Defining novel pharyngeal pressure metrics to predict dysphagia treatment outcomes and clinical prognosis using high-resolution manometry

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ABSTRACT

Oropharyngeal dysphagia, or difficulty swallowing, is a devastating condition that affects physiological and psychosocial functioning in 1 in 25 adults. In 2016, speech-language pathologists working in the VA completed more than 102,905 evaluations and 77,786 treatment procedures for oropharyngeal dysphagia. This highlights not only the incidence of suspected dysphagia in the Veteran population but also the substantial need for dysphagia management with appropriate outcomes tracking. Many dysphagia treatments exist, but our ability to adequately measure treatment outcomes is limited. Pharyngeal high-resolution manometry (pHRM) directly measures swallowing pressures, providing an objective measurement of physiology that characterizes the basic mechanisms of swallowing. pHRM is well-poised to measure outcomes of dysphagia treatments due to its direct, objective, and reproducible measures of swallowing function. We propose that adding pHRM to standard assessments will help address three current issues: 1) lack of objective measures to accurately monitor treatment effects; 2) uncertainty of how physiological measures relate to patient-reported outcome measures; and 3) absence of prognostic algorithms that predict treatment effects. This proposed project will address our central hypotheses that objective swallowing measures (including pHRM) will reveal treatment-mediated swallowing changes, will align with outcome measures, and will be able to predict who will benefit from treatment.

This multi-site prospective study will follow a cohort of Veterans with dysphagia (n=150) for 8 weeks as they undergo clinically guided oropharyngeal exercises with oropharyngeal strengthening as the primary goal. Veterans with dysphagia will be assessed at three time points: baseline, 4 weeks after treatment initiation, and 8 weeks after treatment initiation. A Veteran control group (n=50) will also undergo data collection at parallel time points, without completion of a treatment paradigm. We will then compare patients to controls using pHRM, videofluoroscopy, diet assessment, functional reserve tests, and patient- reported outcome measures. We aim to 1) quantify change in pHRM measures of swallowing function resulting from dysphagia treatment; 2) determine which combination of standard of careand/or pHRM-based metrics best track with outcome measures; and 3) develop multimodal prognostic algorithms that predict treatment success. This research will establish a precise outcome measurement paradigm suitable for dysphagia clinical care and research, thus improving clinical confidence and paving the way for a personalized medicine approach for dysphagia rehabilitation in Veterans.

List of Abbreviations

DUA	Data Use Agreement
EAT-10	Eating Assessment Tool
EMST	Expiratory Muscle Strength Training
FOIs	Functional Oral Intake Scale
FEES	Flexible Endoscopic Evaluation of Swallowing
GCP	Good Clinical Practice
CRF	Case Report Forms
GRECC	Geriatric Research Education and Clinical Center
HGS	Hand Grip Strength Test
HRM	High Resolution Manometry
IOPI	Iowa Oral Pressure Instrument
IDDSI	The International Dysphagia Diet Standardisation Initiative
IDT	Intensive Dysphagia Treatment program
MBSImP	Modified Barium Swallow Impairment Profile
PRO	Patient Reported Outcomes
pHRM	Pharyngeal high-resolution manometry
PI	Principal Investigator
PID	Participant Identification Number
QA	Quality Assurance
SSQ	Sydney Swallow Questionnaire
SOPs	Standard Operating Procedures
SLUMS	St. Louis University Mental Status
UES	Upper Esophageal Sphincter
VFSS	Videofluoroscopic Swallow Study

TABLE OF CONTENTS

INTRODUCTION

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We aim to 1) quantify change in pHRM measures of swallowing function resulting from dysphagia treatment; 2) determine which combination of standard of care and/or pHRM-based metrics best track with outcome measures; and 3) develop multimodal prognostic algorithms that predict treatment success. This research will establish a precise outcome measurement paradigm suitable for dysphagia clinical care and research, thus improving clinical confidence and paving the way for a personalized medicine approach for dysphagia rehabilitation in Veterans.

Program Summary

Oropharyngeal dysphagia, or difficulty swallowing, is a devastating condition that affects physiological and psychosocial functioning in 1 in 25 adults. In 2016, speech-language pathologists working in the VA completed more than 102,905 evaluations and 77,786 treatment procedures for oropharyngeal dysphagia. This highlights not only the incidence of suspected dysphagia in the Veteran population but also the substantial need for dysphagia management with appropriate outcomes tracking. Many dysphagia treatments exist, but our ability to adequately measure treatment outcomes is limited. Pharyngeal high-resolution manometry (pHRM) directly measures swallowing pressures, providing an objective measurement of physiology that characterizes the basic mechanisms of swallowing. pHRM is well-poised to measure outcomes of dysphagia treatments due to its direct, objective, and reproducible measures of swallowing function.

We propose that adding pHRM to standard assessments will help address three current issues: 1) lack of objective measures to accurately monitor treatment effects; 2) uncertainty of how physiological measures relate to patient-reported outcome measures; and 3) absence of prognostic algorithms that predict treatment effects. This proposed project will address our central hypotheses that objective swallowing measures (including pHRM) will reveal treatment-mediated swallowing changes, will align with patient-reported outcome measures, and will be able to predict who will benefit from treatment.

This work begins to address a significant deficit in knowledge and thus clinical care: How does swallowing function change following treatment? Dysphagia is a significant healthcare burden for Veterans; the clinical framework used to justify treatment is weakly supported by research; and dysphagia sequelae represent a major component of U.S. health care spending annually (a half billion dollars). With advances in clinical tools to measure swallowing, we can evaluate function with greater precision. This work leverages several novel recent innovations in instrumentation and mathematical modelling/computer programming to create a more robust clinical environment that will empower clinicians, patients, caregivers, and healthcare networks to provide guided and justified care of dysphagia. Combining objective pHRM data with other measures of swallowing physiology and patient-centered factors will support the creation of algorithms to track and predict rehabilitative success. When these aims are completed, we will set the path for a precision medicine approach that can be used to investigate the role of any new, novel, or even poorly supported dysphagia treatment

that has clinical promise but needs an evidence-base. The support and success of this research vision will lead to a paradigm shift in the care of Veterans with dysphagia.

Specific Aims

Oropharyngeal dysphagia is a devastating condition that affects 1 in 25 adults, leading to debilitating psychosocial sequelae and life-threatening complications, such as aspiration pneumonia, as well as 500 million dollars of annual healthcare spending. In 2016, speech-language pathologists working in the VA completed more than 102,905 evaluation and 77,786 treatment procedures for oropharyngeal dysphagia. This highlights not only the incidence of suspected dysphagia in the Veteran population but also the substantial need for dysphagia management with appropriate outcomes tracking. Clinical tools available for monitoring dysphagia therapy outcomes are limited, preventing the development of prognostic clinical algorithms, limiting accuracy in interventions, and undermining confidence in patient care. Pharyngeal high-resolution manometry (pHRM) provides direct and objective measurement of swallow-related pressure and timing events in the pharynx. Research by our team has resulted in a normative pHRM database and ensured that pHRM quantifies the complex physiology of normal and intentionally perturbed human swallowing with detail, consistency, and reliability. A critical step forward in dysphagia management is evidencing the clinical utility of pHRM.

This study is designed to advance dysphagia management by capturing objective data following treatment, with the long-term goal of improving precision and predictive capabilities of dysphagia diagnostic tools. We propose that adding pHRM to standard assessments, biological data, and patient reported outcome measures will address three issues: 1) lack of objective measures to adequately monitor treatment effects; 2) uncertainty of how physiological measures relate to patient-reported outcome measures; and 3) absence of prognostic algorithms that predict treatment effects. This application is innovative and will influence the management of millions of patients, potentially reduce dysphagia-related mortality, provide realistic treatment expectations, and improve utilization of resources. This multi-site trial will follow a cohort of Veterans with dysphagia (n=150) for 8 weeks as they undergo clinically guided oropharyngeal exercises with oropharyngeal strengthening as the primary goal. During treatment, patients will undergo pHRM, videofluoroscopy, diet assessment, functional reserve tests, and patient-reported outcome (PRO) questionnaires at 3 standardized time points: baseline, 4 weeks after treatment initiation, and after treatment completion (8 weeks). Non-dysphagic controls (n=50) will also undergo data collection at parallel time points.

We propose to achieve our objectives by using the data collected to complete the following three specific aims:

1. **To quantify change in pHRM and other measures of swallowing function resulting from dysphagia treatment.** This aim will a) identify pHRM metrics that characterize the diagnoses of pharyngeal dysphagia due to muscle weakness at baseline; b) document physiological progress, or lack thereof, over the course of dysphagia therapy, and c) determine the normal variability of pHRM and other metrics in non-dysphagic adults over time. Logistic regression will discern which pressure metrics, calculated from baseline pHRM data, best define the patient group compared to normative values. All metrics will be compared across time points to identify which metrics change with therapy, and how they change relative to controls. *Hypotheses*: Clusters of metrics will distinguish the patients from controls at baseline. Metrics will remain stable in controlsover time. Clusters of metrics will change in patients with successful treatment in a direction towards normative values. *Significance*: Identification of clinically-relevant pressure metrics, as well as documentation of natural pressure variability, will improve the validity of pHRM as a clinically useful tool.

2. **To determine which combination of standard of care and/or pHRM-based metrics best track with outcome measures of treatment effect.** Magnitude of change between time points will be calculated for each metric extracted from videofluoroscopy, diet, and pHRM data and analyzed using regression models, with treatment effect (change in total Sydney Swallow Questionnaire (SSQ) score and Modified Barium Swallow Impairment Profile(MBSImP^{TM}) pharyngeal impairment score between time points) as the dependent variable. *Hypothesis*: pHRM metrics will account for significant variance in regression models predicting treatment effect. *Significance*: Identifying a combination of metrics that change in response to treatment will provide clinicians with salient variables to monitor and will provide data for prognostic algorithms.

3. **To develop multimodal prognostic algorithms that predict treatment success from baseline diagnostic measures.** We will use mathematical models (artificial neural network programming and regression models) populated with physiological and patient-specific data to identify metrics most predictive of treatment success (change toward control values on SSQ and MBSImP^{TM}). *Hypothesis*: pHRM data and factors such as age and adherence will nest with treatment success. *Significance*: Currently, no prognostic algorithms exist for dysphagia rehabilitation. This aim will provide a tool to help guide patients and clinicians towards realistic expectations for treatment outcomes.

BACKGROUND

Swallowing Disorders Impact Personal Health, Quality of Life, and Healthcare Cost to Society:
Swallowing is a fundamental, yet biomechanically complex, function of the human body.[1] Standard of care diagnostic and outcome tools used in the evaluation of the oropharyngeal swallowing are largely qualitative in nature and do not allow for the quantification of the pressure abnormalities that occur with swallowing dysfunction (dysphagia). As such, the proposed research is highly significant in applying a novel and objective tool, pharyngeal high--resolution manometry (pHRM), as an adjunct for diagnosis, prognosis, and outcome tracking in personalized clinical care of oropharyngeal dysphagia. Once diagnosed with dysphagia, the ability to restore swallowing function to an optimal state significantly impacts overall health status. Dysphagia is a tremendous financial burden, [2,3] has disabling psychosocial consequences,[4,5] and increases risk of hospitalization and life-threatening medical complications including malnutrition, dehydration, and aspiration pneumonia.[6] Therefore, improvement in precision of dysphagia rehabilitation is imperative.

Oropharyngeal Dysphagia Treatment Outcome Measurement: Current State & Limitations:
Clinical rehabilitation of swallowing function can be directed at one or more physiological goals: 1) improvement in strength of swallowing--related muscle activity; 2) relief of upper esophageal sphincter dysfunction; and/or 3) improvement in the timing and coordination of swallowing events. To address these physiological processes, various therapeutic options are used alone or in combination.[7] While most theories supporting these treatments are physiologically sound, there remains a major gap in the literature confirming the physiological changes following these treatments. Although videofluoroscopy remains custom for dysphagia diagnosis and monitoring of treatment progress, this standard tool alone is ineffective in providing unbiased interpretation,[8] direct and reproducible measurements,[8,9] or complete understanding of mechanism of the dysphagia nor the functional changes following dysphagia treatment. It is also unclear how patient--reported outcome measures for dysphagia, and biological conditions such as age and disease severity, are related to physiological changes in swallowing function.[10-12,13] Our research will fill this critical gap in knowledge and will pave the way for a personalized medicine approach for dysphagia.[14]

Pharyngeal HRM is Poised to Support Dysphagia Treatment Outcome Measurement:
Measurement of intraluminal pressure provides quantification of pharyngeal muscle functionality.[15] Pharyngeal high-resolution manometry (pHRM) is a minimally-invasive, non-radiation based tool used to quantify pressure generation and gradients within the alimentary canal at high spatiotemporal resolution (50Hz, sensors every cm, spanning 36cm).[16] Published reports from around the world have illustrated the successful use of pHRM to define normal pressure events and the effects of maneuvers, [17,18] bolus volumes,[19] and age[20]. pHRM incorporated with impedance [21,22] allows for bolus tracking,[23] pharyngeal residue identification,[24] and airway invasion risk prediction.[25] Thus far, pHRM has been applied to study pressure characteristics in a variety of swallowing dysfunction pathologies.[26,27,28,29,30,31] Preliminary evidence has been published illustrating case examples using pHRM to document progress from pharyngeal muscular strengthening and outlet obstruction relief.[32,33,34] However, the heterogeneous nature of dysphagia warrants study of a large number of patients using multivariate analyses and available relevant data.

Scientific Premise, Central Hypotheses, and Clinical Impact of Proposed Study: The premise of this work lies in the overwhelming evidence of the successful, reproducible, and informative application of pHRM, alongside other standard measures, in the evaluation of healthy swallowing physiology and detection of swallowing dysfunction. Preliminary evidence illustrates that pHRM metrics can improve characterization of the neuromuscular failures underlying any form of dysphagia and can document change with treatment over time (specifically in pharyngeal strengthening and UES dysfunction therapy cases). The strength of these data indicates that pHRM has moved from a state of infancy to a point where it now has the potential to be useful in dysphagia clinical care. However, further study is needed to provide confirmation of its clinical usefulness and discern all the salient metrics in this heterogeneous group of patients. Further, there are currently no prognostic algorithms for swallowing rehabilitation.

Small peer-reviewed studies have shown the potential power in pHRM to train neural network systems to classify pathological states of swallowing. [35-37] We hypothesize that introducing pHRM will add precision to clinical outcome care, allow us to define relationships among physiological changes and patient reported outcomes, and provide prognostic algorithms that predict treatment effects. Studying patient populations with pHRM will also add greatly to the understanding of the mechanisms responsible for unique patient-specific manifestations of dysphagia. By determining objective measures that quantify therapeutic clinical improvement, or lack thereof, this work will result in additional clinical tools that can be used to target treatment plans for patients based on individualized pressure-related metrics and/or prognostic algorithms.

Dysphagia Rehabilitation for Older Veterans: The average number of treatment visits per Veteran with dysphagia has been reported by the VA national Audiology and Speech-Language Pathology office to be 2.5 sessions. Given that this treatment dose is unlikely to result in lasting positive change in swallowing for Veterans with dysphagia, Dr. Rogus-Pulia (Co-Investigator) and her team at the William S. Middleton Memorial Veterans Hospital in Madison, Wisconsin developed the Intensive Dysphagia Treatment (IDT) clinical demonstration program in 2012 with funding from the VA Office of Geriatrics and Extended Care (GEC). The IDT program is a patient-centered multi-disciplinary program focused on providing intensive, progressive strengthening-based treatment for Veterans with dysphagia. Treatments include device-facilitated approaches (e.g., lingual strengthening or expiratory muscle strength training (EMST)) or non-device-facilitated approaches (e.g., Mendelsohn maneuver, effortful swallow, super-supraglottic swallow maneuver). Standardized outcomes tracking with instrumental assessment of swallowing (videofluoroscopy or flexible endoscopic evaluation of swallowing (FEES), physiologic measures of strength (e.g., lingual pressure, expiratory muscle

pressures), dietary level, and patient-reported outcome measures are incorporated at enrollment and completion of the program. The William S. Middleton Memorial Veterans Hospital served as the flagship site for this program and preliminary results were published in the Journal of the American Geriatrics Society (JAGS).[38] The IDT program has now been implemented at 16 sites nationally and continues to expand. Over 550 older Veterans with dysphagia (mean age= 70 years) have been enrolled in this multi-site program over six years. Patients treated for head and neck cancer have comprised the highest proportion of those enrolled in IDT (38%) followed by patients with respiratory disease (e.g., COPD, 29%) and those with neurologic conditions (e.g., stroke).[38] We have developed a multi-site database to track standardized outcome and, with this infrastructure in place, the IDT program will serve as a strong recruitment source for this study.

RESOURCES & PERSONNEL

Study Sites

The William S. Middleton Memorial Veterans Hospital will serve as the lead site for this study with Dr. Rogus-Pulia, Director of the Swallowing and Salivary Bioscience lab in the Geriatric Research Education and Clinical Center (GRECC) as a Co-Investigator on this proposal. Dr. Rogus-Pulia developed the multi-site VA Intensive Dysphagia Treatment (IDT) program in collaboration with Jill Zielinski, the Madison Local Site Investigator (LSI) for this study. This program will serve as an important recruitment source for this study. As the lead site, the Madison VA staff will coordinate study meetings, share best practices, manage regulatory approvals, and coordinate the study database.

Additional sites include the Edward Hines Jr. VA Hospital in Chicago, Illinois and the Cincinnati VA Medical Center in Ohio. These two sites were the earliest expansion sites for the IDT program and the highest performing sites for IDT recruitment (Hines= 113 Veterans; Cincinnati= 52 Veterans). The Local Site Investigators, Dr. Kathy Welden and Laura Chalcraft, currently oversee their IDT programs and are committed to supporting recruitment, training of staff in pharyngeal high-resolution manometry, and high-quality data collection at their study sites. The Hines and Cincinnati sites will perform local recruitment activities, collect data, and submit data and regulatory information to the Madison VA site.

Study Personnel

The Madison VA Research Team will lead the conduct of this study across the participating sites. These staff members will be responsible for the day-to-day operations of the study, including managing participating site communication, supporting recruitment, obtaining informed consent, collecting data during study visits and data entry into REDCap. Recruitment efforts at each site will be supported by the ENT and Speech Pathology clinics.

The Local Site Investigators will be responsible for local site recruitment, verifying local data, identifying issues, and reporting unanticipated problems to the central Multi-site Coordinator at the Madison VA. Research assistants at each site will be responsible for ensuring completion of case report forms, visit guides, and submitting documentation to the Madison VA for central entry. Ongoing data reviews will be performed by the research team at the Madison VA and overseen by the study investigator.

PLAN OF STUDY

Study Population

Our recruitment goal is 200 participants. Participants will include 150 dysphagic Veterans recruited across 3 study sites (50 participants per site) as well as a group of 50 control participants with no history of dysphagia or minimal to mild dysphagia not requiring a strengthening program (“ controls”) recruited from the VA patient population at the study sites (20 at Madison, 15 each at Hines and Cincinnati). Only dysphagic Veterans that have been assessed and determined they would benefit from pharyngeal strengthening exercises will be included in the dysphagia group. Assessment will be based on clinician-driven diagnoses and treatment goals basedon standard of care evaluation**.**

Patients will be stratified into the following groups: Group A) Patients receiving pharyngeal strengthening (n=100); and Group B) Controls (n= 127). Participants’ age may range from 18-99 years old, however, we expect most study participants will be males >60 years old due to the age range typically affected by dysphagia and the patient population characteristics at VA hospitals.

Enrollment Update and Rationale for Over-Enrollment

The study exceeded the originally IRB-approved enrollment ceiling due to the inclusion of additional healthy control participants who were necessary to strengthen the comparison group. During data review, it became clear that a larger control sample was required to ensure adequate statistical power and to balance the distribution of demographic and clinical characteristics across groups. As a result, additional healthy controls were recruited, leading to temporary over-enrollment beyond the initial approved limit.

All additional participants were healthy controls with no history of swallowing disorders. No additional intervention participants were recruited beyond the originally approved number. The inclusion of these extra healthy controls does not increase participant risk, as they underwent only minimal-risk procedures already described in the protocol.

A revised target enrollment reflecting these changes has now been incorporated into the updated protocol.

Inclusion/Exclusion Criteria

	Group A) Patients	**Group B) Controls**
Inclusion	1. Age 18-99 2. Referral for Swallow Study 3. English Speaking	1. Age 18-99 2. Self-reported without swallowingissues or minimal to mild swallowing issues not requiring a strengthening program 3. English Speaking
Exclusion	1. Unable to provide consent 2. History of allergic response to barium 3. History of allergic response to topical anesthetic	1. Unable to provide consent 2. History of allergic response to barium 3. History of allergic response to topical anesthetic

Women with childbearing potential will not be excluded from both groups, as the proposed study would have no potential ramifications on childbearing potential. Pregnancy tests will be performed in participants of childbearing potential in both groups and pregnant women will be excluded due to exposure to ionizing radiation during the videofluoroscopic swallow study.

Eligibility

To be eligible to participate in the Patient Group, the participant must have:

1. Signed an informed consent form
2. Receive a dysphagia diagnosis by a speech-language pathologist and
3. A dysphagia treatment plan with the goal of strengthening the oropharyngeal musculature

Patient study eligibility will be assessed after the videofluoroscopic swallow study. Participants who do not receive a diagnosis of dysphagia or commence a treatment plan with the goal of muscle strengthening are ineligible for the study.

Recruitment Methods

Participants for the patient group will be identified through the ENT and Speech Pathology clinics. The study team will establish communication mechanisms with the ENT and Speech Pathology clinicians to support their identification of potential participants including reminders and meetings as needed to discuss any issues with recruitment. We expect the main sources of recruitment to be identification through the IDT Program, the Speech Pathology clinics , and the Speech Pathology Videofluoroscopy schedule. Clinicians and research staff participating in recruitment are included as study personnel in this protocol. Additional clinicians who would support recruitment will be added to the protocol and complete the required research trainings.

Participants for the control group will be solicited via recruitment fliers in the hospitals at eachsite or referred to the research team through ENT and Speech Pathology clinics and/or other clinics within the VA.

In both groups, potential participants may be given an information sheet about the study, which will include information about the study, how to contact the research team, and compensation rates for participation.

Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB approved and the participant will be asked to read and review the document. A member of the study team will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants.

Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records.

The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their

medical care will not be adversely affected if they decline to participate in this study.

Data Repository

Data from this study will be deidentified and securely transferred to a data repository stored at the University of Wisconsin Madison on secure network drives in the Department of Surgery and managed by the Study Principal Investigator, Dr. McCulloch. Access to the data repository is managed by Dr. McCulloch's lab manager, who ensures that the appropriate approvals and trainings have been completed prior to access. See the Data Management section for additional details.

STUDY PROCEDURES

Study Visits

This study involves three visits: 1) baseline; 2) midpoint; and 3) final. The baseline visit may be combined with the initial standard of care clinical visit for the swallow study or it may be scheduled on a separate day, depending on the participant's preferences and the availability of clinicians and space. Baseline data collection must occur prior to patient participants initiating a strengthening regimen.

Standardized timings have been established to account for rehabilitation approaches (based on the IDT standard 6-to -10week training program), as well as to enable the collection of parallel data between both patient groups and controls. Windows for each visit have been established (see study calendar below) to accommodate scheduling for patients to align with their strengthening program, where the midpoint visit will be within 1-2 weeks of the midpoint of their strengthening program and the final visit will be within 2-3 weeks of the end of the strengthening program. Any major scheduling variances from the proposed windows will be reviewed by the PI and/or LSI to ensure maximum retention of study participants and that data integrity remains intact.

Participant visits will take place in the VA Swallow Service clinics, with the intention of scheduling study visits before or after regularly scheduled clinic visits when feasible.

Participants may experience a delay before initiation of their dysphagia strengthening program or with study continuation after the baseline visit. When the participant is available to commence treatment, the Speech Language Pathologist will review the history and determine if swallowing function is stable or, with the participant's approval, repeat the baseline visit evaluation.

Study Calendar

Each participant's study calendar will be tailored to their expected dysphagia treatment program. Control participants will maintain this schedule as closely as possible.

Visit	**Baseline**	**Midpoint** *Approx. 3-6 Weeks*	**Final** *Approx. 8-12 Weeks*
Window	n/a	+/- 1-2 weeks	+/- 2-3weeks
Demographics & Medical History, SLUMS	X		
Patient Reported Outcomes	X	X	X
Therapy Outcomes		O	O
Functional Reserve Assessment	X	X	X
Videofluoroscopic Swallow Study*	X*^	X	X*
Pharyngeal High-Resolution Manometry	X	X	X
Compensation	$75 - Patients $150 - Controls	$150 - Patients $150 - Controls	$75 - Patients $150 - Controls

X = All study participants;
O = Patient group only;
* = Standard of Care for Patients

^ = For potential dysphagic participants, baseline measurements may be completed during the same visit as the videofluoroscopic swallow study or prior to initiating their strengthening regimen.

Study Procedures

Study participants will be asked not to eat for 4 hours and not to drink for 2 hours before their scheduled appointment, to reduce the effects of satiety. The study procedures will not proceed in the event that participants fail to comply with this instruction, if the study team determines that it will impact evaluations, or will delay the procedures as needed.

- Demographics & Medical History: Participant medical record review will collect the following data: age, sex, body mass index, primary diagnosis, co-morbidities. Medical history from the medical record will be abstracted for relevant information including previous clinic visits related to swallowing, previous swallowing evaluations, history of head and neck cancer and related conditions. Medical history will be verified with the participant to obtain additional detail, including a series of questions about swallowing and history of swallowing disorders. The Veterans Affairs St. Louis University Mental Status (SLUMS) exam[39] will be administered after the interview to assess baseline cognitive status. A dietary history questionnaire will be completed with the participants. The histories and SLUMS exam will only be administered at baseline.

- Patient Reported Outcomes (PROs): Participants will be asked to complete several questionnaires and instructed to answer questions to the best of their ability. PROs will be completed at each study visit, with the exception of the successful therapy question.
    - The Sydney Swallowing Questionnaire (SSQ)[40] is a 17-item visual-analog scale questionnaire evaluating an individual's perception of the ability to swallow different consistencies.
    - The Eating Assessment Tool (Eat-10) is a ten-item rating scale questionnaire to measure swallowing difficulties.[41]
    - The International Dysphagia Diet Standardization Initiative (IDDSI-FDS)[42] will be used to assess diet.
    - The Functional Oral Intake Scale (FOIS)[43] will be used to assess oral intake.
    - *Midpoint and Final visits only*: Treatment Outcomes.
    - *Midpoint and Final visits only*: "Was your therapy a success?"

- Functional Reserve Assessments: Participants will be asked to complete two types of functional reserve assessments for the study. These assessments will occur at each study visit.
    - The Hand Grip Strength (HGS) Test will be performed to correlate for general muscle strength.[44] Participants will squeeze the dynamometer with their hand at maximum pressure 3 times and hold for 5 seconds each. Participants will have 10 seconds rest between each trial.
    - The Iowa Oral Pressure Instrument (IOPI) will be used to evaluate anterior and posterior maximalisometric tongue-pressures. [45] A small (3.5 cm long and 4.5 cm in diameter) air-filled plastic pressure bulb will be placed in the mouth at two different positions: directly posterior to the incisors and at the posterior oral tongue. Participants will be asked tosqueeze the bulb against the roof of the mouth with maximal effort and to perform saliva swallows.[45] Three tasks in each position will be recorded and participants will rest for 10 seconds between each trial.

- Videofluoroscopic Swallow Study: Participants will be asked to complete videofluoroscopic swallow studies at each time point during the study. For dysphagic participants who are receiving treatment, the baseline and final swallow studies are standard of care while the midpoint swallow study is for research only. Swallow studies will be performed according to the Manual of Procedures.
    - The research team will use the TIMS DICOM Swallowing Workstation to capture full resolution fluoroscopic imagines in real time (30 frames per second). Each participant 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.

- Pharyngeal High-Resolution Manometry: Participants will be instrumented by a trained clinician or speech language pathologist on the study team with the Medtronic ManoScan HRM. A 4.2mm HRM catheter with an impedance channel will be inserted through the nose and guided into the proximal esophagus. pHRM will be performed according to the Manual of Procedures
    - Some participants may experience discomfort while the catheter is passed through the nose. If this occurs, a topical anesthetic (Lidocaine) with or without topical vasoconstrictor (Afrin) may be applied to the nasal passage by spraying the anesthetic into the nose, temporarily numbing the nasal cavity and facilitating passageof the catheter through the nose. For some participants, it may be difficult to ensure correct placement of the catheter, especially if they do not have a typical pressure pattern. In this case, a trained speech-language pathologist on the study team will also insert a 4mm endoscope through the subject's other nostril, allowing him to visualize the larynx (voice box) and pharynx (throat) and ensure correct placement. Once the catheter is comfortably in place, the endoscope will be removed. No images or video from the endoscope will be recorded.

Compensation

Dysphagic participants in the experimental group who receive swallowing treatment will have standard of care videofluoroscopic swallow studies at the baseline and final time points and will be compensated $75 for the additional study activities at those visits. The midpoint visit is research only and they will be compensated $150. Control participants will be compensated $150 for each of the three study visits. This information is included in the Study Calendar (above). Participants will be paid by the lead study coordinator, who will have access to social security numbers for the purpose of remunerating participants.

REPORTING

Unanticipated Problems

During visits for study participation, participants will be accompanied by study personnel at all times. Participants will be asked by study staff at subsequent visits to assess for unanticipated problems or complications. If an unanticipated problem takes place, study personnel will be immediately notify the site PI and will take any necessary actions (i.e., request medical support). Any unanticipated problems will be reported to the CIRB, Madison VA R&D Committee, and VA Research Office according to VHA Handbook 1058.01, Research Compliance Reporting Requirements, and the VA Central IRB Table of Reporting Requirements.

Participants will be provided 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.

Withdrawal of Participants

Participants may withdraw from participation in the study at any time by contacting a research team member. Participants may also be withdrawn from the study by the site PI due to changes in medical status, any unanticipated problems making continuing in the study contrary to the participants' wellbeing, or a situation occurs such that continued participation in the study would not be in the best interest of the participant. These decisions will be documented in the participant study chart. If a participant withdraws themselves or is withdrawn by a site PI, additional participants will be recruited to take their place. Data collected up to the point where the participant was withdrawn will be retained unless the participant indicates otherwise.

In addition, if the participant feels uncomfortable at any time during the study procedures, the procedure will be stopped. If the participant is unable to complete the procedure, he or she will be withdrawn from the study and additional participants will be recruited to take their place. Data collected up to the point where the participant was withdrawn will be retained unless the participant indicates otherwise.

DATA MANAGEMENT PLAN

Data Safety & Monitoring

A Data and Safety Monitoring Committee will not be used for the study. The proposed study entails only minimal risk to human participants because the probability and magnitude of harm or discomfort are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102 (h) (i).

Data Documentation

Case report forms (CRFs) will be created at the Madison VA and distributed to the other sites. Clinical and research team members will complete CRFs and enter the data into a centralized REDCap database. In order to standardize the collection of study data, the Madison VA will create Visit Guides and Source Document Worksheets to ensure that all required data elements are captured. These documents will be used to supplement data collected on primary CRFs. These documents will include:

- Checklist of all the procedures to be performed at each study encounter
- Special instructions for procedures and processing of research images
- Required data elements for complete source documentation of study data
- List of the data submission requirements for each study encounter
- Place to indicate visit notes

All data must be documented either on Case Report Forms or on the Visit Guides and Source Document Worksheets. All documents must be signed by the staff that collected or elicited the information in the source documents. Data entry will be performed centrally by the Madison VA

study team staff. All documents will be submitted to the Madison VA (either by fax, or secure e-mail) for entry into the REDCap database. All data is due to the Madison VA within 10 business days of each study visit.

The Madison VA Multi-site coordinator will develop standard operating procedures for data collection and quality checks, as well as data guidelines. Each site will be provided with guidelines for completing Visit Guides, Data Collection Forms (CRFs) and Worksheets. The guidelines will contain instructions for data completion and required data elements for all study related data points.

Participant Identification

Each site will maintain a **screening log**: all screened participants will be assigned a Screening Identification Number (Screen ID). The log will include the date the participant was identified, participant ID, how the participant was identified, if the study was presented to the patient, if not presented to why, date presented to, and whether they are scheduled for screening visit.

Each site will maintain an **enrollment log**: all study participants who complete screening, have been consented and are eligible for the study will be assigned a unique Subject Participant Identification Number (PID). The Enrollment Log includes participant name, last four of social security number, date of screening call, eligibility, date informed consent was sign, date enrolled, dates of research visits and IDT arm assigned based on clinical needs. The Enrollment log is kept separate from the study data in a secure VA location. Study data will be kept separate from the enrollment log and will not include any personally identifying information. Study data will be linked by subject PID.

Each site will use a three-letter code (Madison VA = MVA, Hines VA = HVA, and Cincinnati VA = CVA) and use a sequential three-digit numerical code (e.g. 001, 002) as the basis for the screening and subject identification numbers. Subject identification numbers will be distinct by including a group code (D=Dysphagic;C=Control).

All data submitted to the Madison VA will have personal identifying information removed or obscured and will be re-identified with the subject PID number assigned to that participant.

Once the protocol specific informed consent and HIPAA authorization 10-0493 forms have been signed, an individual is considered to be on study. The following documents must be submitted for all persons signing informed consent regardless of whether they are found to be eligible to participate or not and regardless of whether they fully complete the study or not:

- Protocol-specific signed informed consent
- Baseline Visit Guide or Worksheet with demographic information completed
- An Off Study form indicating the reason for the “off study” designation.
- A Verification Form indicating the data has been reviewed and verified by the Site PI.

Data Quality

Data submissions will be reviewed for accuracy and completeness by a member of the Madison VA study team. The study investigator or designee will be responsible for the review and approval of all study data. Bi-monthly data pulls from the REDCap database will be reviewed by the Madison VA Multi-site coordinator and verified by the Principal Investigator.

The Madison VA Multi-site coordinator will also ensure all required regulatory documents and procedures have been completed appropriately and are up to date, including:

- Performing a record review to verify the data entered into the REDCap database against source documents, ongoing communication to ensure all study procedures are conducted in adherencewith the study protocol
- Verifying all participants have a signed and dated protocol specific informed consent and HIPAA authorization 10-0493 forms obtained prior to conducting any study procedures.
- Continual assessment of site operations, verifying the sites have adequate resources to conduct the protocol
- Review internal QA activities at sites
- Review site accrual and capacity
- Follow up on any problems previously identified

Each study site is expected to perform internal quality management of study conduct, data collection, documentation and completion. Recurring meetings to discuss these topics will be coordinated by the Madison VA Multi-site coordinator.

Data Security

Study data will be coded with the participant identification number, and stored separate from the link to identifiable subject information. All paper documents will be locked in a filing cabinet in a secure room within the Madison VA GRECC Swallowing and Salivary Bioscience Laboratory. All electronic files related to data will be password protected and stored on a password- protected secure network and backed up as per MAD-VHA_CP_SOPv2.0, every three hours. The secure VA REDCap system will be used for the study database (for additional security details, see Initial Product Review-Vanderbilt University Research Electronic Data Capture (REDCap)-Enterprise Security Solutions Service-2014). Only approved research team members will have access to the coded study data and the study database.

Data Transfers

Study Data: Data collected at the Hines and Cincinnati VA sites will be transferred to the Madison VA by secure VA e-mail for entry into the central REDCap study database. To prepare data for transfer from the sites, the local study team verifies that identifiers have been removed or redacted. Sites will be provided the appropriate e-mail information to ensure that these data are received by the Madison VA study team. Upon receiving data from sites, the Madison VA coordinator will ensure that no identifiers have been included and redact and communicate with the site if necessary. Coded study data may also be shared through the use of VA Shared S Drives.

Study Images: Study videos of the videofluoroscopic swallow studies are recorded on TIMS machines, which are classified as non-networked VA computers. These files will be transferred from the TIMS onto a 1 TB encrypted flash drive and mailed to the Madison VA study team via a tracked courier or via secure electronic transfer mechanism approved by the VA. Study images from high-resolution manometry ManoScan software will also be transferred onto a 1TB encrypted flash drive and mailed to the Madison VA study team via a tracked courier or via secure electronic transfer mechanism approved by the VA.

Data will not be shared between study sites until an approved Data Use Agreement (DUA) has

been executed and approved by local site ISO and Privacy Officers.

Data Repository: On a quarterly schedule, deidentified data will be exported from the REDCap study database and transferred to a network drive maintained by the University of Wisconsin-Madison Department of Surgery for analysis and entry into a data repository. This network drive is housed on an enterprise-level storage system, which is regularly backed up to an enterprise-level tape storage system. Access to the network location is strictly controlled and only granted to specific password-protected user accounts. Access to data on this system is audited.

Data Return & Retention

Data collected in this study that is VA-owned information will be returned to the VA at the close of the study if appropriate, or destroyed. Paper data will be redacted and disposed of in secure recycling containers at the VA and electronic data will be removed with guidance from IT. VA research data and information will be maintained per VA Records Control Schedule (RCS) 10-1 regulations.

RISKS

General Risks

We do not anticipate any risks in having participants fast for 4 hours prior to testing. This is common practice and is recommended to those coming for an outpatient clinical MBSS. Before the scheduled study, participants will be informed to take regularly scheduled medication and any precautionary measures should they be diabetic or hypoglycemic.

These studies will be conducted in the Madison VA in clinic spaces that are accessible by crash carts, therefore, medical assistance will always be immediately available during the experimental sessions. The subject will be provided water and brief rest periods upon request. There are no known late effects of these procedures. The subject will be asked to inform the investigator if they have known allergies to numbing medicine (anesthetic), or any known food allergies. They are also encouraged to take breaks whenever necessary. Any unanticipated problems or complications will be reported to the IRB in accordance with IRB guidelines.

Breach of confidentiality is possible, but not likely because of safeguards in place (see Data Security section). All information about the participant 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.

Videofluoroscopic Swallow Study

A videofluoroscopy (VF) swallow study is considered a routine evaluation method for patients with swallowing disorders and thus use of VF can be considered minimal risk by definition as stated previously. However, with any swallow study, there is a small level of risk associated with ionizing radiation exposure. Efforts to ensure that exposure dose during all imaging studies are ‘as low as reasonably achievable’ will be carried out. We estimate that each completed swallow trial will require between 3-5 seconds of active radiation because we are interested in studying the pharyngeal phase of swallowing, which only takes less than one second, with a brief period of time immediately prior to and after the swallow to ensure we have captured the data. As our protocol includes less than 30 trials per visit, we estimate participants will be exposed to radiation from the fluoroscopy unit for a maximum of 90-150 seconds per visit. According to

dose-area product measurements, a standard modified barium swallow evaluation yields a median effective dose to the patient of 0.85 mSv, which is considered a low associated risk (1/16,000) 46-48. The exposure accumulated from the 3 planned videofluoroscopy studies in our study is, therefore, equivalent to less than the average annual natural background radiation exposure an individual accumulates (estimated at 3mSv annually, mainly from radon gas in the home).47 Study participants will be informed about this radiation exposure risk and will provide formed consent to participate. Participation in this study does not prevent the participant from undergoing any medical procedure that would require further exposure to X-ray.

Potentially, patients with dysphagia may experience some difficulty swallowing, including the risk of water/barium entering the airway. The size of the material to be swallowed is considered small and would be very unlikely to cause any airway obstruction or pneumonia if inadvertently introduced into the airway. However, in cases of dysphagia, the smaller bolus volume will be used first, followed by the larger volumes as determined safe. These smaller bolus volumes are considered safe even in severely dysphagic patients.[49] If particular bolus volume or consistency is observed to enter the airway, the speech-language pathologist on the study team performing the swallow study may discontinue further trials with that particular bolus type. All participants will be carefully observed throughout the studies.

If the subject feels uncomfortable during any time of the experiment, it will be stopped. If the subject is unable to complete the tasks, he or she will be withdrawn from the study and additional participants will be recruited to take their place.

High Resolution Manometry

The addition of HRM should not impose substantially greater risks for these participants. Potential risks include gagging, choking, and fainting during the swallow tasks. The likelihood of these risks occurring is small and further reduced by providing the participants adequate time to rest between tasks. A physician and the study team will be immediately on hand if these events should occur. Similar procedures are performed routinely in the otolaryngology clinic, including: laryngoscopy (visual evaluation of the larynx/voice box), pH monitoring and feeding tube placement.

In more than 22 years of clinical practice and the treatment of over 10,000 patients, Dr. McCulloch has not seen one case of allergy to topical anesthetic. If a subject did have an allergy, he or she would most likely know as the anesthetic is the same agent used in dental offices and for all minor procedures. If a subject was unaware of the allergy and subsequently had an allergic reaction, it would consist of local swelling and would be treated with an oral dose of steroid (20 mg of prednisone) and an antihistamine (50 mg of Benadryl). A description of what the allergic reaction would entail (reddening and irritation of the skin, rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing), is provided in the consent forms.

COMMUNICATION PLAN

With oversight from the study PI and Co-Is, the Madison VA Multi-site research coordinator will be responsible for implementing mechanisms to ensure communication between the study sites and the Madison VA. Prior to initiating the study at the local sites, the Multi-site coordinator will ensure that each site has completed their local site application, received local approvals, and all study team members have completed the trainings. Copies of approvals and certifications must be submitted by the local sites to have on file at the Madison VA prior to the initiation meeting.

At any point during the study when a certification or approval must be renewed, each site must submit a copy of the certification or approval notice to the Madison VA site.

Prior to opening the study for recruitment, the Multi-site coordinator will organize a Study Initiation meeting to ensure all sites are trained in the study protocol and procedures, understand the communication plan and requirements, and address any outstanding logistical questions. Requirements and expectations for communication frequency and the all-site meeting schedule will be announced at the initiation meeting. All sites are required to have the Site PI and a member of the research team attend the recurring All Site Study meetings. Unanticipated problems, logistical issues, and data reviews that impact the conduct of the study will be addressed during the recurring All Site Study meetings.

During the study, the Multi-site coordinator is responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol and all applicable federal, state, provincial, and local laws, rules, and regulations relating to the conduct of human subjects research. The Multi-site coordinator is responsible for ensuring all sites are informed of any changes to the protocol, informed consent, HIPAA authorization, and any other IRB-approved documents. The Multi-site coordinator will also perform monitoring visits at the Hines and Cincinnati sites in an effort to ensure study conduct is performed according to protocol.

ANALYSIS PLAN

Aim 1: To quantify pHRM metrics which distinguish dysphagia patients from normal controls.

H_A: Specific clusters of pHRM metrics will distinguish the patient group from controls prior to treatment. pHRM metrics and other clinical measures will remain stable in non-dysphagic controls over time. Individuals and clusters of pHRM and other clinical metrics will change with treatment in the dysphagia group, in a direction towards normative values.

pHRM data collected from the 150 Veterans undergoing dysphagia treatment and 50 non-dysphagic controls at three time points (baseline, midpoint post-treatment, and final post-treatment) will be used. In this aim, we plan to describe baseline and change from baseline measures (Sydney Swallow Questionnaire (SSQ), MBSImP™) in each of our treatment and control groups using plots, means, medians, minimums, maximums, and standard deviations. We will conduct a logistic regression to identify pHRM factors from a baseline sample that would distinguish patients from controls. The SSQ and MBSImP™ will be treated as both continuous and categorical (dichotomous) predictor variables in separate logistic regression models. We will compare changes over time between and within control and treatment groups using a repeated measures analysis of variance.

Aim 2: To determine which combination of standard of care and/or pHRM-based metrics best track with outcome measure of treatment effect.

H_A: pHRM metrics will account for the most variability in predicting improvement with treatment.

Data collected from the three time points will be analyzed using standard, validated tools. Magnitude of change between time points will be calculated for each metric in order to measure changes in swallowing function assessed with standard-of-care physiological outcome measures.

These data and changes in pHRM metrics (data from Aim 1) will be entered as explanatory variables in a regression model. The dependent variable of 'treatment effect' will be measured as the change in total score from Sydney Swallow Questionnaire (SSQ) patient-reported outcome questionnaire as well as the Modified Barium Swallow Impairment Profile (MBSImP) pharyngeal impairment score between time points. We will perform a multiple regression analysis to determine which explanatory variables, or combination thereof, track with treatment-associated change in the SSQ and the MBSImP pharyngeal impairment score.
Separate regression models will be performed for each outcome (SSQ and the MBSImP) and time point comparison, as well as possibly in diagnostic subgroups. For each model, we will carry out unbiased stepwise model selection (forward-backward), using the Bayesian Information Criterion to indicate the best fitting model. As a second approach, we will convert the changes in the dependent variables to binary outcomes. Consistent with a recent study that defined meaningful change in the SSQ 50, we will consider a decrease in the SSQ total score of 200 or more points (more than a 25% point decrease) to be improvement with treatment. For the MBSImP™ pharyngeal impairment score, based on a prior study examining change in this measure following treatment, [22] we will consider a 20% decrease to be improvement with treatment. We will then conduct separate logistic regressions with each binary outcome.

Aim 3: To develop multimodal prognostic algorithms that predict treatment success from baseline diagnostic measures.

H_A: pHRM metrics, as well as patient-specific factors, such as age and functional reserve, will be highly predicative of dysphagia treatment success.

Data from the patient group in Aims 1 & 2 (n=150) will be included. We will use logistic regression models and ANN modelling (Hidden Markov Model) supported by the large baseline dataset to determine the set of factors that predict treatment success in the treatment domain of pharyngeal strengthening. Delineation of therapeutic success as a binary outcome will be based on changes in the SSQ and the MBSImP pharyngeal impairment total scores.

Statistical Power Calculations

This study will be powered to address all three aims. In our calculations, we have taken into account an estimated 20% attrition rate, which would leave us with a final sample of 120 patients with dysphagia and 40 control participants. For Aim 1, with this sample, we are able to detect as significant with at least 80% power, an effect size of 0.515 with a two-tailed, two-sample t-test performed at a significance level of 0.05. Based on prior data examining differences between dysphagic patients and healthy controls [51], it is highly likely that we would observe pHRM Metrics that differ by at least that much between two groups. For Aim 2, we are using univariate regression models, or equivalently, correlation coefficients, to identify the factors that will be entered in those multivariable models. With 120 patients, if the correlation representing the relationship between any of our metrics and the change in the SSQ and the MBSImP™ pharyngeal impairment score is at least 0.4, we will have greater than 90% power for identifying that factor as significant and adding it to our multivariable model. For Aim 3, if we anticipate 50% success rate (60 successful and 60 unsuccessful patients with dysphagia, we would be able to detect as significant with at least 80% power an effect size of 0.516 with a two-tailed, two-sample t-test performed at a significance level of 0.05.

Potential Problems & Alternative Strategies

Aim 1: Given the heterogeneous nature of dysphagia and treatment protocols, we expect that not every patient receiving swallowing treatment will improve or comply with treatment (even when reporting to be adherent). As such, it is possible that it may be more difficult to confidently discern which metrics change with therapy. If this is the case, we will report observational pressure data and perform a hierarchical cluster analysis to determine which groups of patients responded to treatment. In this case, evidence indicating therapeutic appropriateness may be a by-product of this study. Moreover, if this occurs, it will not prevent us from completing Aims 2 & 3. Sub-group analyses can also be performed by specific therapy protocol, as well as analysis of pHRM parameters down to an individual patient level to identify clinically-relevant pHRM parameters. Data from participants who do not complete the three time points can still be used for individual time point analyses.

Aim 2: It is possible, due to the heterogeneous nature of dysphagia and treatment approaches, that no statistically significant model will describe the variability in our patient-reported treatment success measure. If this is the case, we will apply Principal Components Analysis (PCA) to our data set, a statistical method that uses orthogonal transformation to manage complex data sets and identify clusters of relevant multidimensional variables. Our lab has successfully used PCA methodology to identify salient clusters of pHRM and gait variables that distinguish patients with Parkinson's disease from healthy controls.[52] If required, we can also report observational data (change from baseline to post-treatment), perform additional subgroup analyses by specific treatment/therapeutic protocol, or look at each patient descriptively, to determine if outcome measures correlate on an individual basis. Incomplete data sets will not preclude us from analyzing the remaining metrics with one another and will not preclude work to be done in the other aims.

Aim 3: It is possible that binary distinction of swallowing improvement following rehabilitation will not result in separation of even datasets for Hidden Markov modelling. In that case, we will use change in patient-reported outcome questionnaire scores or degree of swallowing physiology change from the regression models in Aim 2 as our parameter of interest and will use another predictive modelling approach, such as regression, signal processing, or support vector machine learning. The Machine leaning models us "discrimination" as a direct model endpoint. We can mitigate machine learning limitations by the use of robustness testing through synthetic counterfactuals; where we can determine how tolerant the final model is by randomly "misclassifying" pHRM/ reported function to show how well the model performs under suboptimal input conditions. Additionally, we can identify a limited number of candidate mechanistic features and create a best model using if/when it outperforms this "gold standard". If the null hypothesis cannot be rejected, the finding would be meaningful for framing treatment expectations: baseline measures do not sufficiently predict change in reported function.

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