1. Protocol Title:

Moderate intensity respiratory muscle training (RMT) in ALS

2. Purpose of the Study:

The purpose of this study is to develop treatments that enhance or preserve respiratory strength and provide meaningful clinical improvements for people with ALS and other neurodegenerative diseases with respiratory muscle involvement. Our central hypothesis is that moderate intensity RMT, individually modulated based on RPE, is necessary to induce meaningful changes in respiratory muscle strength and other outcomes in subjects with ALS. Our objectives are to:

1) Determine the safety and feasibility of moderate intensity RMT in subjects with ALS targeting both the inspiratory and expiratory muscles using patient-reported ratings of perceived effort (RPE) to monitor and regulate intensity.
2) Make preliminary estimates of the effects of moderate intensity RMT on respiratory muscle strength, cough and swallowing, and quality of life.

We expect that moderate intensity RMT regulated with RPE (Foster et al., 2017) will be safe and well-tolerated across subjects, though the magnitude of response, based on changes in respiratory muscle strength, is expected to vary based on baseline respiratory muscle strength. That is, based on effect size calculations, we expect subjects with normal inspiratory muscle strength to demonstrate large to very large increases in respiratory muscle strength, while subjects with mild to moderate inspiratory muscle weakness (40-70% of predicted) will demonstrate a more modest response. Culmination of these objectives will provide pilot data for submission of a competitive NIH grant application to further study RMT in ALS in a larger group of subjects.

3. Background & Significance:

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease of the human motor system that results in progressive muscle weakness. Respiratory muscle weakness is present in more than 80% of patients at diagnosis, progresses as the disease advances, and is the primary cause of morbidity and mortality. Expiratory muscle weakness leads to diminished cough capacity (Park et al., 2010) and development of pneumonia, while inspiratory muscle weakness leads to hypoventilation and respiratory failure. Respiratory muscle strength is correlated with quality of life (QOL) and functional status (Bourke et al., 2001). There are no direct treatments for inspiratory and expiratory muscle weakness in ALS and such treatments are therefore an important unmet medical need.

The estimated prevalence of ALS in the U.S. is 5 per 100,000 (Mehta et al., 2018). Most individuals with ALS die within 2-5 years after diagnosis due to respiratory failure and pneumonia associated with progressive respiratory muscle weakness (Corcia et al., 2008; Wolf et al., 2017). There is no cure for ALS and the lack of proven efficacious treatments is an ongoing challenge. Considering the morbidity and mortality associated with progressive respiratory muscle weakness, treatments that target inspiratory and expiratory muscle weakness in ALS remain an urgent medical need.

Historically, patients with ALS have been counseled to avoid exercise and limit physical activity to preserve muscle strength and function, but this is now known to result in deconditioning and muscle atrophy that exacerbates the disease pathology (Clawson et al, 2017: Merico et al., 2018). Although concerns persist that high intensity exercise may exacerbate ALS disease progression (Lui & Byl, 2009),

recent data suggest that supervised moderate intensity resistance and/or endurance training programs in ALS are safe and well-tolerated (Clawson et al, 2017; Merico et al., 2018) and may enhance functional independence, muscle power, oxygen consumption, fatigue, and atrophy (Merico et al., 2018).

Over the last decade, there has also been increased interest in applying resistance training to the respiratory muscles in ALS. Respiratory muscle training (RMT) is typically accomplished using hand-held devices to provide resistance against inspiration (inspiratory muscle training [IMT]) or expiration (expiratory muscle training [EMT]). Previous data on the effects of RMT in ALS suggests that IMT and EMT are safe and well-tolerated by participants, though the effects on respiratory muscle strength and other outcome measures has been mixed (Cheah et al., 2009; Pinto et al., 2012; Plowman et al., 2016). However, previous efforts suffer many limitations which must be considered in future research. For example, prior investigations have used either IMT (Cheah et al., 2009; Pinto et al., 2012) or EMT in isolation (Plowman et al., 2016) instead of combining these approaches in a comprehensive RMT regimen that addresses both the inspiratory and expiratory muscles. Additionally, prior studies have prescribed relatively low intensity training regimens (Cheah et al., 2009; Pinto et al., 2012; Plowman et al., 2016). Furthermore, a methodology to monitor and modulate RMT intensity in ALS has not been developed. These are critical limitations as low intensity training may provide an insufficient dose of RMT, while high intensity RMT may be unsafe for ALS patients.

Our laboratory has pioneered the use of moderate intensity RMT regimens to provide respiratory muscle resistance training and address progressive neuromuscular weakness (Jones et al, 2011, 2014, 2016). Counteracting respiratory muscle weakness with moderate intensity exercise offers a biologically plausible mechanism to target progressive inspiratory and expiratory muscle weakness in ALS. This research will be the first study of a comprehensive RMT program targeting both inspiratory muscle weakness with IMT and expiratory muscle weakness with EMT in individuals with ALS. We will also utilize a well-defined, moderate intensity RMT regimen and pioneer the use of patient-reported RPE to monitor and regulate intensity. We will use telehealth visits to collect measures of respiratory muscle strength (maximum inspiratory pressure [MIP], maximum expiratory pressure [MEP]) in order to 1) reduce the number of on-site visits required by participants and 2) improve our ability to collect repeated measures of our primary outcomes. We will continue to use the novel modifications, methods, and technologies we have developed to allow progressive, individualized, and calibrated RMT to be delivered across the range of human performance. These include our calibration methodology to ensure accurate, precise RMT pressure-threshold resistance (Jones et al., 2014, 2016) and the Inspiratory Adapter 150 (US Patent Pending) to allow use of expiratory-type devices for IMT (EMST 150; Aspire LLC) and expand the range of resistance.

The results of this study will be used to refine our RMT in ALS treatment regimen, select appropriate outcome measures, and develop the statistical analysis plan for use in a future NIH grant application to further study RMT in ALS in a larger group of subjects.

4. Design & Procedures:

Participants will be recruited from the Duke ALS Clinic or referred through CT.gov or outside hospitals. Twelve adults will participate in a single- subject A_1-B-A_2 study involving 4 visits to Duke over 24 weeks (see **Figure 1**). The 6 week delayed start period represented by A_1 will establish baseline status prior to initiation of RMT and A_2 will determine detraining effects over 6 weeks of RMT withdrawal. Participants will complete four 3-week cycles of progressive RMT during the B phase. We will measure

MIP and MEP weekly. To reduce participant burden and enhance our ability to obtain repeated measures, we will have the ability to obtain measurements of MIP and MEP during web-based telehealth visits.

Participants will complete a full assessment during the first study visit (M1), which may be performed in person or remotely via a web-based session, and receive training/instruction for obtaining MIP and MEP measurements at home with a portable, battery-powered digital pressure gauge manometer (MicroRPM Pressure Meter; Micro Direct). Prior to the pretest visit, participants who opt for remote visits will be mailed instructions for the home-based RMT regimen and the devices as well as a written treatment log. The pretest visit (M7) will include a full assessment after which RMT will commence. During the B phase, participants will complete 12-weeks of moderate intensity RMT, divided into four 3-week cycles, and participate in weekly web-based RMT therapy visits (M8-M18). Posttest assessment (M19) will occur immediately following completion of the 12-week RMT regimen. We will measure MIP and MEP during RMT withdrawal via web-based telehealth visits (M20-24). Following the fourth and final full assessment visit (M25), participants will return all equipment and will be offered the opportunity to initiate a clinical RMT regimen and receive follow-up care by Speech Pathology during future ALS Clinic visits.

	A1 (6 weeks)						B (12 weeks)												A2 (6 weeks)					
Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Measurement	M 1*	M 2[T]	M 3[T]	M 4[T]	M 5[T]	M 6[T]	M 7*	M 8[T]	M 9[T]	M 10[T]	M 11[T]	M 12[T]	M 13[T]	M 14[T]	M 15[T]	M 16[T]	M 17[T]	M 18[T]	M 19*	M 20[T]	M 21[T]	M 22[T]	M 23[T]	M 24[T]	M 25*
MIP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MEP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SNIP	X						X												X						X
PCF	X						X												X						X
ALSFRS	X						X												X						X
EAT-10	X						X												X						X
SF36	X						X												X						X
WHOLQOL-BREF	X						X												X						X
CES-R	X						X												X						X
RMT							X	X	X	X	X	X	X	X	X	X	X	X							
							PRE												POS						
							RMT Cycle 1			RMT Cycle 2			RMT Cycle 3			RMT Cycle 4									

Figure 1. Study Overview. MIP=maximum inspiratory pressure; MEP=maximum expiratory pressure; SNIP=sniff nasal inspiratory pressure; PCF=peak cough flow; ALSFRS=ALS Functional Rating Scale; EAT-10=Eating Assessment Tool-10; SF36=36-Iten Short Form Survey; WHOQOL-BREF=World Health Organization Quality of Life Instrument-BREF; CES-R=Communicative Effectiveness Survey-Revised; RMT=respiratory muscle training (IMT+EMT); PRE=pretest visit; POS=posttest visit. *On-site visit. [T]Telehealth visit conducted via video conference. To minimize participant burden, M7 and M19 will be coordinated with ALS Clinic visits when possible.

Note: If M1, M7, M19, and M25 are completed remotely, the Peak Cough Flow will not be able to be measured.

Participants will be stratified into 2 groups based on baseline inspiratory muscle strength as determined by maximum inspiratory pressure (MIP): six participants with minimal to no respiratory weakness (i.e., MIP ≥ 70% predicted) and six participants with mild to moderate inspiratory weakness (i.e., MIP 40-70% predicted).

The primary outcomes are MIP and MEP. Secondary outcomes include peak cough flow (PCF) and sniff nasal inspiratory pressure (SNIP). Exploratory outcomes include the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS), Eating Assessment Tool – 10 Item (EAT-10), 36-Item Short Form Survey (SF36), World Health Organization Quality of Life-BREF (WHOQOL-BREF), and Communicative Effectiveness Survey-Revised (CES-R). Outcomes will be collected as shown in **Figure**

1 following established guidelines (ATS/ERS 2002; Evans & Whitelaw 2009, Tzani 2014; Kaminska et al 2017; Cedarbaum et al 1999; Belafsky et al 2008; Ware & Sherbourne 1992; Donovan 2013). Clinical spirometry data will be extracted from the participant's electronic medical record if available from a coinciding ALS Clinic visit that occurs +/- 5 days from the assessment visit.

5. Selection of Subjects:

Inclusion criteria:

- Age ≥ 18 years
- Confirmed diagnosis of ALS
- Ability to follow directions for study participation
- Ability to successfully and independently complete RMT repetitions at a minimum pressure-threshold target equal to 30% of MIP or MEP
- Ability to complete telehealth visits using a smartphone or computer with video capabilities
- Ability to complete a home-RMT regimen

Exclusion criteria:

- MIP < 40 cmH20
- Presence of a tracheostomy
- Use of non-invasive or invasive ventilation when awake
- Participant or caregiver(s) inability to manipulate respiratory pressure meter, the RMT device, or calibration equipment for home training
- Inability to complete RMT repetitions successfully
- Concomitant neurologic or neurodegenerative conditions (e.g. stroke, dementia) or other serious conditions that would prevent meaningful study participation as determined at the discretion of the principal investigator
- Inability to give legally effective consent
- Inability to read and understand English

6. Subject Recruitment & Compensation:

Participants will be recruited from the multidisciplinary Duke ALS Clinic, an ALS Association Certified Center that actively follows approximately 400 patients per year. Potential subjects will be identified by review of medical records by study staff. Subjects may also be referred through CT.gov or outside hospitals. Potentially eligible subjects will then be approached by the study coordinator, PI, or other member of the study team trained in conducting the informed consent process. This may be done via Mychart, email, letter or phone. For non-Duke patients, records will be requested from the outside hospital to confirm eligibility. Patient opt-out status within Maestro Care will be reviewed before potential subjects are approached or communicated with. An opportunity to participate in the study will be offered to all DUHS patients or referrals who meet the inclusion/exclusion criteria, regardless of demographic group. Patients will be compensated $25 upon completion of each visit at Duke for a total of $100.

7. Consent Process:

The consent process will be conducted by the PI and study team designated to conduct the consent. The potential subject will have as much time as they need to decide if they would like to participate or not. The potential subject will be encouraged to take the consent home and discuss it with any family members if they wish. Once the study is explained, all questions have been answered, and the subject

agrees, consent will be obtained. Consent will take place via phone script with eConsent, which is available via REDCap. This functionality provides the ability to consent remote participants or participants in clinic via tablets or touchscreen device. Participants will have the capability to sign electronically with a stylus, mouse, or finger. Once the consent form is submitted, participants will receive an email that includes a PDF attachment with a copy of the signed consent form. The PDF will be emailed to Health Information Management from REDCap for incorporation into Epic.

To minimize the possibility of coercion or undue influence, potential participants will be given ample time to ask questions and review the consent form. In addition, it will be stressed that participation in this study does not alter the treatment course and that participation is completely voluntary. The potential participant will be provided with the name and contact information for the study coordinator and the PI and the Duke IRB in the event of questions or concerns after reviewing the consent.

8. Subject's Capacity to Give Legally Effective Consent:

Legally effective informed consent will be obtained for all subjects. "Legally effective" means that the subject 1) has sufficient information to make a decision, 2) understands the consequences of a decision, (3) is able to make a decision, and 4) is able to communicate a decision. If a potential subject is incapable of informed decision-making, consent from their legally authorized representative (LAR) will not be sought, as the cognitive-communication skills necessary for informed consent are also necessary for participation in the research. The study will include high functioning ALS patients who may not be able to physically sign the ICF due to disease related muscle weakness so we will include an LAR and witness signature line.

9. Study Interventions:

During the 12-week intervention period, participants will complete a home-based RMT program and participate in weekly web-based RMT therapy sessions (M8-M18). RMT will be divided into four 3-week cycles. Participants will begin RMT immediately after completing assessments during the pretest visit (M7; see **Figure 1**). During this visit, participants will demonstrate ability to complete RMT repetitions successfully, and will be provided with all the necessary training and equipment to complete home RMT for the next 12 weeks.

Two commercially available pressure-threshold RMT devices that utilize a spring-loaded flange to provide resistance against inspiration and expiration independent of respiratory flow rate will be used to provide the necessary range of resistance. Each participant will use two RMT devices, one for IMT and one for EMT. Device selection will be based on the target pressure-threshold resistance (see **Figure 2**). Participants requiring pressure-threshold resistance between 40 and 150 cm H2O for expiratory training will use the EMST 150 device (Aspire, LLC). Expiratory resistance between 9 and 40 cm H2O will be provided by the Threshold IMT device (Philips Respironics), achieved by placing the mouthpiece on the opposite end of the device. The Threshold IMT device will be used to provide pressure-threshold resistance between 9 and 40 cm H2O for inspiratory training. The EMST 150 will also be used to provide pressure-threshold resistance between 41 and 150 cm H20 for inspiratory training, using the Inspiratory Adapter 150 (Aspire, LLC).

Device	Inspiratory Training Range	Expiratory Training Range
EMST 150	41-150 cm H2O (with Inspiratory Adaptor 150)	40-150 cm H2O
Threshold IMT	9-40 cm H2O	9-40 cm H20

Figure 2. Each participant will receive two RMT devices; device selection is dependent on target pressure-threshold resistance.

We will evaluate the feasibility of telehealth visits by conducting assessment of MIP/MEP, device calibration, and RMT via web-based video conferencing. Participants will perform inspiratory and expiratory repetitions at a calibrated, individualized pressure-threshold resistance based on measurement of MIP (for inspiratory training) and MEP (for expiratory training). A licensed speech-pathologist with expertise in RMT (the "RMT clinician") will provide the intervention following a pre-determined algorithm and shape participant performance with instructions, cues, and demonstrations as necessary to facilitate success during each study visit. Every three weeks, a new RMT cycle will begin and the pressure-threshold target will be adjusted during the web-based visit based on each participant's current MIP/MEP. Participants and/or caregivers will receive guidance to calibrate the RMT devices to the target pressure-threshold. Calibration will be accomplished by establishing a 3-way connection to a portable differential atmospheric pressure gauge/meter to ensure accuracy of dose delivered (Jones et al., 2016). Intensity of RMT will be monitored and regulated visit based on RPE.

During the initial RMT session (M7), all participants will initiate RMT at 50% of their MIP (for IMT) and MEP (for EMT). The pressure-threshold target will be systematically increased or decreased in 5% increments until moderate intensity is established. Safe, well-tolerated moderate intensity RMT is defined as:

1. RPE between 4-5 and <6 (Foster et al., 1998; see **Figure 3**)
2. Pain rating <4 on a standard 0-10 scale
3. Accuracy ≥90% for the last 10 of 25 repetitions in a set
4. Behavioral observations indicate repetitions are well tolerated.

Rating	Descriptor
0	Rest
1	Very, Very Easy
2	Easy
3	Moderate
4	Somewhat Hard
5	Hard
6	-
7	Very Hard
8	-
9	-
10	Maximal

Figure 3. Rating of Perceived Exertion (RPE) Scale. From *Foster C (1998). Monitoring training in athletes with reference to overtraining syndrome. Med Sci Sports Exerc, 30, 1164-1168.*

Once the appropriate target pressure-threshold is established, participants will then complete 1 set each of 25 repetitions of IMT and EMT at this pressure-threshold to ensure safety and tolerance. Intensity will be adjusted as needed during the session based on the accuracy of repetitions, pain ratings, and behavioral observations to ensure that RMT is moderate in intensity and safe and well-tolerated (see **Figure 4**).

Instructions for the home-based RMT program will be provided at the conclusion of each RMT therapy session. Participants will gradually increase RMT intensity during each 3-week cycle by increasing the number of repetitions performed. During the first week of each interval, participants will complete 1 set of 25 repetitions for each IMT and EMT 5 days per week (125 IMT and 125 EMT repetitions, cumulatively). During week 2, the number of RMT repetitions will increase to 2 sets of 25 for both IMT and EMT 5 days per week (250 IMT and 250 EMT repetitions, cumulatively). During week 3, 3 sets of 25 repetitions for both IMT and EMT will be completed 5 days per week (375 IMT and 375 EMT repetitions, cumulatively). Overall, participants will be prescribed 6000 RMT repetitions (3000 IMT and 3000 EMT) over the 12-week treatment phase of the study.

In weeks 2 and 3 of each 3-week cycle, MIP and MEP will be measured and the RMT Clinician will observe the participant completing the appropriate number of repetitions for the week to ensure safety and tolerance. If the participant reports pain >3, RPE >5, accuracy is <90% for the last 10 of 25 repetitions in a set, or if behavioral observations indicate RMT is poorly tolerated after increasing the number of repetitions, the pressure-threshold target will be systematically decreased in 5% increments until moderate intensity is re-established (see **Figure 5)**.

At the beginning of each of the remaining 3-week cycles (M10, M13, M16), the pressure-threshold target will be adjusted in a stepwise fashion with the goal of providing safe, progressive moderate intensity RMT as measured by RPE. The pressure-threshold target will be systematically increased or decreased in 5% increments as previously described until moderate intensity is established.

The maximum training load will be 70% of MIP/MEP, whereas the minimum training load will be 30% of MIP/MEP. This is considered to be the minimum treatment intensity required to induce muscle hypertrophy and strength increases. If a participant is unable to complete RMT repetitions successfully (≥90% accuracy for the last 10 of 25 repetitions in a set) and safely (RPE <6, pain<4) at 30% MIP/MEP, they will be withdrawn from the research by the PI.

Participants will be asked to keep a paper log documenting the number of repetitions they complete each day as well as RPE and any pain they experience associated with home RMT.

See **Figure 4** and **Figure 5** for a detailed treatment decision tree and sequential list of treatment activities for each study visit.

10. Risk/Benefit Assessment:

Research participation is expected to be safe and well-tolerated based on our prior research using moderate intensity RMT in late-onset Pompe disease (Jones et al, 2011, 2014, 2016) and the relevant research in the ALS literature (Cheah et al., 2009; Pinto et al., 2012; Plowman et al., 2016). Multiple elements of our study design have been included to ensure rigorous safety monitoring and minimize risk including:

- Individualized, stepwise pressure-threshold resistance based on each subject's respiratory muscle strength and RPE;
- Weekly contact with the RMT clinician during the 12-week training period to foster adherence and assess for any negative side effects;
- A predetermined algorithm for modulating RMT intensity to ensure participant safety;
- Use of an experienced RMT clinician to conduct the RMT program with training and oversight by the PI;
- Calibration of RMT devices to ensure precise and accurate pressure-threshold resistance.

11. Costs to the Subject:

There are no costs to subjects to participate in this study.

12. Data Analysis & Statistical Considerations:

Descriptive statistics will be provided for all outcomes. Primary outcome measures of MIP and MEP will be analyzed using visual analysis of raw data in graphical format using the method described by Land and Gast (2014). Magnitude of change for our primary outcome measures will be determined using

Cohen's measure of effect size (*d*) as defined by the first equation for single-subject *d* provided by Busk and Serlin (1992). Simply stated, *d* is obtained by subtracting the mean of the first assessment from the mean of the second assessment, divided by the standard deviation of the first assessment. Effect size calculations will be determined to compare results from baseline (M0-M5) to withdrawal (M19-M24) and pretest (M7) to posttest (M18). We will use conservative interpretation guidelines for effect size calculations in which $d < 0.6$ is negligible, $d \geq 0.6$ modest, $d \geq 1.0$ large, and $d \geq 2.0$ very large.

13. Data & Safety Monitoring:

Data will maintained in REDCap and reviewed by the PI at regular intervals to ensure accurate and timely data collection.

During the treatment phase of the study, the RMT clinician will collect safety and adverse event information from study participants each week during RMT therapy telehealth sessions. As described above, if accuracy is below 90% for the last 10 of 25 repetitions in a set, pain rating ≥ 4, perceived effort ratings ≥ 6, or if behavioral observations indicate inspiratory and/or expiratory repetitions are not well tolerated (regardless of pain or effort ratings), treatment intensity will be decreased by modifying pressure-threshold targets in 5% increments until RMT is well tolerated. The RMT clinician will contact the PI for further guidance in the event that these modifications to not result in well-tolerated repetitions. If subjects do not achieve the 90% accuracy criterion during the final 10 IMT/EMT repetitions in the session, the RMT clinician will determine if the trainer settings should remain unchanged or decrease for the subsequent home-based RMT. This determination will be based on the overall subject performance and behavioral observations as fatigue may be a factor impacting performance by the end of the session.

14. Privacy, Data Storage & Confidentiality:

Study records that identify subjects will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Duke University Health System (DUHS). Subjects will be assigned and identified by a unique identification number at the time of enrollment. This number will be used to identify the subject throughout the study and will remain with the subject throughout the duration of the study.

Study data including demographic and experimental data will be stored using REDCap. REDCap is a software tool that does not require client local software and can be accessed from anywhere on the Internet and is secured on a Duke Health Technology Services (DHTS) server. This database will be developed and maintenance performed with support of the School of Medicine (SOM) Duke Office of Clinical Research (DOCR). SOM's DOCR has partnered with the School of Medicine (SOM) to implement REDCap (developed by Vanderbilt's CTSA and currently used and supported by more than 1600 consortium partners. REDCap provides: 1) a stream-lined process for rapidly building a database; 2) an intuitive interface for collecting data (with data validation and audit trail); 3) automated export procedures for seamless data downloads to common statistical packages (SAS, SPSS, etc.); 4) branching logic, file uploading, and calculated fields; and 5) a quick and easy protocol set-up.

REDCap accounts are stored within the DTMI LDAP server hosted by the Duke Office of Information Technology (OIT). Authentication occurs via the OIT implementation of Kerberos. All connections to the system, both external and internal, occur over encrypted channels. Access to components of the system is

role-based and can only be granted by administrators of the system. All collected information is stored on a database server hosted by Duke Health Technology Services (DHTS). The database server resides behind the DHTS internal firewall and access to the server is controlled via firewall rules. All collected data are backed up daily, both on the local server and by the DHTS enterprise backup system. Electronic files including the screening and enrollment log will be retained in a secure, study-specific folder on a secure network, accessible only to study personnel. Regulatory documents will be kept in a locked file in the office of the HNSCS research staff (Room 3576, White Zone), which is locked when not in use. Paper-based source documents will be kept in separate locked files in the office of Dr. Harrison Jones (Room 2504, Blue Zone), which is locked when not in use.

Subject records may be reviewed for compliance with federal or state regulations, or institutional guidance. Reviewers may include representatives from the Food and Drug Administration, the Duke IRB, and the Duke Ethics and Compliance Office. If any of these groups review research records, they may also need to review the participant's medical record.

Potential risk of the loss of confidentiality cannot be eliminated. However, this risk is minimized by use of locked cabinets/containers in locked rooms for storage of physical data; the high level of electronic security for all Duke computer systems; the annual patient confidentiality training required by faculty, staff, students, and trainees at Duke University Health System/Duke University Hospital; and the human subjects research training required by all research personnel.

The study results will be retained for at least 6 years after the study is completed. After that time, research information not already in the medical record will be destroyed or identifying subjects will be removed from such study results at DUHS. Any research information in the medical record will be kept indefinitely. While the information and data resulting from this study may be presented at scientific meetings or published in scientific journals, the identity of research subjects will not be revealed. The results of the study will not be submitted later, or held for inspection by the FDA, for a future device application or marketing application.

Figure 4. Treatment flow chart/decision tree for RMT Cycle 1. Treatment will be individualized following a pre-determined algorithm to establish moderate intensity RMT that is safe and well-tolerated.

<table>
<tr><th colspan="6">RMT Cycle 1</th></tr>
<tr><td colspan="3">Week 1:</td><td colspan="2">Week 2:</td><td>Week 3:</td></tr>
<tr><td colspan="3">Measure MIP and MEP</td><td colspan="2">Measure MIP and MEP</td><td>Measure MIP and MEP</td></tr>
<tr><td colspan="3">Set initial pressure threshold to 50% of MIP/MEP</td><td colspan="2">Review RMT adherence and performance data from prior 3 weeks of home RMT</td><td>Review RMT adherence and performance data from prior 3 weeks of home RMT</td></tr>
<tr><td colspan="3" rowspan="2">Complete up to 5 trial RMT repetitions to establish moderate intensity with RPE = 4-5. Repeat as necessary.</td><td>Home RMT accuracy >90% w/ pain <4 and RPE 4-5: begin repetitions.</td><td>Home RMT accuracy <90%, pain >4, or RPE >6: Subtract 5% from home RMT therapy target and begin training at this % of MIP/MEP</td><td>Home RMT accuracy >90% w/ pain <4 and RPE 4-5: begin repetitions.</td><td>Home RMT accuracy <90%, pain >4, or RPE >6: Subtract 5% from home RMT therapy target and begin training at this % of MIP/MEP</td></tr>
<tr><td colspan="2">Complete 50 IMT and 50 EMT repetitions. Collect pain rating, RPE, and behavioral observations. Calculate overall % accuracy.</td><td colspan="2">Complete 75 IMT and 75 EMT repetitions. Collect pain rating, RPE, and behavioral observations. Calculate overall % accuracy.</td></tr>
<tr><td>RPE 0-3: Increase pressure threshold target by 5% (Maximum = 70% of MIP/MEP) and attempt 5 additional trial RMT repetitions</td><td>RPE 4-5: Appropriate pressure threshold identified</td><td>RPE >6: Decrease pressure threshold target by 5% (Minimum = 30% of MIP/MEP)</td><td>RPE 4-5, pain <4, ≥90% accuracy over last 10 repetitions, and behavioral observations indicate RMT is well tolerated: Pressure threshold target remains unchanged for home RMT</td><td>RPE > 6, pain >4, <90% accuracy over last 10 repetitions, or behavioral observations indicate RMT is not well tolerated: Pressure threshold target reduced by 5% (Minimum = 30% of MIP/MEP)</td><td>RPE 4-5, pain <4, ≥90% accuracy over last 10 repetitions, and behavioral observations indicate RMT is well tolerated: Pressure threshold target remains unchanged for home RMT</td><td>RPE > 6, pain >4, <90% accuracy over last 10 repetitions, or behavioral observations indicate RMT is not well tolerated: Pressure threshold target reduced by 5% (Minimum = 30% of MIP/MEP)</td></tr>
<tr><td colspan="3">Complete 25 IMT and 25 EMT repetitions. Collect pain rating, RPE, and behavioral observations. Calculate overall % accuracy.</td><td colspan="2">Provide instructions for home RMT: Week 2 = 2 sets 25 reps IMT and EMT/day, 5x/week (250 reps/week, each)</td><td>Provide instructions for home RMT: Week 3 = 3 sets 25 reps IMT and EMT/day, 5x/week (375 reps/week, each)</td></tr>
<tr><td colspan="2">RPE 4-5, pain <4, ≥90% accuracy over last 10 repetitions, and behavioral observations indicate RMT is well tolerated: Pressure threshold target remains unchanged for home RMT</td><td>RPE > 6, pain >4, <90% accuracy over last 10 repetitions, or behavioral observations indicate RMT is not well tolerated: Pressure threshold target reduced by 5% (Minimum = 30% of MIP/MEP)</td><td colspan="3" rowspan="2"></td></tr>
<tr><td colspan="3">Provide instructions for home RMT: Week 1 = 1 set 25 reps IMT and EMT/day, 5x/week (125 reps/week, each)</td></tr>
</table>

Figure 5. Treatment flow chart/decision tree for RMT Cycles 2-4. Treatment will be individualized following a pre-determined algorithm to provide progressive, moderate intensity RMT that is safe and well-tolerated.

<table>
<tr><td colspan="6">RMT Cycles 2-4:</td></tr>
<tr><td colspan="3">Week 1:</td><td colspan="2">Week 2:</td><td>Week 3:</td></tr>
<tr><td colspan="3">Measure MIP and MEP</td><td colspan="2">Measure MIP and MEP</td><td>Measure MIP and MEP</td></tr>
<tr><td colspan="3">Review RMT adherence and performance data from prior 3 weeks of home RMT</td><td colspan="2">Review RMT adherence and performance data from prior 3 weeks of home RMT</td><td>Review RMT adherence and performance data from prior 3 weeks of home RMT</td></tr>
<tr><td colspan="2">Home RMT accuracy >90% w/ pain <4 and RPE 4-5: Begin RMT therapy session at 50% of today's MIP/MEP.</td><td>Subtract 5% from home RMT therapy target and begin training at this % of MIP/MEP</td><td colspan="2"></td><td></td></tr>
<tr><td colspan="3" rowspan="2">Complete up to 5 trial RMT repetitions to establish moderate intensity with RPE = 4-5. Repeat as necessary.</td><td>Home RMT accuracy >90% w/ pain <4 and RPE 4-5: begin repetitions.</td><td>Home RMT accuracy <90%, pain >4, or RPE >6: Subtract 5% from home RMT therapy target and begin training at this % of MIP/MEP</td><td>Home RMT accuracy >90% w/ pain <4 and RPE 4-5: begin repetitions.</td><td>Home RMT accuracy <90%, pain >4, or RPE >6: Subtract 5% from home RMT therapy target and begin training at this % of MIP/MEP</td></tr>
<tr><td colspan="2">Complete 50 IMT and 50 EMT repetitions. Collect pain rating, RPE, and behavioral observations. Calculate overall % accuracy.</td><td colspan="2">Complete 75 IMT and 75 EMT repetitions. Collect pain rating, RPE, and behavioral observations. Calculate overall % accuracy.</td></tr>
<tr><td>RPE 0-3: Increase pressure threshold target by 5% (Maximum = 70% of MIP/MEP) and attempt 5 additional trial RMT repetitions</td><td>RPE 4-5: Appropriate pressure threshold identified</td><td>RPE >6: Decrease pressure threshold target by 5% (Minimum = 30% of MIP/MEP)</td><td>RPE 4-5, pain <4, ≥90% accuracy over last 10 repetitions, and behavioral observations indicate RMT is well tolerated: Pressure threshold target remains unchanged for home RMT</td><td>RPE > 6, pain >4, <90% accuracy over last 10 repetitions, or behavioral observations indicate RMT is not well tolerated: Pressure threshold target reduced by 5% (Minimum = 30% of MIP/MEP)</td><td>RPE 4-5, pain <4, ≥90% accuracy over last 10 repetitions, and behavioral observations indicate RMT is well tolerated: Pressure threshold target remains unchanged for home RMT</td><td>RPE > 6, pain >4, <90% accuracy over last 10 repetitions, or behavioral observations indicate RMT is not well tolerated: Pressure threshold target reduced by 5% (Minimum = 30% of MIP/MEP)</td></tr>
<tr><td colspan="3">Complete 25 IMT and 25 EMT repetitions. Collect pain rating, RPE, and behavioral observations. Calculate overall % accuracy.</td><td colspan="2" rowspan="3">Provide instructions for home RMT: Week 2 = 2 sets 25 reps IMT and EMT/day, 5x/week (250 reps/week, each)</td><td rowspan="3">Provide instructions for home RMT: Week 3 = 3 sets 25 reps IMT and EMT/day, 5x/week (375 reps/week, each)</td></tr>
<tr><td colspan="2">RPE 4-5, pain <4, ≥90% accuracy over last 10 repetitions, and behavioral observations indicate RMT is well tolerated: Pressure threshold target remains unchanged for home RMT</td><td>RPE > 6, pain >4, <90% accuracy over last 10 repetitions, or behavioral observations indicate RMT is not well tolerated: Pressure threshold target reduced by 5% (Minimum = 30% of MIP/MEP)</td></tr>
<tr><td colspan="3">Provide instructions for home RMT: Week 1 = 1 set 25 reps IMT and EMT/day, 5x/week (125 reps/week, each)</td></tr>
</table>

15. Bibliography and References Cited

1. Park JH, Kang SW, Lee SC, Choi WA, Kim DH. How respiratory muscle strength correlates with cough capacity in patients with respiratory muscle weakness. Yonsei Med. J. 2010;51(3):392-7.
2. Bourke S. Respiratory involvement in neuromuscular disease. Clin. Med. (Northfield Il.). 2014;14(1):72-5.
3. Clawson LL, Cudkowicz M, Krivickas L, Brooks BR, Sanjak M, Allred P, et al. A randomized controlled trial of resistance and endurance exercise in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2017;19(3-4):250-8.
4. Merico A, Cavinato M, Gregorio C, Lacatena A, Gioia E, Piccione F, et al. Effects of combined endurance and resistance training in amyotrophic lateral sclerosis: A pilot, randomized, controlled study. Eur J Transl Myol. 2018;28(1):7278.
5. Lui AJ, Byl NN. A systematic review of the effect of moderate intensity exercise on function and disease progression in amyotrophic lateral sclerosis. J Neurol Phys Ther. 2009;33(2):68-87.
6. Cheah BC, Boland RA, Brodaty NE, Zoing MC, Jeffery SE, McKenzie DK, et al. INSPIRATIonAL--INSPIRAtory muscle training in amyotrophic lateral sclerosis. Amyotroph. Lateral. Scler. 2009;10(5-6):384-92.
7. Pinto S, Swash M, de Carvalho M. Respiratory exercise in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 20121;13(1):33-43.
8. Plowman EK, Watts SA, Tabor L, Robison R, Gaziano J, Domer AS, et al. Impact of expiratory strength training in amyotrophic lateral sclerosis. Muscle Nerve. 2016;54(1):48-53.
9. Foster C, Rodriguez-Marrayo JA, de Koning JJ. Monitoring training loads: the past, the present, and the future. Int J Sports Physiol Perform. 2017;12(Suppl 2):S22-S8.
10. Yorke J, Moosavi SH, Shuldham C, Jones PW. Quantification of dyspnoea using descriptors: development and initial testing of the Dyspnoea-12. Thorax. 2010;65(1):21-6.
11. Jones HN, Moss T, Edwards L, Kishnani PS. Increased inspiratory and expiratory muscle strength following respiratory muscle strength training (RMST) in two patients with late-onset Pompe disease. Mol. Genet. Metab. 2011;104(3):417-20.
12. Jones HN, Crisp KD, Moss T, Strollo K, Robey RR, Sank J, et al. Effects of respiratory muscle training (RMT) in children with infantile-onset Pompe disease and respiratory muscle weakness. J. Pediatr. Rehabil. Med. 2014;7(3):255-65.
13. Jones HN, Crisp KD, Robey R, Case LE, Kravitz RM, Kishnani PS. Respiratory muscle training (RMT) in late-onset Pompe disease (LOPD): Effects of training and detraining. Mol. Genet. Metab. 2016;117(2):120-8.
14. Warren SF, Fey ME, Yoder PJ. Differential treatment intensity research: a missing link to creating optimally effective communication interventions. Mental retardation and developmental disabilities research reviews. 2007;13(1):70-7.
15. American Thoracic Society/European Respiratory S. ATS/ERS Statement on respiratory muscle testing. Am. J. Respir. Crit. Care Med. 2002;166(4):518-624.
16. Evans JA, Whitelaw WA. The assessment of maximal respiratory mouth pressures in adults. Respir. Care. 2009;54(10):1348-59.
17. Tzani P, Chiesa S, Aiello M, Catellani C, Elia D, Marangio E, et al. The value of cough peak flow in the assessment of cough efficacy in neuromuscular patients. A cross sectional study. Eur. J. Phys. Rehabil. Med.;50(4):427-32.

18. Kaminska M, Noel F, Petrof BJ. Optimal meethod for assessment of respiratory muscle strength in neuromuscular disorders using sniff nasal inspiratory pressure (SNIP). PLoS One. 2017;12(5):e0177723.
19. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci. 1999;169(1-2):13-21.
20. Belafsky PC, Mouadeb D, Rees CJ, Pryor J, Postma GN, Allen J, et al. Validity and Reliability of the Eating Assessment Tool (EAT-10). Ann. Otol. Rhinol. Laryngol. 2008;117(12):919-24.
21. Foster C. Monitoring training in athletes with reference to over-training syndrome. Med Sci Sports Exerc. 1997;30:1164-8.
22. Robison R, Tabor-Gray LC, Wymer JP, Plowman EK. Combined respiratory training in an individual with C9orf72 amyotrophic lateral sclerosis. Ann Clin Transl Neurol. 2018;5(9):1134-8.
23. Organization WH. The World Health Organization quality of life (WHOQOL) - BREF. Geneva, Switzerland: World Health Organization; 2004.
24. Ware JEJ, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). 1. Conceptual framework and item selection. Med. Care. 1992;30(6):473-83.
25. Wolf J, Safer A, Worhrle JC, Palm F, Nix WA, Maschke M, et al. Causes of death in amyotrophic lateral sclerosis: Results from the Rhineland-Palatinate ALS registry. Nervenarzt. 2017;88(8):911-8.
26. Corcia P, Pradat P, Salachas F, Bruneteau G, le Forestier N, Sielhean D, et al. Causes of eath in a post-morten series of ALS patients. Amyotroph. Lateral. Scler. 2008;9(1):59-62.
27. Mehta P, Kaye W, Raymond J, Wu R, Larson T, Punjani R, et al. Prevalence of amyotrophic lateral sclerosis. MMWR CDC Surveill. Summ. 2018;67(7):216-8.