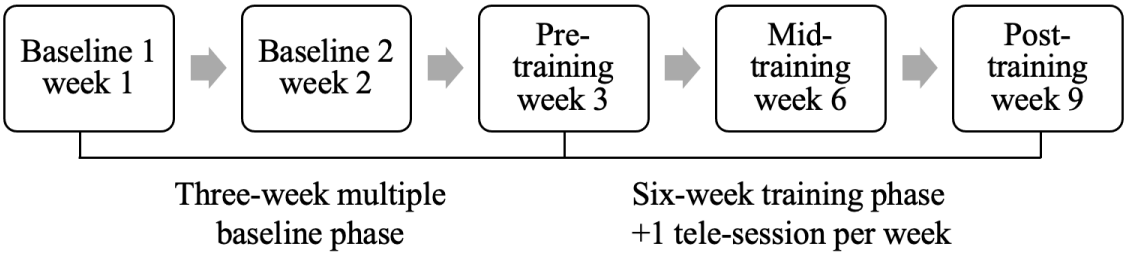
Effectiveness of Expiratory Muscle Strength Training for Improving Communication in ALS
NCT05003167
Study Protocol and Statistical Analysis Plan
February 22, 2022

Study Design:
Participants attended five assessment sessions which spanned nine weeks (Week 1: Baseline 1, Week 2: Baseline 2, Week 3: Pre-Training, Week 6: Mid-Training, Week 9: Post-Training) in the multiple baseline design depicted in Figure 2. During the six-week training phase, participants attended one telepractice session per week. Thus, participants attended nine total sessions.



While enrolled, participants were not allowed to participate in active speech therapy treatment programs but were allowed to see speech-language pathologists as part of routine ALS clinic visits. Participants were allowed to follow their prescribed medication regimens.

General Procedures:
Study procedures were approved by Purdue University's Institutional Review Board (IRB-2020-524). Participants were recruited via contact with neurologists, ALS Association support groups, ALS clinics, and ClinicalTrials.gov (identifier: NCT05003167). Potential participants contacted the researchers to express interest in the study. Once initial contact had been established, a pre-enrollment phone call was scheduled during which the researchers provided potential participants with more information about the study. If the potential participant remained interested, participants verbally consented to being asked a series of questions related to their overall health and ALS diagnosis. This pre-enrollment screening was intended to ensure that participants met the inclusion criteria and were likely in the early stages of disease progression. If the potential participant met the study requirements and elected to enroll, the equipment (peak flow meter and EMST-150/EMST75 Lite) was sent for delivery and the first baseline session was scheduled.

During the Baseline 1 session, study procedures were described to the participant in detail. Once all questions about the study had been answered, the participant reviewed and signed the consent form virtually using Adobe EchoSign. Following consent, participants were administered the MoCA 4.1. The MoCA was adapted in accordance with the telepractice guidelines outlined on the MoCA website (mocatest.org) to compatible for administration through telepractice.

All assessment and telepractice sessions were audio and video recorded through Zoom (versions 5.8.4 and 5.9.1). Participants were allowed to use the electronic device of their choosing (e.g., phone, tablet, computer) for all sessions, but were required to use the same device for all sessions. However, 1 participant's (M24) computer broke prior to the Post-Training session; thus, he used a new device for the last assessment session. Device types used by participants were documented at each session: nine participants used a computer and three used a tablet. The researcher used the same electronic device for all sessions (MacBook Pro 2020).

Initial Surveys:

Participants completed a series of surveys in REDcap throughout the study (Harris et al., 2009). A general health and demographics survey was completed at Baseline 1. Participants were sent a link and access code to the REDCap surveys which asked them questions related to their demographics and overall health. These items included: race/ethnicity, estimated height and weight (to compute BMI), highest education received, date of birth, date of first symptoms, date of diagnosis, description of first symptoms, medical history, medications list, and history of speech/swallowing therapy.

The Beck Depression Inventory (Beck et al., 1988) is a 21-item survey that was completed at Baseline 1 to quantify symptoms of depression which might influence the study aims. Scores range from 1-63 with higher scores indicating greater depression (1-10: these ups and downs are considered normal, 11-16: mild mood disturbance, 17-20 borderline clinical depression, 21-30 moderate depression, 31-40 severe depression, 40: extreme depression). Two participants scored within the moderate depression range, 3 participants scored within the mild mood disturbance range, and all remaining participants scored within normal range. Participant Beck Depression Inventory scores are listed in Table 1.

The Apathy Evaluation Scale (Guercio et al., 2015) is an 18-item survey which quantifies goal directed behavior that might influence the study aims. The participants use a 4-point Likert scale (not at all true, slightly true, somewhat true, and very true) to rate the 18 items. The scores range from 18 to 72 with lower scores indicating greater apathy.

ALS Function Rating Scale-Revised (ALSFRS-R) (Cedarbaum et al., 1999) was used to assess overall physical functionality related to ALS. The survey requires participants to rate how 12 physical functions are impacted by their ALS. The functions include speech, salvation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting bed sheets, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency. For each function, participants are provided with a 4-point Likert scale to rate whether they still have complete control of that function (4) or no ability to perform that function (0). Total scores range from 0 to 48, with lower scores indicating more severe symptoms and higher scores and less severe symptoms. An ALSFRS-R score was collected at Baseline 1, Baseline 2, Pre-Training, and Post-Training. During the Baseline 1 session, the researcher administered the ALSFRS-R. For all other instances, the participants completed the ALSFRS-R independently via REDCap.

Training:

The EMST-150 and EMST75 Lite devices were used to obtain estimations of participants maximum expiratory pressure (MEP) and for training. Both devices house a calibrated spring-loaded valve that overloads the expiratory muscles at a targeted pressure. An adjustable spring within the device allows for blocking of airflow until the targeted expiratory pressure is produced and the device is only open while the targeted expiratory pressure is maintained. The two EMST devices are the same except for the resistance levels available on each device. The EMST-150 device has resistance levels ranging from 30-150 cmH2O. The EMST75 Lite device has resistance levels between 0 and 75 cmH2O. All participants were initially sent an EMST-150 device, but if they were unable to successfully exhale into the EMST-150 to release the valve at its lowest setting during the Baseline1 session, they were sent an EMST75 Lite to accommodate their lower expiratory force. The eight male participants used an EMST-150 and four female participants used an EMST75 Lite device for training. All participants chose to utilize the comfort-fit mouthpiece to help maintain adequate lip seal around the device.

During the training phase, participants attended one tele-session per week with a researcher (the doctoral student and certified speech-language pathologist leading the study). During each weekly session, the participant's MEP was estimated. After the participant's MEP was estimated, the EMST device's resistance level was placed at 50% of their estimated MEP. The participants were instructed to follow the rule of five to complete five sets of five (25 total) exhalations into the EMST device five days a week for six weeks. Participants were encouraged to complete the 25 exhalations in one sitting. To ensure the device was being utilized appropriately, participants completed twenty-five exhalations into the device with the researcher's supervision during each weekly tele-session. Thus, they completed four training sessions independently and one day of training via tele-practice with the researcher. Compliance with the training protocol was monitored using a daily adherence survey sent to the participants via REDCap. On the survey, the participants indicated whether (yes/no) they completed the training protocol each day, and if not, why, as well as whether they needed assistance to complete the training on each day.

Assessments:

Surveys: Surveys were completed independently by participants on REDCap.

Maximum expiratory pressure: To obtain MEP estimations, the participant always started with the EMST device on its lowest setting. If the participant was able to successfully release the valve at the device's lowest setting, the participant was instructed to increase the resistance level of the device by moving the screw on the adjustable knob in one-turn increments until they reached a point where they could no longer force the valve open with their expiratory force. At that point, participants decreased the device's resistance level in quarter-turn increments until they could force the valve open again. The maximum level at which participants could exhale into the device was considered their estimated MEP for the respective session. Successful valve release occurred when the participant or researcher heard the air escaping, while unsuccessful valve release occurred when a release of air was not heard. To ensure the participant was accurately adjusting the device in appropriate increments, they were instructed to move the screw in full and quarter turn increments using the four blue (EMST-150) or green (EMST Lite) plastic gridlines positioned in quarterly increments at the bottom of the device as a guide. Participants showed the screws location to the researcher periodically as MEP was being estimated to make sure they were on track. Once the participant's estimated MEP was determined, the participant showed the final location of the screw to the researcher to confirm that the estimated MEP was accurate.

Speech Tasks: Participants were instructed to sit upright in front of their electronic device so that the researcher could visualize his/her torso and mouth without difficulty. To enhance visualization of respiratory patterns, participants wore a cloth band (Tobwolf self-adhesive bandage wraps, plaid pattern) loosely wrapped around their ribcage while they completed the speech tasks. Participants were instructed to read The Rainbow Passage (see Appendix A) and produce a sixty second monologue discussing a topic of his/her choice. The order of the speech tasks was randomized for each session. Acoustic recordings of the reading passage and monologue were obtained as mp4 files from the audio/video recordings collected via Zoom. mp4 files were then converted to wav files via iTunes to be compatible with Praat for the acoustic analyses.

Cough Tasks: Peak expiratory flow rate (liters per minute) from single and sequential voluntary coughs were obtained from a Peak Flow Meter (Omron PF9940 PeakAir) sent to the participants prior to the Baseline 1 session. For the single voluntary coughs, participants were cued to produce one single strong cough into the device following a clinician model. For the sequential voluntary coughs, participants were instructed to "cough forcefully multiple times as if something went down

the wrong pipe" following a clinician model of producing three sequential coughs. The maximum peak expiratory flow rate was determined from three consistent (within 5%) peak expiratory flow rate values for each cough type. If the first three trials were not consistent, participants were instructed to complete up to two additional coughs for single and sequential coughs. To prevent over-exertion, no more than a total of five attempts per cough type were allowed.

Statistical Analysis Plan:

Maximum expiratory pressure, speech outcomes, cough outcomes: A mixed model ANOVA with session as a main effect and participant as a random factor was run via SAS 9.4. Alpha was set at .05. Reading and monologue tasks were assessed separately. To assess individual change in estimated MEP from Pre- to Post-Training, effect sizes were computed for each participant using the following formula:

Post Mean – Pre Mean / Pre standard deviation

Survey outcomes: Paired t-tests were run in JMP (Version Pro 16).

RESEARCH PARTICIPANT CONSENT FORM

Expiratory Muscle Strength Training for Early-Stage Amyotrophic Lateral Sclerosis

Jessica E. Huber, PhD
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Purdue University

Key Information

Please take time to review this information carefully. This is a research study. Your participation in this study is voluntary which means that you may choose not to participate at any time without penalty or loss of benefits to which you are otherwise entitled. You may ask questions to the researchers about the study whenever you would like. If you decide to take part in the study, you will be asked to sign this form. Prior to doing so, please be sure you understand what you will do as a part of the study and any possible risks or benefits. The researcher is willing to answer all questions you might have.

Amyotrophic Lateral Sclerosis (ALS) causes muscles to weaken. Muscles involved in breathing, eating, speaking, and coughing are of interest in this study. These muscles are typically strengthened with an expiratory muscle strength trainer – a device that works much like how lifting a weight strengthen the biceps. Expiratory muscle strength trainers improve cough, swallowing, communication, and breathing for healthy people and people with neurological diseases (e.g., Parkinson's disease). A recent study found that using an expiratory muscle strength trainer is safe and beneficial for people with ALS, as it strengthens the muscles involved with breathing. This study aims to determine whether expiratory muscle strength training improves speech, cough, and breathing strength for people with ALS. Another aim is to determine whether expiratory muscle strength training can be done through telehealth.

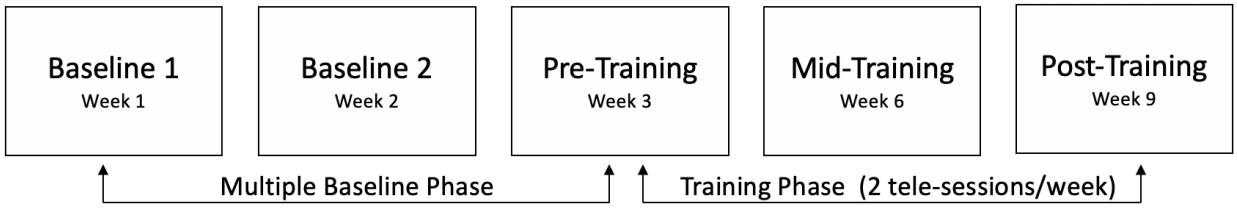
The study is ten weeks. All meetings will take place virtually through Zoom. It requires participants to attend 5 virtual assessment sessions (~1 hour each) and 12 virtual training sessions (2x/week for six weeks, ~30 minutes each session), complete an at-home respiratory strength training program (~25 minutes/day, 5 days/week, for 6 weeks), and complete a series of surveys (~3 hours).

What is the purpose of this study?

You are being asked to participate in this study because you have a diagnosis of ALS and are within the early stages of disease progression. We would like to enroll 30 individuals with early-stage ALS.

The purpose of this study is to provide information on whether expiratory muscle strength training improves communication, cough, and breathing for people with ALS when implemented through telehealth.

What will I do if I choose to be in this study?



If you agree to participate in this 10-week study, you will need to attend 5 virtual assessment sessions. During the training phase of the study (weeks 4-10), you will use the trainer 5 days per week for about 20-30 minutes a day and meet with a speech-language pathologist virtually 2x per week for ~30 minutes each session. You will also complete a series of surveys pre- and post-

training to monitor your quality of life, ALS progression, communication, breathing patterns, and compliance with the training.

The clinical researchers who will guide you throughout the study have experience working with people who have neurodegenerative diseases including ALS.

Training protocol: Expiratory muscle strength training uses a device which you exhale into in order to strengthen the muscles used for breathing – muscles that are also important for speaking, swallowing, and coughing strongly. You will need to breathe out into the device 25 times a day, five days per week, for six weeks. A caregiver/loved-one may be required to help you use the device should any difficulties arise.

Assessment surveys: On the day of each data collection visit, you will first complete a series of surveys and questionnaires. If any concerning issues are raised by your responses to the questionnaires or other information arises that would be of interest to your health, we will inform you and offer to provide the information to your neurologist or primary care physician.

The following screenings will be administered at the first assessment session only. We estimate they should take approximately 20 minutes to complete.

1. You will complete a health questionnaire
2. We will administer a brief test of your thinking skills
3. We will briefly test the muscles of your face

You will complete the following surveys online. The series of surveys should take you approximately 20 minutes to complete (~40 minutes total throughout the entire study).

1. ALS Quality of Life Scale Revised (Pre- and Post-Training): A 50-item questionnaire that measures how ALS effects your overall quality of life .
2. ALS Function Rating Scale Revised (Pre- and Post-Training): A survey that monitors overall disease severity.
3. Communication Participation Item Bank (Pre-Training and Post-Training): A 10-item questionnaire that asks about your involvement in conversations.
4. A System Usability Scale (Post-Training only): To assess how usable you felt the training device was.
5. Psychosocial Impact of Assistive Devices Scale (Post-Training only): To understand whether the training influenced your psychosocial state.
6. Telehealth Satisfaction Questionnaire (Post-Training only): to understand your perception of completing the training protocol online via telehealth.

Each week of the training phase, you will also complete the following survey online. The survey should take you no more than 5 minutes to complete (~1 hour throughout the study).

1. Compliance: A daily log will be to monitor your adherence to the training.
2. Dyspnea Visual Analog Scale: A 0-10 rating scale that measures any breathing difficulty encountered after completing the training.

Assessment Tasks: Additionally, during the five assessment sessions, we will collect data that will allow us to make measurements of speech, breathing, coughing, and respiratory muscle strength. These tasks include:

1. Speech tasks: These tasks will be recorded via Zoom. You will be asked to talk for a period of 2 minutes about a topic of your choice and you will read a short story. In total, these will take approximately 5 minutes.

2. Breathing tasks: For these tasks, you will be asked to breathe out as hard as you can into an expiratory muscle strength trainer device. This task will take approximately 10 minutes.
3. Cough testing: During the cough testing, we will ask you to cough into a peak flow meter. These tasks will take approximately 15 minutes.

Our laboratories record the video and audio from all sessions. You have the option to sign a separate consent form for us to use your sound and video recordings for educational purposes. You will not be excluded from the study if you choose not to sign the audio/video consent form.

How long will I be in the study?

If you agree to participate, you will be in the study for 10 weeks. During the first three weeks of the study, you will attend 3 virtual assessment sessions. During these sessions, you will complete surveys as well as the speech, breathing, and cough tasks outlined above. The first 3 sessions will allow us to capture a clear picture of your baseline measurements which we will later compare your post-training measures to. You will attend two additional virtual assessment sessions during the training portion of the study (at weeks 7 and 10) and 2 virtual training sessions per week (between weeks 3 and 10).

Each assessment session should take approximately 1 hour (~5 hours total throughout the study). You will complete the training daily in the comfort of your home. The training protocol should take no more than 15 minutes for you to complete each day (~7.5 hours total throughout the study). The surveys should take approximately 20 minutes to complete at each timepoint (~4.5 hours total throughout the study).

What are the possible risks or discomforts?

The expiratory muscle strength training device poses minimal risk to you. A small study completed in 2015 found moderate-intensity expiratory muscle strength training to be safe for individuals with early-stage ALS. All of the evaluation procedures have been used frequently in our laboratory and by the doctoral student leading the study. We have a strict data safety monitoring plan in place to reduce any risks while you undergo the training program. If we observe a significant decline in function on the assessment tasks or surveys you complete while in the study, we will provide the results to you and to your physician of choice. If the declines are significantly greater than expected based on your baseline testing, we will cease training.

There is a small chance that you might be uncomfortable answering some questions on the questionnaires. If this is the case, you will have the option to omit any questions.
Breach of confidentiality is always a risk with data, but we will take precautions to minimize this risk as described in the confidentiality section.

Are there any potential benefits?

If expiratory muscle strength training proves to be effective for you, you may benefit from improved breathing, speech production, swallowing, coughing, and/or quality of life. Because this training has been minimally studied with people who have ALS, these effects cannot be guaranteed. The testing procedures that you will complete for this research will likely improve our understanding of the benefits associated with expiratory strength training and other active sources of treatment for people with ALS.

What alternatives are available?

If you choose not to participate in this study, you may consider obtaining speech-pathology, respiratory, and/or pulmonology services within the community.

Will I receive payment or other incentive?

You will be compensated up to a total of $250 dollars for your participation in the study ($40 per session plus an additional $50 dollars for completing the study). Participants who complete the entire study protocol will be awarded an additional $50 dollars at the end of the study. An additional incentive provided to participants is that you will receive a comprehensive evaluation of your speech, breathing, cough, and swallow abilities at no additional cost to you. We will provide a complete written report for you. You will be compensated via check after you attend the final session. If you voluntarily choose to stop participating, or if your participation is terminated by the researcher, you will be pro-rated for the number of data collection sessions you completed. Participants who attend the initial baseline data collection session and do not pass the screenings (see above), will be compensated $10 for their time. For payments over $50, we will need to provide Purdue University's business office with your name, social security number, and address.

Are there costs to me for participation?

No.

This section provides more information about the study

What happens if I become injured or ill because I took part in this study?

If you feel you have been injured due to participation in this study, please contact Jessica Huber, Professor at Purdue University; Brianna Kiefer, PhD Student at Purdue University; or Sandy Snyder, Research Associate at Purdue University at 765-494-6488. You may also contact Michelle Troche, Associate Professor at Columbia University, at (212) 678-3953.

Purdue University will not provide medical treatment or financial compensation if you are injured or become ill as a result of participating in this research project. This does not waive any of your legal rights nor release any claim you might have based on negligence.

Will information about me and my participation be kept confidential?

The project's research records may be reviewed by the study sponsor/funding agency (the National Institutes of Health), Food and Drug Administration (if FDA regulated), US DHHS Office for Human Research Protections, and by departments at Purdue University responsible for regulatory and research oversight.

Your confidentiality will be kept throughout the entire duration of the study. The results of this study will be used to advance the understanding of the effects expiratory muscle strength training on speech, breathing, swallowing, and cough outcomes for people with ALS. The findings will be disseminated through presentations at conferences and meetings, through in-services with clinicians and published journals. Any presentation or publications that result from this study will only use de-identified data. Your information will not be disclosed when the results are published or presented at the completion of the study. Your records (questionnaires, audio recordings, swallowing videos, etc.) will be assigned an anonymous number that is unrelated to your personal information. Your subject number and all data will have no personal identifiers. All digitized data will be de-identified and stored indefinitely in a password protected, encrypted server. Only the investigators and lab associates who are working on the project will have access to your records and data. Our collaborators at Columbia University will also have access to your de-identified data. All paper surveys and data will also be de-identified and locked in a file cabinet in the principal investigators' laboratories, the Motor Speech Laboratory in Lyles-Porter Hall at Purdue University or the Upper Airway Dysfunction Laboratory in Thorndike Hall at Columbia University. When records are destroyed, paper records will be shredded and computer files

will be deleted. For compensation purposes, your name, address, and social security number will be provided to the business office at Purdue University. Only trained staff in the Motor Speech and Upper Airway Dysfunction Laboratories will have access to the excel sheet which includes your name, address, and de-identified subject number.

It is possible that we will use the recordings of your speech at a later point in time for follow-up studies. Follow-up studies may involve perceptual ratings of your speech recordings by unfamiliar listeners from the community. While we have no immediate intent to complete this potential follow-up study, we will employ the same confidentiality procedures described above for any of your data we may use in the future.

Clinicaltrials.gov: A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

Certificate of Confidentiality: This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects. For additional information about CoCs see http://grants.nih.gov/grants/policy/coc/faqs.htm."

What are my rights if I take part in this study?

You do not have to participate in this research project. If you agree to participate, you may withdraw your participation at any time without penalty. Contact Jessica Huber, Brianna Kiefer, or Sandy Snyder at (795) 464-6488 at Purdue University if at any time you wish to withdraw your participation. You may also contact Michelle Troche at (212) 678-3953 at Columbia University.

If the research team notices significant decline in your function above that expected from your baseline sessions, you may be dismissed by the research personnel without consent. Weekly monitoring checks via your survey completions and physical changes noted during assessments will take place. If you do not complete these weekly surveys, you may be dismissed by the research team without consent. If the research team dismisses you from the study, it is with your best interest in mind given that this training program is a relatively novel treatment program for people with ALS and we do not wish to inflict harm on anyone who participates.

Who can I contact if I have questions about the study?

If you have questions, comments or concerns about this research project, you can talk to one of the researchers. Please contact Jessica Huber, Brianna Kiefer, or Sandy Snyder at Purdue University at (795) 464-6488, or Michelle Troche at Columbia University at (212) 678-3953.

To report anonymously via Purdue's Hotline see www.purdue.edu/hotline

If you have questions about your rights while taking part in the study or have concerns about the treatment of research participants, please call the Human Research Protection Program at (765) 494-5942, email (irb@purdue.edu) or write to:

Human Research Protection Program - Purdue University
Ernest C. Young Hall, Room 1032
155 S. Grant St.
West Lafayette, IN 47907-2114

Future Use

Can we use the data (speech recordings, survey responses, health information) collected through this study in future research studies we conduct on ALS, respiratory function, or quality of life?

Yes No

Documentation of Informed Consent

I have had the opportunity to read this consent form and have the research study explained. I have had the opportunity to ask questions about the research study, and my questions have been answered. I am prepared to participate in the research study described above. I will be offered a copy of this consent form after I sign it.

_____ _____

Participant's Signature Date

_____

Participant's Name

_____ _____

Researcher's Signature Date