous month.
- Self-efficacy assessment (quarterly) - The self-efficacy assessment contains questions from the PROMIS item banks on Self-Efficacy for Managing Symptoms (9 items, [PROms2017]), Self-Efficacy for Managing Social Interactions (5 items, [PROsi2017]), and Self-Efficacy for Managing Medications and Treatments (4 items, [PROmt2017]). These assessment tools, designed for use in chronic conditions, are scored as an average of individual components on a 1-5 scale.
- ALS-Specific Quality of Life (quarterly) – Brief Form [Felgoise2018] – 20 questions in 5 domains encompassing quality of life. If the subject has completed this document in the last 30 days as part of clinical care, we may access this data from their chart.

rPFT + NRHC arm: In addition to the rPFT schedule described above, subjects randomized to the NRHC arm will begin monthly coaching sessions, with the first session scheduled as close as possible to the randomization date (week 4). These coaching sessions will take place over the ALS clinic telehealth interface and will last up to 30 minutes. Coaching sessions will end at the completion of the 5th study session, with approximately 12 sessions per subject. Five percent of total sessions (20 subjects $\times$ 12 sessions $\times$ 5% = 12 sessions) will have audio recorded. Audio recordings are collected for review of quality and consistency of NRHC interactions by a second nurse member of the study team.

Coaching checkups will be initiated by a nurse member of the study team who is not involved in patient coaching. These will occur at months 4 and 8 after randomization into the rPFT+NRHC arm and at study exit. These will last 15-30 minutes each.

If a subject records an FVC ≤50% predicted or a MIP > -60 cm H20, the researcher will forward the test report to the ALS clinical team, including nurse, respiratory therapist, and neurologist. If the decision is made to initiate NIV, the ALS clinic physician will provide an order, and the ALS clinic nurse will arrange for initiation of in-home NIV via a third-party vendor according to usual standards of care. At the initiation of NIV, the subject stops rPFT procedures and returns the study equipment. The remaining procedures continue through the end of the study period. The subject can also opt to end the study at any time.

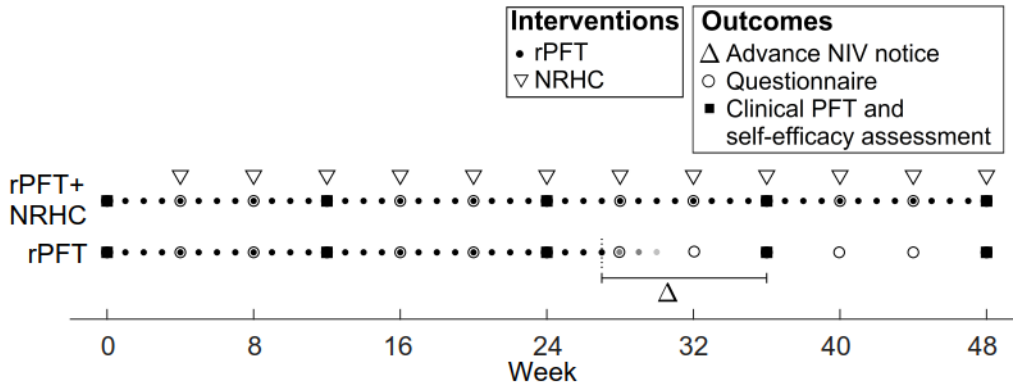

Figure 4: Timeline of study interventions and outcomes. The primary outcome of Aim 1 is the time difference between first identification of NIV need and the next standard clinic visit, (Δ). An example Δ of 60 days is shown following threshold crossing indicated by the dotted vertical line. The outcomes of the second aim are monthly respiratory questionnaires and self-efficacy assessments completed in clinic.

When the subject has completed all study procedures or withdrawn from the study, they may be asked to participate in a focus group which will have them reflect on their experiences in the study regarding the use of technology, nurse coaching, and any behavioral changes observed.

7.3 Duration of Participation

Part 1: The study procedures, including screening, consent, assessment, and survey, are expected to take 45 minutes. Administration of the simulated PFT with patient participants will be performed on the day of a scheduled clinic visit.

Part 2: Patient participants will be enrolled for approximately one year. During this time, patients will engage in approximately five standard PFT assessments during in-person or telehealth clinic activities, requiring no additional time commitment. Participants will also complete approximately 47 rPFTs, each taking 10-30 minutes to complete, depending on level of experience. The respiratory questionnaire and the self-efficacy assessment each take approximately 10 minutes to complete. Finally, those in the NRHC arm will receive up to 12-30 minute coaching sessions and 3-30 minute coaching checkups. Patients receiving nurse coaching can expect a total time commitment of approximately 26.5 hours, and those in the non-coached group can expect 19 hours of time spent on study procedures. Caregivers may be enrolled for the same period or for a shorter period depending whether one is available and needed at the initiation of study procedures.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Approximately (but no more than) 123. We will enroll **40 patient/caregiver teams for Part 1** and up to **60 patient/caregiver teams for Part 2** to achieve 40 pairs completing procedures for Part 2. Participants in the two studies may overlap. Up to **20 practice control participants** may be recruited for Part 1. Up to **three respiratory therapists** will also be recruited for these studies.

8.2 Sample size determination

Our sample size is predetermined based on our subjective ability to recruit patients within the time frame of the study. Power analysis was based on studies of FVC decline. Lo Coco et al., [LoCoco2006], showed that 50% of study participants dropped below 50% predicted FVC in one year. Given that our exclusion criteria for Part 2 will reject many of the 37% of individuals in their study who were "slow progressors," we estimate that 75% of patients enrolled in our study will meet the respiratory criteria to recommend NIV. This results in a sample size per arm of n=15, which provides 80% power to detect a difference in mean outcome between the two groups if the effect size is found to be 0.95.

Assuming a monthly change in FVC of 3.5±3.4% found by Schiffman et al. [Schiffman1993], we conducted 10,000 Monte-Carlo simulations of 40 participants declining at this rate for 12 months. Half were sampled once every three months, and half were sampled every month. 80.6±6.3% of simulated participants met the requirements for NIV recommendation, in roughly equal proportions across groups. The average FVC at recommendation was 47.0% predicted in the experimental group, and 43.4% predicted in the control group. The effect size of the difference in FVC between groups was .964±.343.

8.3 Statistical methods

Part 1: The primary hypothesis is that there is no difference in the results of PFT and rPFT for respiratory assessment of FVC and MIP. We will use a paired sample t-test to determine if the mean test results are comparable between the standard and experimental treatments. We will conduct a qualitative analysis to determine whether the patient, caregiver, and therapist determine the rPFT to be an effective way to conduct tests of breathing function.

Part 2: Aim 1 will be analyzed to determine if the study date of NIV initiation is at least 30 days sooner based on rPFTs compared to standard clinic PFTs. This will be done using a non-parametric two sample test of means, the Wilcoxon-Mann-Whitney rank sum test. For analysis of Aim 2, a linear mixed effects model will be used to analyze the change from baseline between study groups of self-efficacy scores and respiratory health [Verbeke2000]. The effect size will be quantified from the model using the difference in means between the groups with their associated 95% confidence intervals.

9.0 Confidentiality, Privacy and Data Management

Please see HRP-598 Research Data Plan Review Form

10.0 Data and Safety Monitoring Plan

N/A

11.0 Risks

The risks posed to subjects in the study will be no different than those presented during standard of care administration of pulmonary function testing. In addition to guidance from the research team, those participating in remote assessments will be required to have a caregiver present to aid the patient in case assistance is required.

Loss of confidentiality is a risk of this study, but steps are taken to project the participants' identities. Personal information, clinical assessments, test results, and survey responses will be labeled with a participant code assigned by REDCap and stored in this database. All data containing PHI will be collected either from the electronic medical record or in person. Data transmitted through the Air Smart Spirometer app will be labeled with the user's initials, gender, date of birth, and height, end ethnicity. Audio from telemedicine interactions during nurse coaching interventions may be stored on REDCap for review by a member of the research team. Video from telemedicine interactions and focus groups will not be stored.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

Participants in Part 2 may benefit from timelier recommendation of NIV support.

12.2 Potential Benefits to Others

This knowledge gained by this study may benefit those who are managed remotely using telemedicine. This will enable virtual care to be more equivalent to in-person care.

13.0 Sharing Results with Subjects

Participants will be informed of the results of their breathing tests at each visit. The respiratory therapist and nurse clinician will be responsible for making appropriate recommendations based on those results, and following up with the neurologist for NIV recommendation if necessary.

Participants will not be informed of overall study results unless they request it. Study results include the public presentation of research at academic conferences or through peer-reviewed journals.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

There will be no compensation in Part 1. For Part 2, the patient participant will be compensated $10 per month they are in the study, capped at a total compensation of $120.

15.0 Economic Burden to Subjects

15.1 Costs

Subjects will incur no cost for their participation.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

For Part 1, the consent procedure will be conducted within the ALS Clinic at 30 Hope Drive on the Hershey Medical Center campus. The clinic houses a room set up by the Penn State Hershey information technology department that is dedicated to ALS telemedicine. This room will also be used as the site for the respiratory therapist to conduct the rPFT assessment. This research room is in a private location and contains all the tools necessary for engaging in secure videoconferencing.

For Part 2, consent may be obtained in the ALS clinic or over the telemedicine interface. The home of the patient will be the site of most of the study procedures. When engaging in procedures via telehealth, a member of the study team will communicate with the participant from a private office or from a research room in the ALS clinic. The study team will exclusively use the HIPAA-compliant HMC Telemedicine system by AmWell that is used for routine clinical care of ALS patients.

16.2 Feasibility of recruiting the required number of subjects

We anticipate high interest in Part 1 due to the short time commitment and participation during a single clinical visit. We anticipate no issues recruiting 40 individuals for this study. The resource and timing limitations of Part 2 will make enrollment more challenging. We expect to screen and consent 60 participants, with the goal of having 40 participants meet the endpoint criteria. We anticipate the participation of two respiratory therapists to aid with rPFT administration.

16.3 PI Time devoted to conducting the research

The PI has devoted 25% time to oversight of this project, involving discussion the goals, procedures, analysis, and data review, as well as input on clinical matters as requested by members of the study team.

16.4 Availability of medical or psychological resources

If any medical or psychological resources are found to be needed during the course of the study, the participant will be directed to contact his/her Primary Care Provider or emergency care if warranted.

16.5 Process for informing Study Team

Before recruitment and any time a change is made to the protocol, the study team will meet to discuss changes in their role within the study, if applicable.

17.0 Other Approvals

17.1 Other Approvals from External Entities

N/A

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Clinical Research Center (CRC) Advisory Committee – All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

N/A

19.0 Adverse Event Reporting

19.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

The study will be monitored by the Clinical Trial Monitoring Team from the Department of Public Health Sciences at Penn State Hershey College of Medicine. The monitors will provide an independent review of the regulatory and subject records and the data collected to assure compliance with the protocol, GCP, and applicable federal regulations. The monitoring will occur at regular intervals after the enrollment of the first subject and the times will be predetermined by the monitoring plan developed by the Clinical Trial Monitoring Team.

21.0 Future Undetermined Research: Data and Specimen Banking

21.1 Data and/or specimens being stored

Clinical tests, surveys, and respiratory assessment results will be retained indefinitely for undefined future research. All data will be labeled with the subject's REDCap code.

21.2 Location of storage

Digital data including respiratory test results and surveys will be retained on Dr. Geronimo's Hersheymed.net drive in a password protected folder. Clinical tests that are administered in paper form will be retained in the locked offices of the research team.

21.3 Duration of storage

Data will be stored for six years after study closure.

21.4 Access to data and/or specimens

The study team will have access to the data.

21.5 Procedures to release data or specimens

Coded data, including surveys, clinical tests, and respiratory assessments will be made available to individuals performing research in ALS. We will require a formal request from such researchers on Institutional letterhead.

21.6 Process for returning results

We will not return to study participants results derived from future undetermined research.

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