PennState

HRP-591 - Protocol for Human Subject Research

Protocol Title:

Remote pulmonary function testing in amyotrophic lateral sclerosis (ALS)

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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: Monitor more closely the course of respiratory function over time in patients with ALS by using remote pulmonary function testing, performed via telemedicine.

Primary Hypothesis: Home respiratory assessment enables thresholds for Non-invasive ventilation (NIV) recommendation to be met in the experimental group significantly closer to the initiation criteria, at a time when quality of life is higher, compared to the control group.

Secondary Hypothesis: Telemonitoring of respiratory health in the experimental group will maintain higher quality of life, and lengthen survival.

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 FVC and 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 each person in the study is the completion of the fifth clinical visit, during which the control arm should have complete data for the following outcomes:

1) The results of five PFT administrations at 3 month intervals
2) Patient and caregiver monthly surveys

In addition, the experimental group will have engaged in eight additional guided rPFT assessments with the respiratory therapist over the telemedicine interface.

1.3 Secondary Study Endpoints

Study participants will be followed after completion of study procedures, and their survival data will be 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.

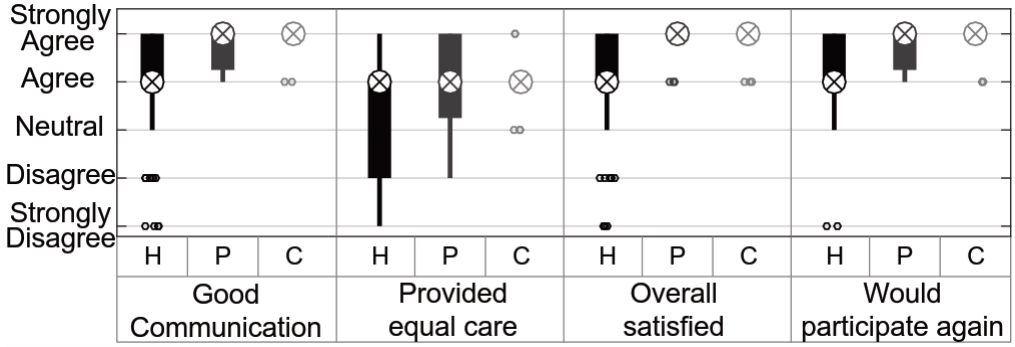

Figure 1: Patient (P), caregiver (C), and health care provider (H) ratings of the ALS telemedicine pilot in four domains [Geronimo2017]. Circles containing an X mark the medians, thick lines span the first to third quartile of data, with thin lines extending up to two times this range. Outliers are those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

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 participate in the study.

4) Symptom onset within the last three years.
5) Intent to attend the Penn State Hershey ALS clinic every three months for the next year.
6) Have home wireless internet service sufficient for engaging in telemedicine sessions.

3.2 Exclusion Criteria

Part 1

Patients:

1) Cognitive impairment, as judged by the ALS clinic neurologist, that prevents participation in the study.
2) ALS Functional Rating Scale (ALSFRS-R) [Cedarbaum1999] score on day of screening of less than or equal to 2 on all of the items for speech, swallowing, and salivation. These items are indicators of bulbar dysfunction, which limits the reliability of PFT administration.

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 or MIP > -60 cm H_2O.

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 team exhibits one or more of the exclusion criteria during the course of the study.

3.3.2 Follow-up for withdrawn subjects

The research team will follow up with withdrawn subjects at their home to collect the research equipment. If the participant team agrees, they will be given the endpoint assessment to document their reason for withdrawal. There will be no 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.

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 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. 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 participant team 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 inadequate internet access to participate (in the case of Part 2). The participant team 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.

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 all 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.

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. A copy of the consent form will be provided 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 from the prospective participant team 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 age, diagnosis, gender, and ALSFS-R scores. Social security numbers are collected for payment purposes.

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.**).

Part 2: This is a randomized controlled study to determine whether regular monitoring of respiratory function at monthly, rather than every 3-month intervals, over the course of a year, can lead to better

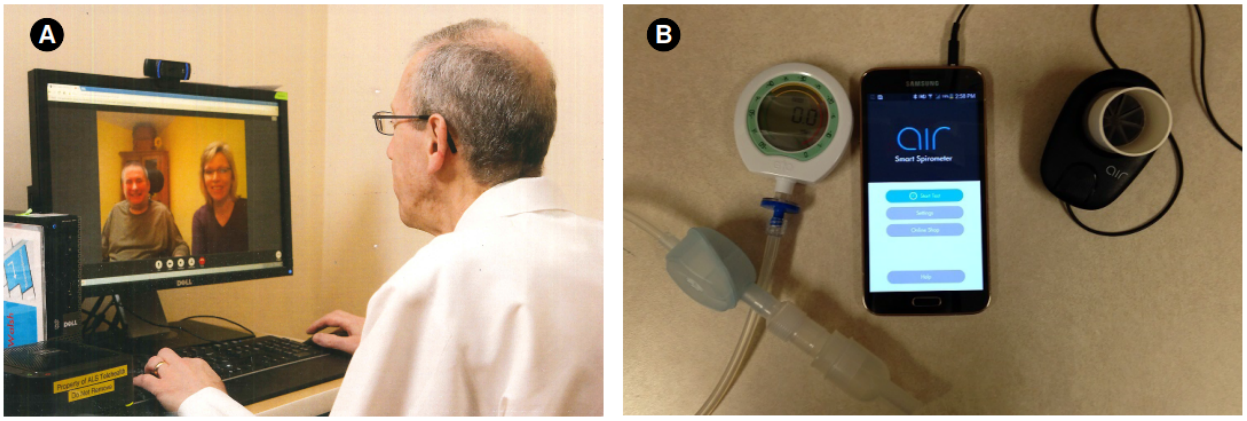

Figure 2: (A) Image of the telemedicine interface used by the Hershey ALS clinic. (B) The rPFT toolkit. From left to right: The GiO 4 respiratory pressure meter and mouthpiece, smartphone running the spirometry application, and Air Smart Spirometer and turbine.

patient outcomes. In the experimental group, standard FVC and MIP measurements obtained by the respiratory therapist in the ALS clinic every 3 months are supplemented with telemedicine-guided rPFT performed at monthly intervals (**Error! Reference source not found.** 1). Controls receive standard PFT assessments only. Patient outcomes, NIV recommendation, quality of life, and survival over one year, will be compared between experimental and control groups.

The researcher and respiratory therapist will be present either in person or virtually for all study sessions and will guide the patient and caregiver in the appropriate use of the equipment. Two devices are used to measure two aspects of respiratory function:

1) Air Smart Spirometer, Pond Healthcare Innovation AB

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

"Air Smart Spirometer is intended to measure the forced expiratory volume in 1 sec (FEV1) and the forced vital capacity (FVC) in a forced expiratory maneuver. These measures can be used for the detection, assessment and monitoring of certain lung diseases. 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 with iPhone and connects via its cable to the headphone input jack. The Air Smart Spirometer has a built-in battery designed to function for at least 2 years or 1 000 single tests. When the battery is drained, dispose of the device as electronic waste. 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."

2) GiO 4 Digital Pressure Gauge, Respiralogics

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

"GiO Pressure Gauge is a high accuracy digital gauge that displays pressure measurement in both analog bar and digital reading. The GiO Gauge can be used in various settings and has a wide range of

applications in both medical and non-medical fields. GiO Digital Pressure Gauge is designed to detect and display pressure reading to a high degree of accuracy. This means it may also be sensitive to changes in pressure and is so fast in responding to the changes that you may find it difficult to determine the reading you would like to record. The P&H or Peak and Hold function is a design that captures and holds the display of peak pressure reading. The GiO 4 measures pressures from -60 cm H_2O to 0 cm H_2O."

During each rPFT administration, the respiratory therapist will guide the patient and caregiver through three valid maneuvers of the FVC and MIP tests. The therapist informs the caregiver to 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 therapist 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 further until the therapist is satisfied with three valid maneuvers. The application on the tablet computes the FVC and percentage predicted value using the NHANES III criteria [Hankinson1999]. The largest FVC from a valid run is recorded.
To perform the MIP test, the therapist instructs the patient to breathe normally. The caregiver turns on the GiO pressure meter and attaches the mouthpiece, which is placed in the mouth of the patient. The patient is told they will be asked to draw breath in as quickly and powerfully as possible, for at least one second. The therapist 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. As the therapist instructs, the patient performs three repetitions of this task, noting the reading each time. 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, the 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.

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

On or before the date scheduled for the start of the study, 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. The researcher will then collect demographic information for purposes of randomization to an arm of the study: age, gender, and time since symptom onset. The participant team will undergo the initial in-person pulmonary function testing as part of their clinical visit.

Month	0	1	2	3	4	5	6	7	8	9	10	11	12
Exp. Arm (n=20)	C+S PFT	S rPFT	S rPFT	S PFT	S rPFT	S rPFT	S PFT	S rPFT	S rPFT	S PFT	S rPFT	S rPFT	S PFT
Control Arm (n=20)	C+S PFT	S	S	S PFT	S	S	S PFT	S	S	S PFT	S	S	S PFT

Table 1: Part 2 schedule. Participants will be enrolled at month zero, and randomized into a study arm depending on clinical characteristics of age, gender, and time since symptom onset (C). All participants attend clinic (indicated by gray shading) approximately every three months to have PFT administered by a respiratory therapist. Patients in the experimental group will conduct monthly rPFT assessments in the two interim months. Each month, all participants are required to complete the study survey (S).

Following the initial visit (month 0), participants will undergo randomization. Those randomized to the experimental group will be shipped an rPFT kit and scheduled for monthly telemedicine appointments between clinic visits. On the dates of the telemedicine appointments, the respiratory therapist administers the study survey and conducts an rPFT from clinic with the patient in their home. This is repeated for the 2nd month. On the 3rd month, the participant dyad is seen by the therapist during their normal clinic visit. This pattern is repeated until the 5th clinical appointment (including the visit at month 0), resulting in 5 in-person assessments and 8 intermediate tele-assessments over the course of approximately 12 months. The control arm will receive standard assessments during regular ALS clinic appointments (Table 1), and be required to complete a study survey each month. Study procedures will be followed until the study endpoint at month 12, even if NIV is initiated during this period. The treating neurologist will make the decision to end the protocol early if the patient is unable to perform the procedures. The patient can also opt to end the study at any time.

The study survey is administered once a month for participants in both study arms and consists of four parts. The initial survey administered at month 0 will be completed with a researcher present. The remaining surveys will be completed online. If it coincides with administration of a PFT or rPFT, it will be administered first. It is designed to measure the impact of daytime breathlessness and sleepiness on QoL and consists of the following components.

1) Sleep Apnea Quality of Life Index (SAQLI) - part D [Flemons1998]. It is designed to assess quality of life pertaining to sleep disturbances, as well as the impact of treatment on QoL. It has been used as a sensitive measure of health-related QoL in ALS [Bourke2006, Jackson2001, Bourke2003].
2) Motor Neurone Disease Dsypnoea Rating Scale (MDRS) - subscale D [Dorman2007]. Dorman et al. described an ALS-specific assessment, the Motor Neurone Disease Dsypnoea Rating Scale (MDRS), as one with high construct validity and responsiveness. The dyspnea subscale (MDRS-D) of this tool has patients choose which activities of daily living they have experienced shortness of breath in the past two weeks and how severe the episode was [Dougan2000].
3) Short Form 36 (SF-36) [Ware1992]. This is a generic, coherent, and easily administered quality-of-life measures which has been shown to be sensitive for mental and physical health assessment in ALS [Bourke2006, Jackson2001, Bourke2003].
4) SAQLI parts E and F (NIV users only). These sections ask about problems that may have arisen due to NIV use and how respiratory symptoms may have been alleviated due to treatment during this period.

Each session concludes with recommendations from the therapist based on the results of respiratory tests. These can include behavioral modifications or recommendation for NIV. Recommendation of NIV is based on a measured FVC ≤50% predicted or for dyspnea accompanied by MIP > -60 cm H2O. This recommendation will be reviewed by the ALS clinic 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.

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: The participant team will be enrolled for approximately one year. During this time, participants will engage in approximately five standard PFT assessments as part of normal clinical activities, requiring no additional time commitment. All participants will complete monthly surveys which will take 15 minutes each. Those in the experimental arm will also complete eight rPFTs, each taking 30 minutes. Control participants will be required to devote approximately 3.25 hours over the course of the study, and those in the experimental arm will devote approximately 7.25 hours.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Approximately (but no more than) 103. We will enroll 40 patient/caregiver teams for Part 1 and 40 patient/caregiver teams 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. Similarly, the two measures of QoL obtained at NIV recommendation are powered with an 80% chance to detect improvement of quality of life in the experimental group if the effect size is also found to be 0.95. This corresponds to a mean score difference of 1.52 on the SAQLI, assuming a standard deviation of 1.6 [Flemons1998]. Although there is no published data on the standard deviation of MDRS-D scores, the range and format of questions is similar enough to estimate a comparable difference between groups is needed.

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: The primary outcomes will be analyzed to determine if respiratory parameters are closer to the actionable threshold at NIV recommendation and whether QoL is better sustained at this point in individuals in the experimental group. This will be done using a non-parametric two sample test of means, the Wilcoxon-Mann-Whitney rank sum test.

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. At all times participants will complete the study procedures under the guidance of a licensed respiratory therapist. In addition to expert guidance, 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 subject code, gender, age, and height. No part of the telemedicine video or audio recordings will be permanently stored.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

The experimental group in Part 2 may benefit from improved quality of life and survival.

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 around 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 participant team will be compensated $5 per completed survey and $10 per rPFT administration. They will be paid for the sessions they complete, with total compensation capped at $65 for those in the control arm and $145 for those in the experimental arm. Subjects will be required to provide their social security number and address for payment

15.0 Economic Burden to Subjects

15.1 Costs

As a part of the normal study procedures, subjects will incur no cost for their participation. The participant team will be loaned research equipment owned by Penn State University. If damage were to come of this equipment, Penn State University or their insurer might seek recovery for these costs from the patient's homeowner's insurance policy if it was found that they were at fault for the damage.

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 for the participant team. A member of the study team and the respiratory therapist will communicate with the participant team over the telemedicine interface in the research room of the ALS clinic.

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. Forty participants, half of which will be randomized to the experimental group, will take place in this year-long study. 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 5% 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.).

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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