

## **Scientific Protocol**

**Title:** Effects of Device-Facilitated Isometric Progressive Resistance Oropharyngeal (I-PRO) Therapy on Dysphagia Related Outcomes in Patients Post-stroke

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**Project Summary:** The overall goal of this randomized controlled pilot study is to characterize effects of SwallowSTRONG® Device-Facilitated Isometric Progressive Resistance Oropharyngeal (DF I-PRO) therapy in a dose response framework on swallowing-related outcomes in a group of unilateral ischemic stroke patients. These results will be used to determine adequate sample size in order to support a larger clinical trial focused on the efficacy of this therapy approach for improving swallowing safety. The first aim is to determine differences in swallowing physiology and bolus flow measures a) between a group of unilateral ischemic stroke subjects undergoing SwallowSTRONG® DF I-PRO therapy and controls and b) between 8 and 12 weeks of treatment. The second aim is to examine changes in level of oral intake and swallowing quality of life in post-stroke patients undergoing DF I-PRO therapy as compared to a control group and as they relate to treatment duration response at 8 weeks and 12 weeks. The third aim is to evaluate effects of DF I-PRO therapy on overall health status reflected by the number of pneumonia diagnoses and overall hospital readmission rates in post-stroke subjects undergoing DF I-PRO therapy compared to controls.

## **Background and Significance**

**Prevalence:** Every 40 seconds, on average, someone in the United States experiences a stroke.<sup>1</sup>

Due to the advancing age of the US population, by 2030, an estimated four million additional people will have had a stroke, a 21.9% increase in prevalence from 2013.<sup>1</sup> Dysphagia is estimated in up to 76% of acute stroke patients<sup>2,3</sup> and is known to increase the risk for critical post-stroke health sequelae, including pneumonia, malnutrition, dehydration, and mortality.<sup>2,4-6</sup>

**Complications:** Developing pneumonia post-stroke results in a significantly increased relative risk (2.99) of death within 30 days of hospital discharge.<sup>2</sup> Those patients who experience aspiration are *seven* times more likely to develop pneumonia than those who do not aspirate.<sup>7</sup> Relatedly, patients with dysphagia following stroke experience significant decreases in quality of life, increased eating dependency, diminished rehabilitation potential, and longer hospital stays.<sup>2,8,9</sup>

**Swallowing physiology:** Videofluoroscopic findings in patients post-stroke include poor tongue control, increased bolus transit times, reduced laryngeal closure duration, decreased and/or incomplete laryngeal elevation, and higher (worse) penetration-aspiration scale scores compared to controls.<sup>9,11</sup> Sensory deficits also are common following stroke leading to silent aspiration. Oral sensory deficits also may occur making it difficult for a patient safely to control the bolus or to initiate a swallow.<sup>9</sup>

**Tongue strength:** Swallowing consists of a series of pressure changes that begin at the lips and the muscular tongue is a major propulsive force during the swallow. Pressures produced when the tongue contacts the palate play a critical role moving the bolus through the oropharynx and into the esophagus.<sup>13</sup> Patients with dysphagia post-stroke<sup>3</sup> have lower average maximal isometric tongue pressures than those without dysphagia. Tongue pressure production has been found to be closely related to post-stroke dysphagia.<sup>14</sup>

**Age effects:** The vast majority of all strokes occur in people over age 65.<sup>9</sup> Healthy older adults swallow more slowly and generate lower maximum isometric lingual pressures than younger controls.<sup>13</sup> These reductions in strength are likely due, at least in part, to the effects of sarcopenia, age-related skeletal muscle loss of the head and neck musculature.<sup>15</sup> Swallowing pressure reserve, the difference between isometric (maximal) tongue pressures and tongue pressures during swallowing (submaximal), is reduced with age which places older adults at higher risk for dysphagia following additional insult, such as stroke.<sup>16</sup> Kays et al<sup>17</sup> studied the effects of consuming an entire meal on tongue endurance in healthy young and old adults and results indicate that both groups experience reduction in tongue strength and endurance post-meal.<sup>17</sup> Older adults perceived increased effort and fatigue upon completing a meal and coughing or throat clearing later in the meal, suggesting airway invasion. These results reflect that the act of dining decreases tongue strength and tongue endurance with potentially harmful effects (aspiration) in older healthy individuals. Such findings have great implications for dysphagic stroke patients who already demonstrate impairments in tongue strength.

**Swallowing Interventions in Patients Post-stroke:** Traditionally, interventions to improve swallowing in elderly patients are focused on energy conservation and are largely compensatory in nature minimizing the need for intense activity. Postural adjustments, such as a chin tuck or head turn, are frequently recommended in order to modify bolus flow. Diet modifications, such as withholding thin liquids or restricting liquid intake to thickened liquids, are commonly used in hospitals and long-term care facilities to minimize or eliminate thin liquid aspiration. Evidence for these approaches is limited.<sup>18-20</sup> In addition, these practices may negatively affect health

status, particularly the recommendation of honey-thickened liquids.<sup>19</sup> They also affect quality of life and fail to capitalize on the neural basis of recovery post-stroke. Finally, these techniques require use with each swallow which may be disruptive to the eating process and difficult to maintain.

**Resistance Training and Swallowing:** Past assumptions that the swallowing process is a function of the reflexive neural underpinnings and is not responsive to voluntary modification have been proven incorrect through studies reporting the occurrence of dysphagia following, not only brainstem stroke, but also bilateral and unilateral cortical stroke.<sup>9,21</sup> Now considered a patterned sensorimotor process or response within a complex neural network involving both automatic and volitional systems that respond to sensory inputs, swallow function is amenable to restoration.<sup>3</sup> Intensive, repetitive strengthening that results in central neuroplastic modifications as well as peripheral increases in muscle mass and strength has been found to substantially improve swallow muscle physiology and functional outcomes related to swallow behavior.<sup>3</sup>

Effects of sarcopenia that occur with aging in striated musculature have been shown to be largely reversible through studies of healthy older adults.<sup>22</sup> Eight weeks of progressive resistance training by frail elders has been associated with increased gait speed, activity level, stair climbing and diminished risk for falls.<sup>22</sup> In addition, stroke subjects who complete a strengthening regimen for the extremities have shown improvements in functional activities such as timed stair climbing, walking and chair rising.<sup>23,24</sup> Progressive resistance strength training can be defined as progressive increases in resistance to a muscle or group of muscles as training results in greater ability to create and maintain forces.

Just as participation in progressive resistance training can strengthen striated limb musculature to improve mobility<sup>22</sup>, it also benefits bulbar-innervated striated muscles of the head and neck. A recent study of community-dwelling individuals aged 70 years and older demonstrated positive correlations between isometric tongue pressure and grip strength and jump height. These data support the effects of sarcopenia on the head and neck musculature and consideration of oropharyngeal functional decline as part of the sarcopenia syndrome.<sup>25</sup> Results of a study by Robbins et al<sup>13</sup> demonstrated positive changes in lingual isometric and swallowing strength of healthy adults over 70 years of age following progressive isometric resistance (high intensity, repetitive, non-specific) exercises for the tongue and related musculature using the Iowa Oral Performance Instrument (IOPI). In 2007, Robbins et al<sup>3</sup> used the same approach with ten patients post-stroke. Subjects demonstrated statistically significant changes in isometric tongue strength as well as pressures generated by the tongue during swallowing, indicating carryover into functional activity. Aspiration and oropharyngeal residue were reduced with liquids in these stroke subjects; and a subset of subjects demonstrated an increase in tongue volume as measured by magnetic resonance imaging implying enhanced tongue muscle mass.<sup>3</sup>

**Device-facilitated I-PRO therapy:** Device-facilitated (DF) Isometric Progressive Resistance Oropharyngeal (I-PRO) therapy is an approach to oropharyngeal strengthening based on core principles of exercise physiology derived from the sports medicine literature.<sup>22</sup> At the start of therapy, the patient's one repetition maximum, or the maximum amount of pressure s/he can produce with the tongue against the palate, is calculated. Then, the patient is instructed to press against a sensor located along the palate at 60 to 80% of that maximum. Therapy involves pressing the tongue against each sensor ten times, three times per day, and three days per week for eight weeks. Maximum pressures are re-determined every 2 weeks to progress therapy targets as patients become stronger.

Existing studies of DF I-PRO therapy showing improved swallow function have utilized the IOPI,<sup>3,13</sup> which comprises a single air-filled plastic bulb attached to a hand-held pressure transducer.<sup>26</sup> The smooth plastic bulb may slide in the oral cavity as patients apply pressure and may cause varying pressure readings due to inconsistent placement.<sup>26</sup> In contrast, the Madison Oral Strengthening Therapeutic (MOST<sup>®</sup>) device 1.0 (Swallow Solutions LLC, Madison, WI, USA) has an intraoral mouthpiece that comprises 5 air-filled sensors that independently target the anterior, posterior, left, right, and middle tongue.<sup>26,27</sup> This mouthpiece is custom-fit to the hard palate, registers to the anterior upper dentition or alveolar ridge, facilitating consistent placement over time.<sup>26</sup> The MOST<sup>®</sup> device recently has undergone its second iteration which uses a touch screen tablet and is now referred to as the SwallowSTRONG<sup>®</sup> device.

A federally-funded Clinical Demonstration Program, the Swallow STRengthening OropharNGeal (Swallow STRONG) program, has shown positive results for a group of 40 Veterans with oropharyngeal dysphagia resulting from a variety of medical etiologies including stroke.<sup>28</sup> Veterans underwent 8 weeks of MOST<sup>®</sup> DF I-PRO therapy and were assessed at baseline prior to beginning the program as well as following completion. Maximum isometric pressures were found to increase significantly at the front and back sensors ( $p<.001$ ) selected for the regimen. Decreases were observed in penetration-aspiration scale scores for 3ml and 5ml thin liquid boluses. Scores on the eating desire, physical, fear, social, fatigue, and mental health subscales of the Swallowing Quality of Life (SWAL-QOL<sup>29</sup>) questionnaire improved ( $p<.03$ ). Ratings of effort with swallowing decreased ( $p<.01$ ) as did ratings for the statement “Food sticks in my mouth when eating” ( $p<.01$ ). Functional Oral Intake Scale<sup>30</sup> (FOIS) scores improved significantly ( $p<.02$ ), representing progression from feeding tube dependency to full oral intake. For patients who could be tracked 6 months or longer following enrollment, the number of pneumonia diagnoses decreased by 88% and hospital admissions decreased by 79%.<sup>28</sup>

This initial work supports the potential of this therapy approach to affect health-related outcomes in addition to swallowing-specific outcomes in a variety of patient groups. However, the efficacy of SwallowSTRONG<sup>®</sup> DF I-PRO therapy for treating dysphagia and overall health status in patients post-stroke has yet to be established in a larger, more homogeneous group of subjects and with comparison to a control group.

*Salivary Analyses:* A decrease in ratings of mouth dryness has also been observed in patients enrolled in the VA Clinical Demonstration Program previously referred to. The reason for this decrease in mouth dryness is unclear. Additionally, levels of substance P, a protein in saliva, have been shown to be related to the occurrence of silent aspiration in patients post-stroke. Some preliminary data have shown that intraoral stimulation may increase levels of substance P. Stimulation of the salivary glands provided by repeated lingual presses may have the same outcome. Analyses of salivary flow rate as well as the quality of saliva will be important in more clearly understanding these observed changes in this group of patients post-stroke.

*Dose Response:* In order to encourage optimal outcomes of SwallowSTRONG<sup>®</sup> DF I-PRO therapy, while simultaneously considering patient tolerance and compliance, knowledge of ideal treatment duration is critical. In previous work, DF I-PRO therapy has been implemented as an 8 week program; however, acute and chronic post-stroke patients have continued to demonstrate improvement at completion of the program.<sup>3</sup> This suggests that a subset of patients may benefit from a longer protocol (dose).

## **Specific Aims**

This randomized controlled pilot study will characterize effects of SwallowSTRONG® Device-Facilitated Isometric Progressive Resistance Oropharyngeal (DF I-PRO) therapy in a dose response framework on swallowing-related outcomes in a group of unilateral ischemic stroke patients. These results will be used to determine adequate sample size in order to support a larger clinical trial focused on the efficacy of this therapy approach for improving swallowing safety. This randomized study will expand upon previous work examining effects of this therapy approach on swallowing and health-related outcomes now limited to a heterogenous cohort of Veterans with dysphagia from a variety of etiologies. It will focus specifically on patients post-stroke who have been shown to experience improvements in swallow function following DF I-PRO therapy.<sup>3</sup>

**Specific Aim 1:** To determine differences in swallowing physiology and bolus flow measures a) between a group of unilateral ischemic stroke subjects undergoing SwallowSTRONG® DF I-PRO therapy and controls and b) between 8 and 12 weeks of treatment.

**Hypothesis 1a:** Subjects treated with DF I-PRO therapy at both treatment duration points will demonstrate greater improvements in swallow physiology (isometric and swallowing pressures) as well as bolus flow measures (levels of airway invasion, post-swallow residue/stasis, oral transit times, and stage transition duration times) as compared to the control group.

**Hypothesis 1b:** Subjects treated with DF I-PRO therapy will experience improvements in swallow physiology and bolus flow measures at the 12 week duration compared to 8 weeks.

**Specific Aim 2:** To examine changes in level of oral intake and swallowing quality of life in post-stroke patients undergoing DF I-PRO therapy as compared to a control group and as they relate to treatment duration response at 8 weeks and 12 weeks

**Hypothesis 2a:** Patients undergoing DF I-PRO therapy will require less restrictive diets and will report improved swallowing-related quality of life compared to those in the control group at both treatment duration points.

**Hypothesis 2b:** Twelve weeks of DF I-PRO therapy will result in greater improvements (least restrictive diets and improved quality of life) compared to the 8 week duration.

**Specific Aim 3:** To evaluate effects of DF I-PRO therapy on overall health status reflected by the number of pneumonia diagnoses and overall hospital readmission rates in post-stroke subjects undergoing DF I-PRO therapy compared to controls.

**Hypothesis 3a:** There will be a greater decrease from pre- to post-enrollment in the number of pneumonia diagnoses and overall hospital readmissions for those subjects who complete 12 weeks of DF I-PRO therapy compared to controls.

## **Research Design and Methods:**

### **Subjects**

Forty medically stable unilateral ischemic stroke subjects with dysphagia will be consecutively accrued from the University of Wisconsin Hospital and Clinics (UWHC). There is a counterpart application that is currently under review with the IRB for enrollment of Veterans into this study as well (IRB #2014-0939). Therefore, the forty subjects will be the sum of those enrolled through this protocol as well as the VA protocol under review.

Recruitment Process: Inpatients or Outpatients who meet the inclusion criteria related to their stroke diagnosis (unilateral or bilateral ischemic or hemorrhagic stroke within 6 months of diagnosis) with none of the exclusion criteria will be referred by Dr. Justin Sattin, a stroke neurologist and Medical Director of the UW Comprehensive Stroke Program or a member of his team, to participate in the study. Patients also may be referred by the UW Voice and Swallowing Clinic clinicians involved in this study. In order to have earlier identification of inpatients who are potential participants, Dr. Michael Pulia, an Emergency Department physician, will be screening the list of admitted emergency patients daily for those who meet study criteria based on stroke diagnosis. He will then notify Dr. Nicole Pulia of these potential participants and she will confirm eligibility with Dr. Sattin, his team, or the ENT clinicians. Once general eligibility for meeting inclusion criteria is confirmed via Dr. Sattin's review of the patient's medical record and it has been determined that the patient will require videofluoroscopic examination (VFSE) of his/her swallowing as part of routine clinical care, Dr. Justin Sattin, a member of his team, or a clinician from the UW Voice and Swallowing Clinic will ask the patient to fill out a permission-to-contact form and subsequently will notify Dr. Nicole Pulia that this form has been signed so that she can follow-up with the patient.

If an Outpatient, those who meet inclusion criteria and require a VFSE will be contacted by phone by Dr. Sattin or their SLP clinician to inquire regarding interest in the study. If they indicate interest and verbally provide permission to be contacted, Dr. Nicole Pulia or Allison Limke would be notified and will follow-up with the patient. The general purpose and the length of the study will be explained to potential participants either by phone (if outpatient) or in-person if an inpatient or at the hospital for outpatient visit. Dr. Nicole Pulia will see inpatients in their hospital room to obtain informed consent prior to the VFSE. For Outpatients, a 30 minute visit in the Voice and Swallowing Clinic or Speech, Swallowing, and Dining Enhancement (SWAL-ADE) Program's laboratory immediately prior to their VFSE will be scheduled during which time more information about the study will be provided and informed consent will take place by Dr. Nicole Pulia. Throughout the informed consent process, the potential participant will be provided with multiple opportunities to seek clarification of any information that is presented. Following review of the informed consent document, the potential participant will be asked to accept or decline further participation. Should s/he accept, the participant will indicate agreement with all study procedures by signing the informed consent form. The participant will be provided with a copy of the consent form, along with contact information for affiliated investigators.

Following consent, the subject will undergo a videofluoroscopic examination of swallowing according to the protocol outlined below. If the subject does not meet diagnostic criteria for dysphagia on the videofluoroscopic swallowing exam (Penetration-Aspiration Scale score of 3 or higher and/or a score of 2 on the Residue scale at any location), s/he will not be randomized to a study group and will no longer continue participation in the study.

For those patients who have already had a recent videofluoroscopic swallow study, the consent process will take place after completion of this swallow study. Potential subjects must meet diagnostic criteria for dysphagia on their videofluoroscopic swallowing examination. If during this exam the patient meets specified inclusion criteria, the UW ENT clinicians will subsequently approach the patient regarding participation. If the patient is interested in participating, the study staff will be notified and will follow-up with the patient. Once general eligibility for meeting inclusion criteria is confirmed by review of the patient's medical record, the general purpose of

the study and the length of the study will be explained to potential participants either by phone (if outpatient) or in-person if an inpatient or at hospital for outpatient visit. If the potential participant expresses interest, more details about the study will be provided, including a copy of the consent form. Then, the same process for obtaining consent will be followed.

**Inclusion criteria:** 1) clinical diagnosis of unilateral or bilateral ischemic or hemorrhagic strokes by attending physician (according to the National Institute of Health Stroke Scale<sup>31</sup> (NIHSS)); 2) within 6 months of acute stroke diagnosis; 3) referral for a videofluoroscopic swallowing study; 4) a score of 3 or higher on the Penetration-Aspiration scale<sup>32</sup> OR a score of 2 on the Residue scale at any location (oral cavity, valleculae, or pharynx) that is instrumentally documented by a participating SLP during the standardized videofluoroscopic swallowing study; 4) between the ages of 21 and 95; 5) ability to perform the strengthening protocol independently or with the assistance of a caregiver; 6) physician approval of medical stability to participate and 7) decision-making capacity to provide informed consent (confirmed through discussion with the subject's primary physician); 8) phone access; and 9) ability to return to the clinic for required follow-up appointments.

**Exclusion Criteria:** 1) degenerative neuromuscular disease; 2) prior surgery to the head and neck region that would affect muscles involved in swallowing; 3) history of radiotherapy or chemotherapy to the head and neck; 4) patient unable to complete the exercise program; 5) taking medications that depress the central nervous system; 6) allergy to barium (used in videofluoroscopic swallowing assessment); 7) currently pregnant.

## **Intervention**

Participants who meet criteria for dysphagia on the videofluoroscopic swallowing examination will be randomly assigned into one of two groups: 1) a control group that will be receiving compensatory treatments only or 2) 12-week DF I-PRO therapy *plus* compensatory treatments, such as thickened liquids and/or postural strategies during natural swallowing activities for 12 weeks. Patients will be enrolled and trained in DF I-PRO therapy by Dr. Pulia who regularly uses the SwallowSTRONG®-facilitated I-PRO therapy in clinical practice or a UW Voice and Swallowing clinician involved in this study who has been adequately trained in DF I-PRO therapy. Regardless of the treatment group to which a subject is randomized, they will be evaluated in the hospital at baseline and 8-week time points. If a patient in either group no longer meets criteria for dysphagia (Penetration-Aspiration Scale score of 3 or higher OR a rating of 2 on the Residue scale in any location) on the 8-week videofluoroscopic swallowing examination, s/he will no longer continue participation in the study. If a patient in either group remains dysphagic at the 8-week visit, s/he will continue participation in the study through the 12-week assessment point. Dr. Pulia or a UW Voice and Swallowing clinician will conduct the 8 and 12 week assessments.

**Group 1: Compensatory treatments only:** This group will receive standard swallowing intervention, which is identified by the SLP as appropriate to treat the patient's dysphagia and is common clinical practice. This group is not receiving experimental therapy. Their therapy may include: 1) modifying the foods the subject eats or the fluids s/he drinks; 2) changing his/her posture when eating or drinking (for example, by a simple chin tuck) or using a swallowing maneuver while eating or drinking; 3) having him/her eat more slowly or in a quiet environment to make swallowing easier and safer; or 4) performing range of motion or vocal exercises for

swallowing or speech. Any progressive strengthening regimens or any type of lingual strengthening protocols specifically will be delayed until subjects have completed participation in this study in order to eliminate confounding influences on outcomes. No subjects will be at risk due to this delay as compensatory approaches mentioned above will be used and other strengthening regimens do not have enough evidence to support their inclusion in standard of care. Weekly check-in phone calls will be scheduled throughout the subjects' participation in the study.

**Group 2: SwallowSTRONG® device-facilitated I-PRO therapy plus compensatory treatments:**

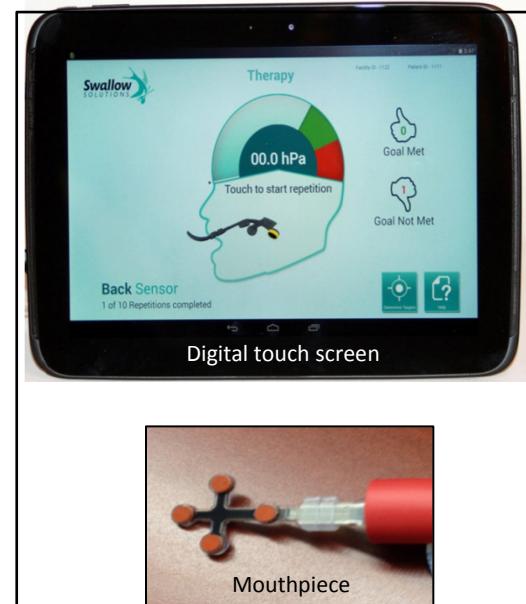
Isometric tongue strengthening will be completed using the SwallowSTRONG® device (see Figure 1).

This device hand-held instrument provides numeric readout of pressure (hPa) and digital feedback of performance. It consists of a short cord (approx. 10 inches), which is attached to a small digital touch screen display. The 4-sensor array is custom-molded to the hard palate to ensure consistent placement.

Tongue press exercises consist of pressing the tongue against the sensors. Isometric exercises will focus on the anterior and posterior sensor. Subjects will be given a target pressure value for both the anterior and posterior sensor locations for which to aim during strengthening. Visual feedback on the display will signal the subject that they have attained their target pressure goal.

Prior to initiation of the strengthening regimen, baseline one repetition maximum (1RM) lingual pressures will be obtained at the anterior and posterior sensors independently by gathering 3 tongue press trials at each site that differ by less than 5% to adjust for variability in these measures. Subjects will take the SwallowStrong® device home with them and will complete 20 repetitions of the exercise (10 repetitions at the front sensor; 10 repetitions at the back sensor), three times per day on three days per week for twelve weeks. It will take approximately 10 minutes to complete 20 repetitions of the exercise resulting in about 30 minutes total for each home exercise session. During week one of the regimen, the target value of each repetition will be 60% of the 1RM. For the remaining eleven weeks of the program, the target value will be increased to 80% of the 1RM. These values of 60% and 80% were chosen based on previous work that employed progressive resistance training for the limbs and lingual musculature with healthy elders and patients post-stroke.<sup>13,22,33</sup> At weeks three, five, seven, nine, and eleven, the baseline will be re-measured by phone and the 80% target value re-calculated. In addition, check-in phone calls also will be scheduled the other weeks of the study period.

**Figure 1**



## **Visits**

**Baseline visit only:**

After the informed consent process has been completed but prior to videofluoroscopic examination of swallowing, each participant will complete a medical history questionnaire to ensure they meet inclusion/exclusion criteria. This questionnaire will include items related to current medical status, medical history, and medication usage. UW medical records also will be referenced to ensure the subject's eligibility for participation. As part of this screening, patients will undergo a urine pregnancy test to ensure they are not pregnant prior to participation. The Mini-Mental Status Examination (MMSE) will be administered only at baseline as a common examination of cognitive functioning. In addition, the Barthel index will be administered to assess severity of impairments in activities of daily living. For each patient, a form with demographics as well as a medication list will be filled out. These questionnaires and tests will take approximately 45 minutes to complete. For those subjects randomly assigned to Group 2, during this baseline visit, it also will take approximately 30 minutes to train the participant on how to do and record the exercises properly. In addition to the consent process and these procedures that will occur only at the baseline visit, the procedures described below will also be completed at this visit. The entire baseline visit will last about 2.5 hours. For the baseline visit and 8 week visit, videofluoroscopic examination of swallowing will need to be completed before the other procedures outline below as the outcome of that examination will determine the patient's continued participation in the study. If s/he does not meet criteria for dysphagia on the videofluoroscopic swallowing exam, s/he will either not be randomized to a study group (at baseline visit) or will not continue participation past the 8 week point (if dysphagia has resolved).

*Measures at each assessment point (baseline, 8 weeks, and 12 weeks):* The 8 week and 12 week visits will last about 90 minutes per session. The study includes up to 3 sessions which will require up to 7 hours in total. In addition if in Group 2, participation in the home exercises will last about 10 minutes per session, 9 sessions per week for up to 12 weeks, which will require up to 18 hours total.

*Quality of Life Questionnaire:* Each subject will complete the Swal-QOL<sup>29</sup>, a validated questionnaire focused on swallowing-related quality of life. It comprises 10 multi-item scales, 2 general scales, and a 14-item symptom battery. Care will be taken so that patients will not receive the tool from their treatment clinician, thereby avoiding potential bias in their responses. This questionnaire will take 10-15 minutes to complete.

*Dietary Questionnaire:* Each subject will complete a questionnaire detailing his/her quantity and variety of nutritional intake. From these responses, a Functional Oral Intake Scale<sup>30</sup> (FOIS) score will be derived. The FOIS is a validated scale that represents level of oral intake from no oral intake (enteral feeding) to total oral intake with no restrictions. This questionnaire will take 10-15 minutes to complete.

*Isometric tongue pressure measurement:* One repetition maximum (1RM) isometric lingual pressures will be measured at the front and back sensors of the device. Subjects will be instructed to press with their tongue as hard as possible against the front and back sensors positioned on the palate. Three 1RM values will be collected for both front and back sensors, with a 20-second rest between each measurement.

*Saliva collection and analyses:* Saliva samples will be collected from patients at each study visit. We will attempt to schedule study visits between the hours of 12pm and 2pm when saliva

production is at its peak for the day. Before collection, patients will be asked to rinse their mouth thoroughly with distilled water to remove any food debris. Saliva will be collected under an unstimulated condition (expectorating into a tube for 5 minutes without swallowing or moving the tongue or jaw) as well as a stimulated condition (expectorating into a tube for 5 minutes while moving the jaw in a chewing motion to the rhythm of 70 beats per minute set with a metronome). The order of conditions will be randomized for each patient. A rest period of 10 minutes will be provided between collection conditions. Salivary flow rate will be determined by recording the volume of saliva produced in 5 minutes under each condition. Samples will be aliquoted into two separate tubes (per collection condition) and placed immediately on ice. One aliquot per condition will be transported to the laboratory of Rich Hartel, PhD in the Department to Food Science. In Dr. Hartel's laboratory, rheological and tribological analyses of the samples will be completed to characterize the fluid flow properties of saliva as well as its lubrication qualities. The protocol for collection, transport, and discarding of saliva samples has been approved by the Office of Biological Safety (#B00000105). Procedures outlined in that approved protocol will be followed to ensure proper handling of samples. Another aliquot per condition will be stored in the freezer within the laboratory of Dawn Davis, MD, PhD in the Department of Medicine for later completion of enzyme-linked immunosorbent assay to quantify levels of Substance P in the samples. Dr. Davis' lab is approved for analyses and storage of human samples (biohazardous materials).

*Videofluoroscopic (VFS) assessment:* The KayPENTAX® Digital Swallowing Workstation (DSW) will be used to capture full resolution fluoroscopic images in real time (30 frames per second). Each subject will be seated and viewed in the lateral plane. The image intensifier will be focused on the lips anteriorly, posterior pharyngeal wall posteriorly, hard palate superiorly, and just below the upper esophageal sphincter (UES) inferiorly. The oral cavity and pharynx will remain in view after the swallow for 2 seconds to assess oropharyngeal residue. Subjects will swallow each of the following boluses twice: 3mL thin liquid, 10mL thin liquid, sips of thin liquid from a cup (approximately 10-15mL each sip), 3mL semi-solid boluses, and barium-infused cookie boluses. Subjects will also swallow one barium pill taken either with thin liquid barium from a cup or in approximately 3mL of semi-solid barium depending on how the patient normally takes pills. Finally, subjects will swallow two 3mL semi-solid boluses in the anterior-posterior view to allow for assessment of symmetry of the swallow. This will result in a total of 13 swallows. Based on the barium given during these 13 swallows, a total of 56 ml of liquid barium sulfate solution (Varibar Thin, Bracco), up to 12ml of pudding barium sulfate solution (Varibar pudding, Bracco), two barium sulfate infused cookies (Wanda's Barium Cookies, 1.5" in diameter); and a barium pill will be ingested. These boluses will be clinician-administered via teaspoon (3-ml) or self-administered via cup (10-ml, natural sips), or self-determined (portion of or whole cookie). If aspiration occurs, that bolus condition will be terminated once the cause of the aspiration is determined to provide clinical remediation. This VFS protocol is consistent with standard practice at the UW facilities. This assessment will take about 35 minutes.

*Swallowing Pressures:* Swallowing pressures will be measured using three small air-filled bulbs (Kay Pentax, Lincoln Park NJ) mounted on a silica strip attached longitudinally with adhesive anteriorly to posteriorly at the midline of the hard palate. The Kay system allows time-linking of swallowing pressure data with videofluoroscopic images.

## **Outcomes**

The *primary outcome measure* will be changes in the *one repetition maximum (IRM) isometric lingual pressures* measured at the front and back sensors of the device. Secondary outcomes include *bolus flow durational measurements* taken from videofluoroscopic recordings, *swallowing pressures, SWAL-QOL scores, and FOIS scores*. In addition, we will compare the *number of pneumonia diagnoses* for community, hospital-acquired, and aspiration pneumonia for the same period of time prior to enrollment and following completion of the study (up to nine months). We also will track the *number of hospital re-admissions* for the same period of time prior to enrollment and following completion (up to 9 months). Treatment compliance also will be tracked within the SwallowStrong® device and will serve as a covariate in statistical analyses.

### **Data Reduction and Analysis**

*Videofluoroscopic Analysis:* The videofluoroscopic images will be coded and sent to the Speech Swallowing And Dining Enhancement (SSwal-ADE) Program. Clinicians blinded to subject information will obtain measures of bolus flow kinematics-direction (Penetration/Aspiration Scale<sup>32</sup> scores), duration, and completeness (Residue Scale<sup>34</sup> scores) from fluoroscopic recordings for each subject using Adobe Premier Pro software. Visual perceptual review will be performed by judges viewing each swallow at normal, slowed, and frame-by-frame speeds as often as needed for confident judgments. Twenty percent of the swallows will be chosen randomly and re-measured by the same judge and a different judge (one of the experienced UW SLPs) to assess inter and intra-judge reliability for all variables. Bolus flow durational measurements<sup>35</sup> (oral transit time, stage transit duration, pharyngeal transit time, total swallow duration) will quantify timing of structural movement and bolus flow. *Computational analysis of swallowing mechanism (CASM) will be performed in order to track anatomical coordinates during the swallow. This will allow us to quantify displacement of various swallowing related structures.*

*Pressure Analysis:* Maximum isometric and swallowing pressures and their temporal characteristics (i.e., rise rate) will be quantified using the SwallowSTRONG® device and the DSW. Swallowing pressures will be quantified relative to the videofluoroscopic images to ensure that the pressure being measured is relevant to bolus flow and not bolus manipulation prior to the swallow. Twenty percent of the pressure wave forms will be chosen randomly and re-measured by the same judge and a different judge to assess inter- and intra-judge reliability.

*Swal-QOL:* Responses will be extracted and scored for subsequent statistical analysis using a database scoring program. All of the Swal-QOL scales will be scored by using Likert's methods of summated ratings.

*Saliva Analyses:* Each measure of viscoelasticity and lubrication properties will be recorded three times per sample. Apparent viscosity will be determined using a TA Discovery, HR-2 rheometer (TA Instruments, New Castle, DE, USA) equipped with a Peltier plate temperature control unit (233212.902). All measurements will be carried out with a flat plate geometry with a diameter of 20 mm and an operating gap of 200 µm. Each sample will first be allowed to equilibrate for 30 seconds at 37°C on the rheometer stage. Viscosity will then be measured at 37°C at shear rates ranging from 0.1 to 100 1/s. In Dr. Davis' laboratory, samples will be frozen until all have been collected. Then, an enzyme-linked immunosorbent assay (ELISA) will be completed in order to quantify levels of the protein Substance P within the samples.

**Hospital Readmissions and Pneumonia Diagnoses:** The number of pneumonia diagnoses and overall hospital readmissions will be compared for the same period of time prior to enrollment and following completion of the study (up to 9 months) for each subject. Discharge reports will be used to tally the number of readmissions and clinic notes will be reviewed to determine number of pneumonia diagnoses (community, hospital-acquired, and aspiration pneumonia) for each subject.

### **Study Timeline**

We estimate achieving our target enrollment in 9 months and completion of the project within the specified 12-month period as outlined below in Table 1. Patients will be referred from the UWHC Neurology Department where approximately 500 ischemic stroke patients are seen yearly. This large volume of patients ensures that 40 subjects will be easily accessible for recruitment into the proposed study.

Tasks	1/1/2015-12/31/2015			
	Q1	Q2	Q3	Q4
Database build & training of study staff	→			
Subject enrollment	→	→	→	
Study close out, data analysis				→

### **Data Safety and Monitoring**

During visits for study participation, subjects will be accompanied by study personnel at all times. Subjects will be contacted by study staff weekly to assess for unanticipated problems or complications. If an unanticipated problem takes place, study personnel will be immediately aware and will take action (i.e., request medical support). As this is a low risk study, adverse events are expected to be very rare. Any unanticipated problems will be reported to the IRB according to posted guidance. Subjects will also have a study contact number and be encouraged to contact study staff with their questions or concerns. Throughout the study, we will notify participants of new information that may become available and might affect their decision to remain in the study.

There are no known social, legal, psychological, or financial risks associated with participation.

***Confidentiality:*** Breach of confidentiality is possible, but not likely because of safeguards in place. The procedures for protecting the participants' confidentiality are in place. All participants will sign the informed consent document prior to participating in the study. All paper documents will be locked in a filing cabinet in a secure room within the University of Wisconsin-Madison's Department of Medicine UW Speech, Swallowing, and Dining Enhancement (SSWAL-ADE) laboratory and only study staff will have access to that cabinet. All electronic files related to data will be password protected and stored on a password-protected hospital network. Once enrolled, each subject will be assigned a code number crossing over to the private health information (PHI) gathered from his/her medical record, and all data gathered under the research

protocols will be recorded only by this code number. The link connecting the subject and code number will be password-protected stored separately in electronic format on the password-protected hospital network and only the PI (Nicole Pulia) will have access. Only the approved project research staff (Allison Limke, Justin Sattin) will have access to the coded study data. All information about the subject will be treated confidentially and will not be revealed unless required by law. All HIPAA regulations pertaining to protection of participants and eliminating identification will be followed. Data will be de-identified at the close of the study. Any breach of confidentiality will immediately be reported to the IRB. Individual medical records will be accessed twice during the one year duration of this study: once by Dr. Sattin initially to confirm the subjects' eligibility for the study and then again at the end of the study (one year point) to determine number of pneumonia diagnoses and hospital readmissions for the same number of months pre- and post-enrollment. Results of study-related procedures performed solely for research purposes (not standard of care) will not be placed in the subjects' medical record.

*Videofluoroscopic Swallowing Assessment:* Subjects are at risk for aspirating during the VFS assessment. If aspiration occurs during the VFS assessment, the particular bolus condition will be terminated once the cause of the aspiration is determined. Following completion of the study protocol, compensatory approaches to treatment (e.g., postures, diet modification) may be attempted in order to determine which strategies are most effective in reducing or eliminating the occurrence of airway penetration and/or aspiration, thereby ensuring safety with swallowing for patients in both treatment groups.

Subjects will be exposed to radiation exposure equivalent to one to two years of background radiation (less than 2.5 minutes) during the videofluoroscopic swallowing study. The risks of that amount are considered to be very small, and there is no indication of harmful effects to an individual. Subjects will not be included if they are pregnant. Radiation exposure during the VFS assessment will be limited as much as possible through attention to time restraints and adherence to ASHA's Guidelines for Speech-Language Pathologists Performing Videofluoroscopic Studies. Protective apparel with lead-shielding (lead apron, thyroid shield) will be worn at all times.

*Muscle Soreness:* Subjects who report muscle soreness during the treatment protocol will be offered breaks throughout treatment sessions if needed.

*Abstaining from strengthening approaches to dysphagia treatment in the acute post-stroke phase of recovery:* There may be unknown risks for subjects randomized to Group 1 who will be abstaining from strengthening approaches for the treatment of dysphagia that might be included as part of standard care. As there is not a clear standard regarding strengthening approaches for dysphagia rehabilitation post-stroke, it is unclear if omission of these approaches will result in adverse effects.

## **Statistical Analyses**

Prior to data analyses, the data collected under this study will be combined with data from its VA counterpart (IRB #2014-0939). Statistical analyses will be performed using this combined data set.

**Aim 1:** A repeated measures analysis model will be used to model changes in tongue strength in treatment and control groups, adjusted for age, gender, and baseline tongue strength. Each subject will have three observations: change between baseline and 8 weeks, baseline and 12

weeks, and 8 weeks and 12 weeks. This model will allow for comparison of differences between a) treatment durations (dose response) and b) between control and treatment groups.

**Aim 2:** Changes in oral intake and swallowing quality of life between baseline and 8 weeks, baseline and 12 weeks, and 8 weeks and 12 weeks will be modelled in a repeated measures analysis on treatment, adjusting for age, gender, and baseline outcome.

**Aim 3:** Change in number of new pneumonia diagnoses and number of hospital readmissions over a 1 year period, pre and post-study, will be modelled in linear regression models on treatment, adjusting for age, gender, and pre-study outcome.

All analyses will be performed on a randomized, or intention to treat basis, regardless of the actual treatment received. Study dropout by the subject will result in inclusion of incomplete data for that patient.

#### Sample size calculation:

Due to funding restrictions, we propose a sample size for this pilot study of 15 subjects per group. We plan to enroll 40 subjects to account for dropout of patients who do not meet the radiographic criteria for dysphagia on their initial videofluoroscopic swallowing examination.

Previous data have been collected on the proposed treatment and measurement device through our Swallow STRONG clinic (N=40). These data have shown changes in maximum isometric lingual pressures at the front and back sensors of the MOST® device over 8 weeks of DF I-PRO therapy. The

mean difference in pressure between baseline and 8 weeks was 103 hectopascals (hPa) (SD=100 hPa) at the front sensor, and the mean difference in pressure at the back sensor was 90 hectopascals (SD=94 hPa). If we assume an SD=100 hPa for treatment and control groups, with a sample size of 15 per group, the power to detect a difference, based on a 2-sample t-test, is shown in Table 2. For the treatment group we can expect an improvement of 100 hPa on average. For a control group with no strength training, we might expect an improvement of 20 hPa. This would give us approximately 56% power to detect a difference, which is adequate for a pilot study. All analyses will be conducted in SAS (SAS Institute, Cary NC).

Table 2: Power to detect a difference between treatment/control groups, SD = 100, alpha=0.05	
Difference between case/control mean change	Power
100 hPa	75%
80 hPa	56%
60 hPa	35%
40 hPa	18%

#### Data and Record Keeping

Dr. Nicole Pulia and Allison Limke will manage the study data. All paper documents will be locked in a filing cabinet in a secure room within the University of Wisconsin-Madison's Department of Medicine UW Speech, Swallowing, and Dining Enhancement (SSWAL-ADE) laboratory and only study staff will have access to that cabinet. All electronic files related to data will be password protected and stored on a password-protected hospital network. Once enrolled, each subject will be assigned a code number crossing over to the private health information (PHI) gathered from his/her medical record, and all data gathered under the research protocols will be recorded only by this code number. The link connecting the subject and code number will be password-protected stored separately in electronic format on the password-protected hospital network and only the PI (Nicole Pulia) will have access. Only the approved project research staff (Allison Limke, Justin Sattin) will have access to the coded study data. All

information about the subject will be treated confidentially and will not be revealed unless required by law. All HIPAA regulations pertaining to protection of participants and eliminating identification will be followed. A clinical report following the videofluoroscopic swallow evaluations will be entered into Healthlink for each subject and the actual videofluoroscopic swallow images will be loaded into the Patient Archiving and Communication System (PACS).

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