Interventions for Patients With Alzheimer's Disease and Dysphagia

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Scientific Protocol

Title: Impact of Novel Rehabilitative Approaches for Dysphagia in patients with Alzheimer's Disease and Related Dementias

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1.0 PROJECT SUMMARY/ABSTRACT

This career development proposal is designed to provide Nicole Rogus-Pulia, PhD, CCC-SLP, a Speech-Language Pathologist and an expert in dysphagia (swallowing dysfunction) at the University of Wisconsin-Madison School of Medicine and Public Health with the training required for success as an independent, clinician scientist researching interventions to improve the care of dysphagia in patients with Alzheimer's Disease and Related Dementias (ADRD). Dysphagia frequently develops in patients with ADRD and leads to decreased quality of life as well as serious health consequences, including malnutrition, pneumonia, and death. Common treatments for dysphagia in patients with ADRD employ compensatory approaches that alter bolus flow to avoid aspiration (entrance of food or liquid into the airway). These approaches do not result in sustained improvements in swallowing physiology and often negatively affect quality of life. There are currently no effective treatments for dysphagia in patients with ADRD that can be practically applied or have lasting effects on the physiology of the swallow. The goal of Dr. Rogus-Pulia's proposed research is to develop effective dysphagia rehabilitative interventions for patients with ADRD at risk for pneumonia development. Progressive-resistance lingual strengthening and saliva substitute are two interventions that have been shown in preliminary studies to positively influence swallowing function in older adults. This proposal will consist of a small, pilot randomized clinical trial to 1) determine the impact of two novel interventions on proximal swallowing outcomes in patients with ADRD and 2) identify subgroups of patients most likely to benefit from these interventions. Patient-caregiver dyads will be randomized to lingual strengthening, saliva substitute use, a combination of the two, or usual care. Saliva and swallowing-related outcomes will be collected at baseline and following the 8 week intervention period. These data will support a larger, multi-site R01 funded study to determine effectiveness of these interventions for prevention of pneumonia development in patients with ADRD. As a junior faculty member at an institution with extensive infrastructure to support early stage investigators, Dr. Rogus-Pulia is in an ideal environment to complete the proposed research and pursue advanced training. Her career development plan includes both coursework and mentored training in the areas of 1) clinical trials design and analysis, 2) Alzheimer's disease research, 3) advanced statistical techniques, 4) implementation science, and 5) human factors and healthcare systems engineering. To ensure success, she has identified committed, expert mentors in these disciplines and secured protected time for this work. This award addresses a significant clinical dilemma and serious gap in ADRD research while affording the education and mentored research experience critical for Dr. Rogus-Pulia to lead an independent dysphagia research program.

2.0 INTRODUCTION

2.1 Overview: Pneumonia is a leading cause of decreased quality of life and hospitalization in patients with Alzheimer's Disease and Related Dementias (ADRD).[1] Dysphagia, resulting in aspiration of liquid or food into the lungs, frequently leads to pneumonia development as well as malnutrition and dehydration. Up to 45% of institutionalized patients with dementia are estimated to suffer from dysphagia[9] and up to 40% will die of pneumonia.[2]

2.2 Dysphagia is Common in ADRD: As compared to normal aging, patients with ADRD experience increased difficulties with swallowing as documented via videofluoroscopic assessment.[2-5] Dysphagia in ADRD is likely due to a combination of factors, including changes in swallowing biomechanics, salivation, and oral sensation. Patients with ADRD experience hyposalivation, or decreased saliva production, beyond that of normal aging, which is likely to impact the composition of saliva, its lubrication properties and its impact on oral sensation (taste and texture sensitivity); all of which impact swallowing.[6-8]

2.3 Lack of Effective Treatment for Dysphagia: There are currently no effective treatments for dysphagia in patients with ADRD that have lasting impact on the physiology of the swallow. Current treatments are solely compensatory in that they redirect bolus flow but do not alter swallow physiology itself.[6,9] Postural adjustments (chin tuck or head turn) and diet modifications (withholding thin liquids or restricting liquid intake to thickened liquids) are commonly used to minimize aspiration. Several of these approaches have been shown to reduce airway invasion in patients with dementia.[10] However, these approaches need to be used with each swallow, may negatively affect quality of life, are often unsatisfactory to patients, difficult to maintain, and, in certain cases, increase pneumonia risk.[11,12] There is great need for effective treatments that lastingly impact swallow physiology and result in more lasting dysphagia management.

2.4 Treatment Options for Impacting Physiology of the Swallow: To optimize swallow safety, novel interventions must be developed that consider the various factors contributing to dysphagia in patients with ADRD. Two promising options available now and in pressing need of study in ADRD patients are:

Lingual Strengthening: The tongue is the primary propulsive force for bolus movement into the esophagus during swallowing. Maximum isometric lingual pressures, or pressures produced when the oral tongue is pushed as hard as possible against the hard palate, decline with age[13] and in patients with dysphagia.[14] Just as participation in progressive resistance training can strengthen striated limb musculature to improve mobility in healthy older adults[15], it also benefits bulbar-innervated striated muscles of the head and neck.[16] Lingual strengthening therapy based on core principles of exercise physiology[15] employs high intensity, repetitive, non-specific exercises for the tongue. Positive changes following lingual strengthening in lingual isometric and swallowing strength have been shown for healthy older adults[24] and patients post-stroke.[17,18]

Saliva Substitute: While strengthening the tongue should improve bolus control and propulsion, lingual strengthening does not address inadequate lubrication providing resistance to bolus flow. To alleviate dry mouth, older adults often use commercial saliva substitutes as a replacement for natural saliva. The most commercially successful products are Biotene® products, a hybrid between biopolymer plant mucilage and salivary enzyme–based substitutes. Salivary substitutes decrease mouth dryness[19] and need to drink water to swallow[20] in older adults. However, it remains unclear if these are feasible or impactful therapies for dysphagia in patients with ADRD.

2.5 Preliminary Data: Preliminary data from our federally-funded clinical program suggest that lingual strengthening and saliva substitutes can improve swallowing in non-demented older adults with dysphagia. Following lingual strengthening, 127 Veterans (mean age= 69 years) with videofluoroscopy-diagnosed dysphagia significantly improved: lingual pressures at the front (p<.001, effect estimate=86.3) and back (p<.001, effect estimate=80.1) tongue (Figure 1); swallowing-related quality of life (p<.05); perceived swallowing effort (p<.03); level of oral intake (p<.001); and severity of airway invasion with thin liquid (p<.04).[21] Furthermore, in a subgroup of 27 patients with salivary collection, those patients with higher unstimulated salivary viscosity reported higher swallow effort (SR= 50 1/s; p=.02). Greater oropharyngeal residue on semi-solid boluses was observed in those with reduced stimulated salivary quantity (p<.04) and higher salivary viscosity (SR= 50 1/s; p<.03). Additional pilot data collected by our team showed that healthy older adults with higher mouth dryness ratings had higher perceived effort with swallowing (r=.60; p<.001), with average ratings of perceived swallow effort decreasing significantly after use of saliva substitute (p<.02; Figure 2).

FIGURE 1: LINGUAL PRESSURES

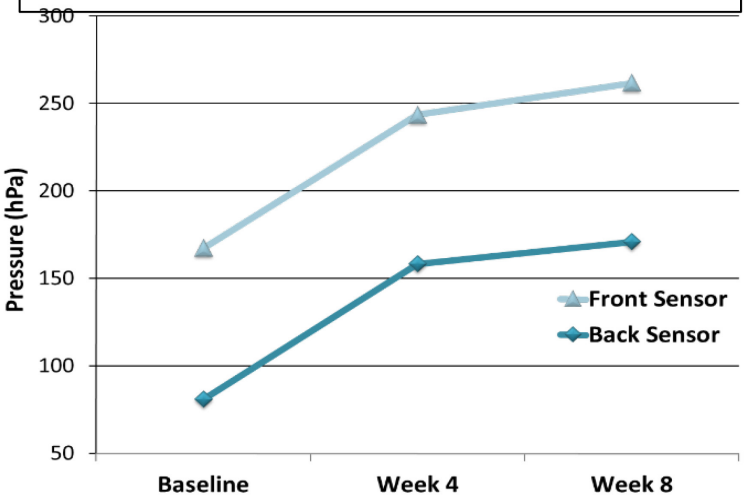
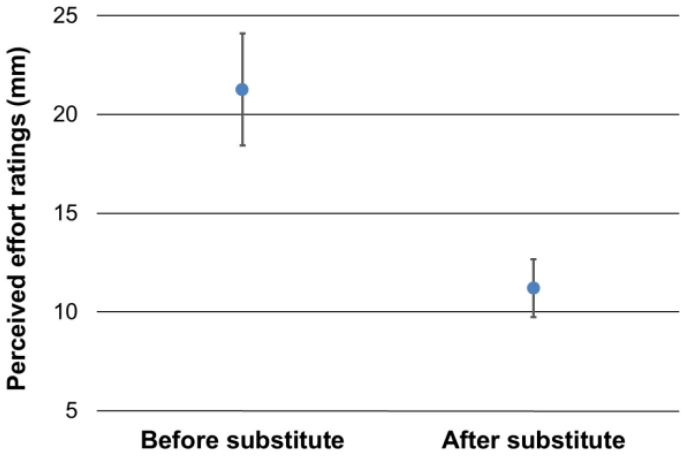


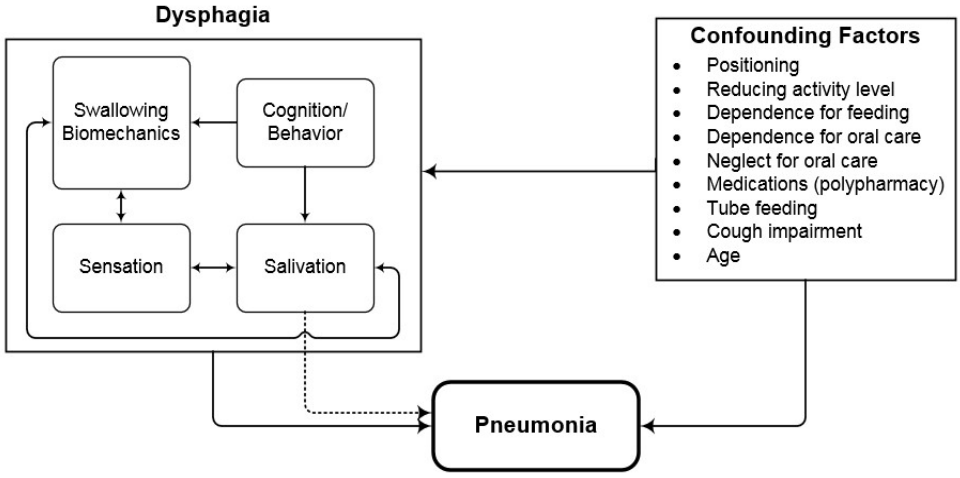
FIGURE 2: PERCEIVED SWALLOW EFFORT



2.6 2.6 Overarching Conceptual Model: To address the major gaps detailed above, Dr. Pulia proposes a conceptual model based on the hypothesis that the processes underlying dysphagia are multifactorial as is the contribution of dysphagia to pneumonia development (Figure 3). The model builds upon previous AD-related swallowing

biomechanical research, but is innovative in that it considers the novel contribution of other factors, specifically salivation, sensation, and cognition/behavior, to dysphagia development in ADRD. Additionally, this model represents the role of dysphagia in the development of pneumonia and the influence confounding factors (e.g., positioning, activity level, dependence for feeding or oral care) on this trajectory. A more thorough understanding of these complex relationships will allow for improved intervention development and targeting.

FIGURE 3: CONCEPTUAL MODEL



3.0 STUDY AIMS/STUDY OBJECTIVES

3.1 Primary Objective: The primary goals of this proposal are to: 1) Determine impact of two novel interventions on proximal (i.e., early) swallowing outcomes in patients with ADRD; 2) Identify subgroups of patients most likely to benefit from these interventions; and 3) Determine associations among lingual pressures, saliva production, dysphagia status in patients with ADRD.

3.2 Secondary Objectives: The secondary objectives of this project are to elucidate relationships among oral microbial diversity, salivary profiles, oral health, and swallowing function and to examine how these measures relate to pneumonia development in persons with ADRD.

3.3 Study Aims

1) Determine the impact of two novel interventions (lingual strengthening and saliva substitute) versus usual care on swallowing-related outcomes in patients with mild-moderate ADRD.

   H_A: Patients who receive lingual strengthening plus saliva substitute will experience the greatest decrease in post-swallow oropharyngeal residue as compared to the other groups.

2) Identify subgroups most likely to benefit from treatment by examining associations amongst key mechanistic variables for patients with ADRD in relation to treatment response (including swallowing physiology, saliva, and cognition).

   H_A: Those patients with mild ADRD, severe swallowing impairment [oropharyngeal residue and airway invasion], and altered salivation [quantity and viscosity] will

experience the greatest decrease in oropharyngeal residue and increase in quality of life following treatment.

3) Characterize associations among lingual pressures, maximum expiratory pressures, voluntary cough measures, saliva production, and dysphagia status on videofluoroscopy in patients with ADRD.

   H_A: Patients with dysphagia will have lower lingual pressures, lower maximum expiratory pressures, a weaker voluntary cough, and altered salivation (quantity and viscosity) as compared to those without dysphagia on videofluoroscopy.

4) Determine the oral microbiota profiles, saliva characteristics, oral health status, and swallowing function in ADRD dementia and test the extent to which swallowing impacts the composition of oral microbiota.

   H_A: Those with lower oral microbial diversity and greater salivary alterations will show greater swallowing impairment.

5) Determine the relationships among oral microbial diversity, saliva characteristics, and incidence of pneumonia.

   H_A: Persons with ADRD with less oral microbial diversity and greater salivary alterations will have a higher incidence of pneumonia.

6) Conduct semi-structured interviews with participants to understand barriers and facilitators to the interventions used in the RCT and to following swallowing recommendations provided to those in the usual care arm.

   H_A: Relevant themes, facilitators, and barriers regarding utilization of swallowing interventions and swallowing recommendations will be abstracted from interviews through use of a qualitative codebook and directed content analysis.

4.0 SELECTION OF PATIENTS

4.1 Study Population: 240 inviduals (120 participants and 120 caregivers enrolled as a dyad) will be recruited through the University of Wisconsin Hospitals and Clinics and at the Madison VA under a separate VA-specific version of this protocol. Participants will include patients with dementia or mild cognitive impairment and a caregiver. Enrollment will continue until at least 240 inviduals (120 participants and 120 caregivers enrolled as a dyad) patients undergo baseline testing and 76 patients are enrolled in the RCT portion of this study.

4.2 Eligibility Criteria

4.2.1 Inclusion Criteria for Patients

4.2.1.1 Age 50-99

4.2.1.2 English-speaking

4.2.1.3 Diagnosis of dementia or cognitive impairment or memory loss

4.2.1.4 Clinical Dementia Rating score between 0.5 to 2

4.2.1.5 Actively involved caregiver

4.2.1.6 Resides at home, assisted living facility, or other long-term care facility

4.2.2 Inclusion Criteria for Caregivers
- **4.2.2.1** Age 18 or older
- **4.2.2.2** English speaking
- **4.2.2.3** Contact with patient at least 1 time a week
- **4.2.2.4** Has access to a working telephone

4.2.3 Exclusion Criteria for Patients
- **4.2.3.1** Dementia due to cerebrovascular disease as primary cause
- **4.2.3.2** History of head and neck cancer or other structural deformity that can affect swallowing
- **4.2.3.3** Allergy to barium
- **4.2.3.4** Currently breastfeeding or pregnant or planning to become pregnant

4.2.4 Exclusion Criteria for Caregivers
- **4.2.4.1** Lacks ability to give consent

Definitions

4.1.1 Diagnosis of dementia or cognitive impairment or memory loss will be determined by reviewing the patient problem list as well as the patient medical history and may include clinical notes indicating suspected or probable diagnoses not formally listed in the patient's problem list.

4.1.2 Caregiver is defined as a family member, friend, or acquaintance who has contact with the patient at least 1x/week.

4.1.3 Mild-to-moderate dementia is defined as a score of 0.5-2 on the Clinical Dementia Rating (CDR) screening tool:

Score 0.5	Very Mild Dementia
Score 1	Mild Dementia
Score 2	Moderate Dementia

5.0 RESEARCH DESIGN AND METHODS

4.2 This is a prospective cross-sectional study with a nested randomized controlled pilot trial for lingual strengthening and saliva substitute use as dysphagia therapy. We will enroll patient-caregiver dyads who give written informed consent, meet the eligibility criteria, and remain eligible after screening. All enrolled dyads will undergo baseline testing. Those patients identified with dysphagia on the videofluoroscopic swallow studies will be offered participation in the RCT portion.

Enrollment will continue until at least 240 inviduals (120 participants and 120 caregivers enrolled as a dyad) undergo baseline testing and 76 patients are enrolled in the RCT portion of this study. Those with dysphagia will be randomly assigned to one of four groups to receive 1) usual care; 2) the lingual strengthening with the Iowa Oral Performance Instrument (IOPI) intervention plus usual care; 3) the saliva substitute intervention plus usual care; or 4) the lingual strengthening with the IOPI combined with saliva substitute intervention plus usual care.

4.3 Pre-screening

4.3.1 Inpatient Recruitment

4.3.1.1 *Method #1:* Patients will be recruited through the inpatient UW Swallow Service at the University of Wisconsin Hospitals and Clinics in Madison, WI. The research coordinator for this study will identify potentially eligible patients based on pre-hospitalization diagnoses of dementia or cognitive impairment or memory loss, anticipated discharge setting, and caregiver involvement via review of electronic medical records for patients being seen by the Swallow Service. The research coordinator will notify the Swallow Service clinical staff of the patient's potential eligibility based on dementia diagnosis and caregiver involvement.

Swallow Service clinicians may also notify the research coordinator of potentially eligible patients. Once receiving this notification, the research coordinator will assess potential eligibility via electronic medical record review. If the patient remains potentially eligible, the research coordinator will then visit the patient in the hospital to discuss the study or follow up with the patient and/or legally authorized representative (LAR) after discharge.

4.3.2 Outpatient Recruitment

4.3.2.1 *Method #1:* The research coordinator will *screen a list of scheduled outpatient swallow studies through the UW Hospital Swallow service*. If the research coordinator identifies a potentially eligible participant, they will call the patient and caregiver/LAR using the outpatient phone screening script. If both parties are interested, a consent form will be mailed/emailed to the participants for review, and the consent process will occur in person at the visit prior to the swallow study.

4.3.2.2 *Method #2:* The *attending physicians in the UW geriatrics clinics will refer eligible patient-caregiver dyads* to the research coordinator based on review of eligibility criteria and referral for a swallowing evaluation based on concern for dysphagia. The geriatricians will confirm with the patient-caregiver dyad that it is acceptable for a member of the study team to reach out to the patient-caregiver to provide more information about the study. Following notification of a potentially eligible dyad, the research coordinator will review the patient's medical records for potential eligibility based on dementia diagnosis. If potential eligibility is confirmed, the research coordinator will call the patient and caregiver/LAR using the outpatient phone screening script. If both parties are interested, a consent form will be mailed/emailed to the participants for review, and the consent process will occur in person at the visit prior to the swallow study.

4.3.2.3 *Method #3:* In *collaboration with the Alzheimer's Disease Research Center (ADRC) Clinical Core*, subjects who have enrolled in the Clinical

Core and answered affirmatively to questions regarding difficulty swallowing will be sent a letter, inviting them to learn more and potentially participate in this study by contacting the study team. Subjects sent a letter who do not reply may be called by the study team using the ADRC Script to inquire whether they are interested in participating in the study. If interested, a consent form will be mailed/emailed to the participants for review, and the consent process will occur in person at the visit prior to the swallow study.

4.3.2.4 *Method #4:* We will *share approved recruitment flyers in the community* (e.g. at community outreach events) Interested individuals who either contact the study coordinator listed on the flyer or share their contact information with the study team at outreach events will be asked questions using the phone screening script. If the patient has interest in the study, a consent form will be mailed/emailed to the participant for review, and the consent process will occur in person at the first visit prior to conducting any research procedures.

4.3.2.5 Method #5: In collaboration *with the attending physicians in the UW geriatrics clinics*, a clinical research coordinator from the study team will be present in the UW geriatrics clinics up to 1-2 times per week. If a geriatrician on the study team identifies a potential participant in clinic based on review of eligibility criteria and referral for a swallowing evaluation based on concern for dysphagia, they will confirm with the patient-caregiver dyad that it is acceptable for a member of the study team to meet with them during the clinic visit to provide more information about the study. If the patient-caregiver dyad is agreeable, the clinical research coordinator present in the clinic will meet with the dyad to discuss the study further, answer questions, and provide copies of the consent form for their review. The full consent process will occur in person at the visit prior to the swallow study. Only geriatricians who are study team members will be making eligibility determinations for this population.

4.3.3 Recruitment methods will be the same for potential participants who residue in long-term care facilities as for individuals living independently or in assisted living facilities.

4.4 Potential Future Research Opportunities

4.4.1 Participants in this study may be eligible for other research opportunities within the Swallowing and Salivary Bioscience Lab or with SSBL collaborators studying people living with dementia and their care partners. For participants who have completed the research study, the SSBL will send study flyers for additional research opportunities they may be eligible for via mail.

4.5 Consent

4.5.1 Capacity to consent is presumed to exist unless there is evidence to the contrary. The research coordinator will review the medical chart for information to determine whether or not there has been a determination that a participant does

not have the capacity to consent. In situations where there is no note in the medical record but the research coordinator feels it is not clear that the patient is able to consent, they will follow the process in 5.3.3. For patients with clinical determination of **capacity to consent**:

4.5.1.1 The research coordinator will explain the study and obtain verbal informed consent from the patient and caregiver if contacted via telephone and follow up with signed informed consent from the patient and caregiver during the in person visit prior to the swallow study.

4.5.2 For patients recruited through the ADRC, they have already collected information about who the participant's LAR is and we will obtain this information from the ADRC. If the ADRC does not have this information, we will follow the priority order: research POA if one exists, court-appointed guardian, healthcare POA, or next of kin (defined in the following order: the spouse or registered domestic partner, adult child, parent, adult sibling, grandparent, adult grandchild, or a close friend of the potential participant).

4.5.3 The research coordinator will review the medical chart to determine whether a participant has the capacity to consent and consult a clinician on the research team or Swallow Service if a capacity assessment is needed. For patients who have a clinical determination they **lack capacity to consent**:

4.5.3.1 The research coordinator will explain the study, obtain verbal informed consent from the participant’s LAR.

4.5.3.2 The research coordinator will explain the study and obtain verbal assent from the patient. The research team will go over the study and the participant’s involvement using the assent document. The patient must show willingness to participate and sign the assent document to be enrolled in the study.

4.5.3.3 The research coordinator will answer any questions from the caregiver.

4.5.3.4 The research coordinator will contact the legal authorized representative separately (if differs from caregiver) and will explain the study, obtain verbal informed consent and written HIPAA authorization on behalf of the patient. If the caregiver and legal authorized representative are one in the same, the research coordinator will obtain verbal informed consent and written HIPAA authorization after screening for eligibility.

- For any subjects who are lacking consent capacity, surrogate consent may be obtained from: a Research power of attorney, Court-appointed guardian, or Power of attorney for healthcare

4.5.3.5 If the potential participant has no research power of attorney, guardian, or healthcare power of attorney, then next of kin may consent on the person’s behalf, in the following order: spouse/registered domestic partner; adult child, parent, adult sibling, grandparent, adult grandchild, or close friend.

4.5.4 Consent process

4.5.4.1 The consent process will occur in a private room. In the instances in which either the caregiver and/or LAR are not present, the research coordinator will be contacting them via telephone to obtain oral consent. These phone calls will be made from a secure clinical environment. Oral consent will be obtained by the following method:

- The study team will contact caregivers/LAR and provide a basic introduction to the study. The study team will then obtain permission from those contacted to email or fax the consent form for their review. After the recipients have received the forms, the study team member will provide a basic summary of the main sections of the form with caregivers/LARs and the recipients will have the opportunity ask questions.
- To obtain caregiver/LAR permission to email the consent form, the following script will be read to these individuals: “Email is generally not a secure way to communicate sensitive or health related information as there are many ways for unauthorized users to access email. You should avoid sending sensitive, detailed personal information by email. Email should also not be used to convey information of an urgent nature. If you need to talk to someone immediately or would prefer not to receive study communication by email, please contact the Study Coordinator at 608-262-9995.”
- The caregiver/LAR permission to email these forms will be documented in research records, and the email with the attached consent form would also include the preceding, quoted paragraph.

Note: Study staff will monitor changes in the patients' capacity to provide consent after the initial contact with the patient-caregiver dyads. Clinicians on the Swallow Service or trained research staff will see the patient for their videofluoroscopic swallow study at the 8 week time point and the study team will re-assess capacity at that time. If it is determined that the patient has regained the capacity to consent, we will complete the consent process with the patient for continued participation in the study.

Note: If the research team observes that the patient-subject appears unduly distressed during any study visits or telephone visits, the research team will pause all procedures. We will reaffirm assent prior to continuation of study procedures. If assent cannot be obtained, study procedures will not be continued and the subject will be withdrawn. Any data collected prior to withdrawal will be used, however, no further data will be collected after a patient has indicated they would like to withdraw or there are indications that patient should be withdrawn.

Note: Caregivers of veteran participants who have enrolled through the VA-specific version of this protocol will be consented as above using the caregiver-specific consent forms.

5.3.4.2 Request for Waiver or Alteration of Informed Consent for Sharing De-identified Data: The study team is requesting a waiver of informed consent

for sharing of de-identified videofluoroscopic swallow study images and Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) swallow study rating data with outside entities for use in training of lab members or other research projects not related to the current study. The study team will enter into a Data Use Agreement with outside entities prior to the sharing of fully de-identified fluoroscopy images and DIGEST ratings. Several entities will ensure that no PHI is contained within these images or ratings, and no one at the outside entity will have access to any key linking these images or ratings back to study participants. Also, the results of any research projects will not be utilized for the current study, and all data will be destroyed by outside entities following completion of the project.

The study team believes that this waiver for data sharing will not adversely affect the rights and welfare of the subjects, as no PHI or identifiable information will be contained within the images, DIGEST rating data, or files being shared. Additionally, this data sharing will be of minimal risk to participants, as they will not have to complete any additional research procedures and none of their identifiable information is attached to the images. This data sharing could not be practicably carried out without the waiver of informed consent, as it would be very difficult for the study team to re-consent all previously consented participants in person due to a number of reasons, including but not limited to time and travel burden for participants and their care partners, changes in capacity to consent following their off-study date, and participants who have expired since completion of study participation. Study subjects will not be able to be informed of any additional information or results that come from the project the data is being shared for, as all images and shared rating data will be de-identified and no results or data will be sent back to the study team for dissemination.

4.6 Screening and Enrollment

4.6.1 Screening measures for the **patient participant** include:

4.6.1.1 A videofluoroscopic swallow study (VFSS) evaluation

- For patients who have been referred to the UWHC Swallow Service for a VFSS, this will be performed as standard of care (SOC) and a copy will be recorded for research.
- For patients who do not have a referral, this will be performed as a research procedure and research orders will be placed by the study team. Research study staff performing research swallow studies will be Speech-Language Pathologists who maintain an active American Speech Language Hearing Association (ASHA) Certificate of Clinical Competence and are licensed to practice Speech Language Pathology in the state of Wisconsin. These research staff will have the same level of credentialing and licensure as clinical staff and will complete studies with oversight from a Radiologic Technologist at UW Health.
- For this study, the VFSS bolus administration protocol is standardized for research to allow for thorough assessment and ensure consistency in data collection for this study. The VFSS is also recorded at 30 frames per second for research. See the Drugs and Devices section for additional information.

4.6.1.2 The patient portion of the Clinical Dementia Rating scale.

4.6.2 Screening measures for the **caregiver participant** include:
4.6.2.1 A question regarding caregiver involvement in patient's care.
4.6.2.2 The caregiver portion of the Clinical Dementia Rating scale

4.6.3 **Screen Failure:** Any dyads who do not complete the screening procedures or meet eligibility criteria after the screening measures have been performed.

4.6.4 **Enrollment:** Patients who are consented and remain eligible after the screening procedures have been completed will be enrolled in the study based on the results of their videofluoroscopic swallow study.

4.6.4.1 Dysphagic Group (RCT Portion): If the patient meets the following criteria they will be enrolled in the Dysphagic Group and proceed to the randomization step.

Dysphagic Group Criteria: meets either criterion below:

- Penetration-Aspiration scale score of ≥ 3
- MBSimP® score of ≥ 2 on the pharyngeal residue component (component 16)

4.6.4.2 Non-dysphagic Group: If the patient does not meet criteria on the videofluoroscopic swallow study for dysphagia, the patient will still undergo baseline testing and will complete follow-up questionnaires as part of the Non-Dysphagic group.

4.7 Randomization

4.7.1 For subjects who are enrolled in the **Dysphagic Group (RCT portion)**, the research coordinator will complete the randomization module in REDCap.
4.7.1.1 The statistical team has developed a 1:1 randomization stratifying by dementia severity to determine group assignment (usual care vs. one of three intervention groups) in a REDCap module for the study team.

4.8 Dual-Enrollment into K76 and 2023-0189

4.8.1 For participants who are dually enrolled in the K76 study 2023-0189 who have completed any of the below listed measures within the last 6 months, their results may be collected retrospectively from the 2023-0189 study visit. In the case that a dual-enrollment participant completes the 2018-0835 visit prior to their first K76 visit but remains within the 6-month timeframe, results from the below listed measure will be shared with the 2023-0189 study. This is to reduce burden for dual-enrollment participants, as they can complete the measures once and the results can be used for both K76 and 2023-0189 instead of completing the same measures twice in a short timeframe. Individuals who are listed as study team members on both the K76 study and 2023-0189 will be responsible for confirming dual enrollment to determine which procedures need to be completed and to assist with the transfer of data from one study database to other as needed

4.9 Baseline Assessment

4.9.1 Upon enrollment, the research coordinator will review the study schedule with participating patient-caregiver dyads and schedule study visits. All enrolled dyads will be asked to complete measures of demographic data, swallowing history, previous swallowing interventions, comorbidities (using the Charlson comorbidity score approach)[25], and medication use.

- *Montreal Cognitive Assessment* (MoCA), a cognitive screening tool used in the identification of mild cognitive impairment and dementia, will be administered by the research coordinator.
- *Toronto Bedside Swallow Screening Test (TOR-BSST)*: We will administer the TOR-BSST, a validated tool for screening for the presence of dysphagia clinically. This tool includes a judgment of voice quality, tongue movement, and signs of aspiration during a water swallow test (10 one teaspoon swallows followed by cup drinking).
- *Brief Oral Health Status Examination: oral health status assessment*
- *Caregiver questionnaires:* Caregiver participants will be asked to fill out a demographic questionnaire, Caregiver Activity Survey (CAS), CARES Questionnaire, and the Zarit Caregiver Burden Scale.
- *Patient questionnaires:* Patient participants will be asked to fill out several questionnaires, including the Eating Assessment Tool (EAT-10), the Swallowing Quality of Life questionnaire (Swal-QOL), a dietary intake form that will yield a Functional Oral Intake Scale (FOIS) score, the Xerostomia Inventory (XI), and the Xerostomia-Related Quality of Life questionnaire (XeQoLs).
    - The dietary intake form (Dietary History Questionnaire) will be audio recorded and transcribed. Participants will be instructed not to share identifying information during the recording.
- *Salivary Measures*
    - *Whole saliva production rates* (sialometry) will be measured under unstimulated and stimulated saliva collection conditions.
    - *Residual mucosal saliva* (RMS, which correlates with hyposalivation and dryness perception) will be collected from the anterior hard palate (AHP), anterior tongue (AT), and lower labial (LL) surfaces using SialoPaper strips (Oraflow Inc., Smithtown, NY, USA). These strips will be applied for 10 seconds and measured using Periotron device (Oraflow Inc.).[24]
- *Maximum Expiratory Pressures (MEPs):* Digital manometers will measure MEPs (cm H2O) as a measure of expiratory force generation in all patients enrolled. The MEP will be calculated as the average of three trials within 10% variance. This will take approximately three minutes total.
- *Voluntary Cough:* Peak airflow during voluntary cough (PCF) will be measured using a peak airflow meter (Mini Wright Peak Flow Meter). PCF will be calculated as the average of three trials within 10% variance. This will take approximately three minutes total.
- *Maximum Lingual Pressures:* Participants will have maximum lingual pressures measured using an Iowa Oral Performance Instrument (IOPI). This will take approximately 8-10 minutes total.

4.9.2 For those patient-caregiver dyads in the RCT portion of the study, the research coordinator will then schedule follow-up calls with the patient and caregiver.

4.10 Intervention Period (RCT portion only)

4.10.1 For patients in the ***usual care group*:**

4.10.1.1 Follow-up phone call or WebEx assessments will take place 7 days, 14 days, 28 days, 42 days, 90 days, and 180 days following baseline visit.

4.10.1.2 These assessments will include:

- Questions regarding dietary intake and dysphagic symptoms
- Questions regarding any rehospitalizations and emergency department visits since discharge. This will include dates and reasons for any rehospitalizations/ED visits and a request to pull related hospital records
- Questions regarding the use of other recommended treatments for swallowing
- Date of death, if applicable.

4.10.2 For patients in one of the ***three experimental treatment groups*:**

4.10.2.1 Interventions with Saliva Substitute: During the baseline assessment or as a follow-up clinic visit, those patients randomized to the saliva substitute intervention or lingual strengthening plus saliva substitute intervention will be provided with a commercially available gel-based saliva substitute, Biotene® Oral Balance Gel. Patients will be instructed to apply an amount equivalent to about 1 cm of gel with a finger to the tongue and most intensely affected areas of the oral cavity three times a day for 8 weeks. The research coordinator will provide patient and caregiver with a log to track application of the saliva substitute and any barriers to its use.

4.10.2.2 Interventions with Lingual Strengthening: Following the baseline assessment or as a follow-up clinic visit, those patients randomized to the lingual strengthening intervention or lingual strengthening plus saliva substitute intervention will receive training in lingual strengthening with the Iowa Oral Performance Instrument (IOPI). Patients will be instructed to follow a progressive strengthening exercise regimen for 8 weeks. The research coordinator will provide patient and caregiver with a log to track performance of the lingual strengthening exercises and any barriers to performing them.

4.10.2.3 Follow-up phone call or WebEx assessments will take place at 7 days, 14 days, 28 days, and 42 days following randomization:

The **7 day follow-up** assessment will include:

- **Lingual Strengthening Intervention Groups Only:**
  - Adjustment from 60 to 80% of maximum lingual pressures.
  - Redetermination of maximum lingual pressures.
- **All Groups, Including Lingual Strengthening Groups:**
  - Questions regarding dietary intake and dysphagic symptoms

- Questions regarding any rehospitalizations and emergency department visits since discharge. This will include dates and reasons for any rehospitalizations/ED visits and a request to pull related hospital records.
- Date of death if applicable

The **14 day, 28 day, and 42 day** follow-up assessments will include:

- **Lingual Strengthening Intervention Groups Only:**
  - Redetermination of maximum lingual pressures.
- **All Groups, Including Lingual Strengthening Groups:**
  - Questions regarding dietary intake and dysphagic symptoms
  - Questions regarding any rehospitalizations and emergency department visits since discharge. This will include dates and reasons for any rehospitalizations/ED visits and a request to pull related hospital records.
  - Date of death if applicable

4.11 Follow Up Assessment (RCT Portion only)

4.11.1 Participants in the RCT portion of the study will complete the follow up research study visit at the same time as, or within a week of, their follow up videofluoroscopic swallow study (approximately 8 weeks following their dysphagia diagnosis).

- *Swallow Study:* Participants will undergo a videofluoroscopic swallow evaluation.
  - For patients originally referred to the UWHC Swallow Service for a VFSS (baseline of this study), this will be performed as standard of care (SOC) and a copy will be recorded for research.
  - For patients who did not have a referral, this will be performed as a research procedure and research orders will be placed by the study team.
  - For this study, the VFSS bolus administration protocol is standardized for research to allow for thorough assessment and ensure consistency in data collection for this study. The VFSS is also recorded at 30 frames per second for research. See the Drugs and Devices section for additional information.
- *Caregiver questionnaires:* Caregiver participants will be asked to fill out a demographic questionnaire, Caregiver Activity Survey (CAS), CARES Questionnaire and the Zarit Caregiver Burden Scale.
- *Patient questionnaires:* Patient participants will be asked to fill out the same questionnaires as at the baseline visit, including the Eating Assessment Tool (EAT-10), the Swallowing Quality of Life questionnaire (Swal-QOL), the dietary intake form for a Functional Oral Intake Scale (FOIS) score, the Xerostomia Inventory (XI), and the Xerostomia-Related Quality of Life questionnaire (XeQoLs).
- *Brief Oral Health Status Examination*: oral health status assessment
- *Salivary Measures and maximum lingual pressure* measurements (same as baseline).

4.11.2 The research coordinator will collect the logs for tracking performance of lingual strengthening exercises and/or use of saliva substitute.

4.12 90-Day Follow Up (RCT Portion only)

4.12.1 A medical record review at 90 days post-enrollment will be completed for participants enrolled in the RCT portion of the study by the research coordinator.

4.12.1.1 The following data will be collected: Patient medical record number, Index hospitalization admission/discharge dates, discharge diagnosis, Rehospitalization dates, diagnosis data and discharge summaries, Emergency room visit dates, diagnosis data and discharge summaries, Patient comorbidities, Presence of acetyl cholinesterase inhibitors and psychotropic medications, Presence of xerostomia-inducing medications, Date of death if applicable.

4.12.1.2 The study coordinator will also call the patient to ask about any rehospitalizations or incidences of pneumonia.

4.13 180-Day Follow Up

4.13.1 At 180 days post-enrollment, all enrolled patient-caregiver dyads will be asked to complete the same patient and caregiver questionnaires as at the baseline visit. These forms will be mailed to all enrolled participants and returned to the research coordinator via mail. The research coordinator will also complete a medical record review at 180 days for all enrolled patients to collect the same data as outlined above for the 90 day follow-up. The study coordinator will also call the patient to ask about any rehospitalizations or incidences of pneumonia.

4.13.2 If dyads do not return the 180 day post-enrollment forms within two weeks of receiving them, a member of the study team will contact the patient via telephone three times over the course of 30 days, and will document each attempt in a communication log. If there is no response following the 30 days and 3 attempts to contact the dyad, they will be marked as “off-study” and will not receive further communication from the study team regarding their 180 day forms.

4.14 Compensation

4.14.1 Each patient-caregiver dyad will be reimbursed $50 each for the baseline assessment.

4.14.2 Patient-caregiver dyads enrolled in the RCT portion of the study will also be reimbursed $50 each for the 8 week assessment and $5 for each follow-up phone call and the 180 day questionnaires (a possible total of $125 each for full participation).

4.14.3 Patient-caregiver dyads without dysphagia will also receive an additional $5 reimbursement for the follow-up phone call and forms at 180 days post-enrollment (a possible $55 each for full participation).

4.15 Study Schedule

	Screening	Baseline Assessment (Day 0)	Follow Up Calls (Day 7, 14, 28, 42)	Follow Up Visit (Day 56-70)	Follow Up Call (Day 90)	Follow Up Call/Mail (Day 180)
			RCT Portion			
Informed Consent	X					
Clinical Dementia Rating (CDR)	X					
Videofluoroscopic Swallow Study	X			X		
Eligibility Determination	X					
Randomization		X				
Demographics, Medical History, Smoking History		X				
Charlson Comorbidity Form		X				
Montreal Cognitive Assessment (MoCA)		X				
Toronto Bedside Swallowing Screening Test (TOR-BSST)		X				
Brief Oral Health Status Exam (BOHSE)		X		X		
Caregiver Questionnaires • Caregiver Activity Survey (CAS) • Zarit Caregiver Burden Scale		X or Mail		X or Mail		Mail
Patient Questionnaires • Eating Assessment Test (EAT-10) • Swallowing QoL (Swal-QoL) • Dietary History (FOIS) • Xerostomia Inventory (XI) • Xerostomia Quality of Life (XeQoL)		X or Mail		X or Mail		Mail
Oral & Salivary Measures • Saliva Production Rates • Residual Mucosal Saliva		X		X		
Swallow Measurements • Maximum Expiratory Pressures • Maximum Lingual Pressures • Lingual Endurance • Voluntary Cough Measurements		X		X		
Collect Intervention-specific Tracking Logs				X		
Telephone Follow-up			Call or WebEx		Call	Call
Medical Record Review Form • Rehospitalizations and Pneumonia Diagnoses			EHR	EHR	EHR	EHR

6.0 REGISTRATION PROCEDURES

Subject registration information will be entered into the OnCore and REDCap databases by the research coordinator.

7.0 TREATMENT/INTERVENTION PLAN

7.1 Participants with dysphagia will be randomly assigned to one of four groups: 1) usual care only; 2) the saliva substitute intervention plus usual care; 3) the lingual strengthening intervention plus usual care; or 4) the saliva substitute plus lingual strengthening intervention plus usual care.

7.2 Saliva substitute intervention. Each patient-caregiver dyad will be provided with a commercially available gel-based saliva substitute, Biotene® Oral Balance Gel. Patients will be instructed to apply an amount equivalent to about 1 cm of gel with a finger to the tongue and most intensely affected areas of the oral cavity three times a day for 8 weeks.

7.3 Lingual strengthening intervention. Isometric tongue strengthening will be completed using the Iowa Oral Performance Instrument (IOPI; Figure 4) during an 8-week program. This device hand-held instrument provides numeric readout of pressure (hPa) and digital feedback of performance. Anterior and posterior tongue isometric exercises consist of pressing the tongue against a pressure bulb, with each subject given a target pressure value to aim for as determined by the baseline one repetition maximum (1RM). These baseline 1RM lingual pressures are obtained by having the patient press against the IOPI bulb at an anterior and a posterior location along the hard palate. The patient will perform three trials per day on three days per week with the IOPI bulb at each location, with 10-15 seconds of rest between each trial. Each trial consists of 10 tongue press repetitions at the anterior location and 10 repetitions at the posterior location. During week one of the regimen, the target value of each repetition will be 60% of the 1RM. For the remaining seven weeks, the target value will be increased to 80% of the 1RM. At weeks three, five, and seven, the baseline will be re-measured by phone and the 80% target value re-calculated. The final assessment point will be after completion of lingual strengthening.[33,34] The 8 week time frame for this therapy approach is consistent with previous studies[33,35] and our preliminary data.[34]

FIGURE 4: IOPI



7.4 Saliva substitute plus lingual strengthening intervention. Each patient will perform lingual strengthening exercises with the IOPI as described above. Each patient will also be provided with the Biotene® Oral Balance Gel to apply to the oral cavity three times per day.

7.5 Usual Care. Usual care group patients will receive standard swallowing interventions identified by the Speech-Language Pathologist as appropriate to treat the patient's dysphagia and common in clinical practice. Such treatment would likely consist of dietary (e.g., thickened liquids or pureed foods) or postural compensatory strategies (e.g., chin down posture while swallowing). No progressive lingual strengthening approaches or regimented salivary substitute protocols are utilized for this patient population in routine clinical care provided through the UWHC Swallow Service.

7.6 Adverse Event Reporting Requirements. Adverse events will be monitored during the RCT intervention at each Follow Up Call with study participants (see Study Schedule). Any adverse events will be discussed at weekly research team meetings and will be reviewed by a Data Safety and Monitoring Board.

7.7 Duration of Intervention. The intervention duration is 8 weeks (56 days) following enrollment. The research coordinator will monitor intervention effects through 180 days.

8.0 MEASUREMENT OF FEASIBILITY

8.1 Recruitment and Retention Rates. From the total number of eligible patient-caregiver dyads identified, we will record the number who are approached and participate, decline participation, and enroll but withdraw.

8.2 Adherence to Protocol. The lingual strengthening device automatically records each treatment session and whether the target pressures were attained. In addition to these data, each patient-caregiver dyad will be asked to log lingual strengthening and saliva substitute applications, and barriers/adverse events to these interventions.

9.0 MEASUREMENT OF INTERVENTION EFFECT

9.1 Improvement in swallow function

Videofluoroscopic (VFSS) assessment and analysis. Videofluoroscopic swallow studies will be completed for all study participants, coinciding with the baseline study visit as scheduling allows, or within 1 week of the baseline visit. Patients who are diagnosed with dysphagia will have follow up videofluoroscopic swallow studies, the timing of which will coincide with the follow up visit, or within 1 week of the visit, for this study for patients who enrolled in the RCT portion of the study.

The TIMS DICOM Swallowing Workstation will be used to capture full resolution fluoroscopic images in real time (30 frames per second) of the swallow study. This video is a copy of the study that is performed and placed in the medical record.

During the videofluoroscopic swallow study, patients swallow the following types of barium (contrast agent) boluses: thin liquid via teaspoon (total of 15mL), thin liquid via cup (total of 140mL) mildly-thick liquid via teaspoon (5mL), mildly-thick liquid via cup (60mL)moderately-thick liquid via teaspoon (5mL) semi-solid bolus (10mL), and a cracker or cookie coated with barium (6mL). Participants also swallow a mildly-thick liquid bolus via teaspoon (5mL) and a semi-solid bolus via teaspoon (5mL) in the anterior-posterior view. This typically results in a total of 18 swallows, dependent upon clinician discretion in cases where aspiration has occurred. This research-specific VFSS protocol is consistent with standard practice at the UW facilities. This assessment will take about 10 minutes. See the Drugs and Devices section for additional information.

The videofluoroscopic images will be transferred from the TIMS system to Dr. Rogus-Pulia's Department of Medicine storage drive. Raters in Dr. Rogus-Pulia's laboratory blinded to

participant information will obtain measures of bolus flow kinematics-direction (Penetration/Aspiration Scale scores) and completeness (Normalized Residue Ratio Scale (NRRS) scores) from fluoroscopic recordings for each participant. Modified Barium Swallow Impairment Profile (MBSimP®) component scores (13 components) and total scores will be derived from images. Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) scores will be derived from Penetration/Aspiration Scale scores and 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 to assess inter and intra-judge reliability for all variables. Bolus flow durational measurements (oral transit time, stage transit duration, pharyngeal transit time, total swallow duration) will quantify timing of structural movement and bolus flow.

9.2 Reduction in patient-reported symptoms of dysphagia and mouth dryness

Each patient will be asked to complete questionnaires regarding swallowing difficulties (EAT-10) and mouth dryness (Xerostomia Inventory and Xerostomia Quality of Life Scale) . These questionnaires will be administered during the baseline assessment, the 8 week follow-up for patients in the intervention trial, and 6 months post-enrollment for all patients.

9.3 Improvement in dietary intake

Each participant will complete a questionnaire detailing his/her quantity and variety of nutritional intake. From these responses, a Functional Oral Intake Scale[40] (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. This questionnaire will be administered during the baseline assessment, the 8 week follow-up for patients in the intervention trial, and 6 months post-enrollment for all patients. At the baseline and 8-week visits, the questionnaire will be audio-recorded and the results transcribed to capture additional detail not quantifiable on the data collection form.

9.4 Improvement in swallowing-related quality of life

Each participant will complete the Swal-QOL[21], 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 someone other than the patient's treating clinician will administer the Swal-QOL. This questionnaire will take 10-15 minutes to complete. 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. This questionnaire will be administered during the baseline assessment, the 8 week follow-up for patients in the intervention trial, and 6 months post-enrollment for all patients.

9.5 Increased tongue pressure production

Lingual strength will be measured against a pressure transducer on the hard palate at the front and back tongue locations. After a brief training, patients will be asked to perform three tongue presses for each condition of interest (maximum isometric press, maximum endurance press, saliva swallow, water swallow). If the first three tongue presses for the maximum isometric measurement are greater than 5% variable, the participant will be asked

to perform additional presses until three presses are identified that are 5% or less variable. From these, 1-repetition maximum values will be used to calculate the following measures of interest: 1) maximum isometric lingual strength (MILS), 2) maximum endurance, 3) mean lingual pressure during swallowing (saliva and water), and 4) lingual functional reserve. Published benchmarks of MILS are available for historical comparison of our findings to data from 1,729 patients in 38 series comprising healthy and disordered samples (summarized recently in a systematic review)[41]. Endurance measures will be taken by having the study participant maintain 50% of their highest maximum lingual pressure for as long as possible. Mean swallowing pressures will be sampled from saliva and water swallow tasks, both of which demonstrate validity in computation of functional lingual reserve[42]. Functional reserve will be measured per published guidelines as the difference between maximum isometric pressure and mean swallowing pressure, normalized by transformation to a proportion of the individual's MILS[42]. These measurements will be taken at baseline for all patients and after 8 weeks for those with dysphagia in the intervention trial.

9.6 Improvement in saliva production

Saliva samples will be collected from all patients at the baseline assessment and after 8 weeks for those patients with dysphagia enrolled in the intervention trial. We will attempt to schedule study visits between the hours of 12pm and 2pm when saliva production is at its peak for the day. Patients will be asked to refrain for 30 minutes from smoking, eating, drinking, or using oral hygiene products. 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 80 beats per minute set with a metronome. Salivary flow rate will be determined by recording the volume of saliva produced in 5 minutes under each condition. Samples will be aliquoted into separate tubes (per collection condition) and placed immediately on ice. Aliquots will be transported to Dr. Pulia's wet lab on the 2nd floor of the VA hospital.

Salivary compositional analyses will focus on aspects previously found to relate to oral health and swallowing function. Descriptive, rheological, and pH analyses of the samples will be completed immediately following the visit to characterize the acidity, fluid flow properties, and descriptive features of saliva. Extensional viscosity will be determined using an extensional rheometer (Thermo-Fisher CaBER). Each measure of viscosity will be recorded three times per sample. Salivary pH will be measured using a digital pH meter. Following viscosity measurement, the remaining sample will be aliquoted into smaller tubes and frozen at -80°C. Once all samples are collected, an enzyme-linked immunosorbent assay (ELISA) will be used to quantify protein. Substance P, amylase, and mucin concentrations will be analyzed using Substance P (Enzo Life Sciences), amylase (Salimetrics), and mucin MUC5B (LSBio) ELISA assay kits.

9.7 Oral Microbiome Analysis

Sequence data will be analyzed by first removing all short length or poor quality sequences using the program mothur. Chimeras will then be removed and all remaining sequences clustered into groups that differ by at most 97% sequence similarity. Sequence classification will be determined using the Greengenes and SILVA taxonomic databases. This corresponds to the accepted level for resolving sequence identity at the species level

(operational taxonomic units, OTUs). The composition and structure of the oral microbiota will then be determined via 16S rRNA gene analysis. Comparisons between samples will be performed using a Bray-Curtis dissimilarity analysis, which quantifies the compositional dissimilarity between microbial communities in terms of both total diversity and phylogenetic distance, allowing for visualization as a principal component analysis (PCA). A downstream correlation analysis will be performed on total community structure (Bray-Curtis dissimilarity and relative abundance) and composition using analysis of similarity (ANOSIM) in R. These analyses will be performed separately for each sample type (buccal mucosa, tongue dorsum, and saliva). Taken together, these analyses will illustrate differences in the oral microbiota of older patients with dysphagia receiving probiotic treatment. We will be able to determine which specific OTUs are found to contribute significantly to the overall differences in oral microbiota composition across the three study points.

9.8 Decrease in re-hospitalization and incidence of pneumonia

A detailed review of medical records associated with any rehospitalizations will be completed at 90 and 180 days. The presence of any rehospitalization will be assessed in a phone call directly to the patient and caregivers during the RCT portion for subjects in the Dysphagic group and for all enrolled subjects at 90 and 180 days if found during chart review. During follow-up phone calls, patients/caregivers will be asked, “Since your hospital discharge on <date>, have you been readmitted to any hospital?” Since over 75% of UWHC patients are rehospitalized back to UWHC, the detailed UWHC medical record review will help ensure that we account for a majority of non-reported rehospitalizations. This combined patient interview/medical record approach for determining the presence of rehospitalizations is currently the standard in investigator-initiated, prospective transitional care research.[43,44] The frequency of any rehospitalization at 7, 14, 28, 42, 90, and 180 days, and average time to first rehospitalization, will be reported for the dysphagic group (as well as usual care versus intervention groups), overall and stratified by dementia severity. Similar combined methods of asking patients/caregivers about pneumonia diagnoses and reviewing medical records at the 7, 14, 28, 42, 90, and 180 day time points will be used to tally occurrences of pneumonia (community, hospital-acquired, and aspiration pneumonia) for each patient. These follow-up assessments will take place for the non-dysphagic group at 90 and 180 day post-enrollment.

9.9 Decrease caregiver stress

To measure caregiver stress at baseline for all patients, 8 week assessments for the dysphagic group, and 6 months post-enrollment for all patients, we use the 22-item Zarit Caregiver Burden Scale[45,46] and the 6-item CAS,[47,48] both currently standards for caregiver stress measurement in dementia research.[49-51] The Zarit Caregiver Burden Scale is used as a measure of caregiver psychological stress and the CAS is used as a measure of time spent caregiving – both critical to a caregiver’s overall stress/burden. For each item on the Zarit Caregiver Burden Scale[45,46] (e.g., “Do you feel you have lost control of your life since your relative’s illness?”), caregivers report the extent of agreement on a scale ranging from 0 (never) to 4 (always). The last item is “Overall, how burdened do you feel in caring for your relative?” with a response format from 0 (not at all) to 4 (extremely). Responses are summed to produce a total score ranging from 0 to 88, with high scores indicating greater burden.

The Zarit Caregiver Burden Scale is valid when measuring changes in caregiver stress over time.[51] The CAS assesses the amount of time a caregiver spends each day in caregiving tasks, by asking caregivers to report on 'typical' days prior to the assessment.[47,48] For the baseline assessment in this study, we will ask caregivers to reflect back to a 'typical' day sometime during the week prior to the hospitalization. For the 8 week and 6 month assessments, caregivers will be asked to think about a 'typical' day during the week prior. Responses are summed to produce a total score, with high scores indicating greater burden. CAS is also valid in measuring changes in caregiver stress over time.[48] Total mean Zarit Caregiver Burden Scale and CAS scores will be calculated and stratified by dementia severity.

Data from the CARES questionnaire will be deidentified and shared with a collaborator to be validated against data from the the Zarit Caregiver Burden Scale. No identifying information will be shared and these data will be transferred using a secure service provided by DOM IT (ZendTo). Once the validation is complete the deidentified data will be destroyed by the recipient.

9.10 Covariates

9.10.1 *Age, Gender, Race, Income, and Education.* Age, gender, race, income and education will be collected from the demographics form.

9.10.2 *Comorbidities.* Comorbidities will be collected using the Charlson comorbidity score approach from the medical records.

9.10.3 *Dementia Severity.* Dementia severity will be determined using the Alzheimer's Disease Cooperative Study-Clinical Dementia Rating Scale. ADCS-CDR scores will be summarized with a Total Score and the Sum of Boxes. There will be 3 strata: very mild (Total CDR = 0.5), mild (Total CDR = 1) and moderate (Total CDR = 2).

9.10.4 *Neuroleptic medications.* Presence of neuroleptic medications at baseline will be collected from the baseline screening forms.

9.11 Descriptive measures

9.11.1 *Demographic Form.* Self-report items address age, gender, race/ethnicity, income, and education.

9.11.2 *Medical Record Review Form.* This form will collect data regarding rehospitalization dates, diagnosis data and discharge summaries. It will also collect patient comorbidities and date of death, if applicable.

10.0 STUDY PARAMETERS

(See Study Schedule)

11.0 DRUGS & DEVICES

11.1 Iowa Oral Performance Instrument

The Iowa Oral Performance Instrument (IOPI) is a hand-held instrument that provides biofeedback (a numerical readout of lingual pressures) for participants when completing oral motor exercises. Patients press down on a small bulb (which is attached to the bottom of the device) with their tongue to perform these exercises. This device is FDA approved and the study specific use of the IOPI is consistent with the FDA approved indication.

Participants randomly assigned to and arm including lingual strengthening will be provided with IOPI instrument and replacement IOPI bulbs. IOPI instruments and bulbs will be stored in the Swallowing Lab research office in the GRECC and only approved research staff and/or SLP clinicians will provide devices to research participants. The patient may experience some tongue or jaw soreness as result of the exercises. Adjustment in target pressure value will be made as needed to decrease discomfort.

11.2 Biotene Oral Gel

Biotene Oral Balance Gel is an FDA-approved product used to relieve symptoms of oral dryness and also sooth oral irritation. This device will be used according to its FDA approved indications. The IRB has determined that the use of Biotene in this protocol is being assessed for treatment purposes and involves an FDA-regulated investigational use. The IRB determined that an IDE was not required from the FDA since the device as used in this study involved non-significant risk (NSR), as the device does not present a potential for serious risk to the health, safety or welfare of participants.

Participants will be instructed to spread approximately one centimeter of gel 3x/day for 8 weeks. The gel has minimal risks or side effects. There is a risk of an allergic reaction if the patient is allergic to any of the ingredients. If a research subject is randomly assigned one of the two arms with the saliva substitute, the study team will provide the participant with the Biotene Oral Gel. Dispensation of the Biotene to the participant is tracked by the research coordinator.

11.3 Videofluoroscopy and Barium

For the purposes of this research protocol, the barium bolus administration will follow a specific protocol. The administration protocol is required for research and based on clinical guidelines, and clinical discretion is used while administering boluses to ensure participant safety.

Barium is lawfully marketed in the United States. This research is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for barium. This research is not intended to support a significant change in the advertising for the product. This research does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. This research

is conducted in compliance with the marketing limitations described in 21 CFR 312.7. The IRB determined the use of barium in this research protocol is IND exempt.

For this study, the VFSS procedures are at times occurring for study purpose due to the research-specific bolus administration and frame rate requirements. The VFSS bolus administration protocol is standardized for research to allow for thorough assessment and ensure consistency in data collection for this study. The VFSS is recorded at 30 frames per second for research.

The IRB determined in this case the procedures are consistent with the FDA approvals for the drugs (barium) and devices (fluoroscopy equipment). The use of VFSS swallow study drugs (barium) is IND exempt and the VFS devices are not being evaluated for safety or efficacy.

12.0 STATISTICAL CONSIDERATIONS

13.1 Method of Randomization and Stratification

Participants will be identified by clinical staff and/or Dr. Rogus-Pulia's research coordinator as eligible, screened for capacity to provide consent and, if found to meet criteria for dysphagia on the videofluoroscopic swallow study, will be assigned to receive usual care, lingual strengthening intervention, saliva substitute intervention, or lingual strengthening plus saliva substitute intervention. Randomization will be stratified based on the ADCS-CDR scale. There will be 3 strata: very mild (Total CDR = 0.5), mild (Total CDR = 1) and moderate (Total CDR = 2).

13.2 Statistical Power Calculation for Aims 1 and 2

The Normalized Residue Ratio Scale (NRRS)[37] was chosen as the primary outcome measure given that both interventions are hypothesized to improve amount of bolus clearance (efficiency). Additionally, oropharyngeal residue is associated with increased risk of airway invasion. Patients above a score of 0.09 on the NRRS for the valleculae are at twice the risk of airway invasion.70 A prior study reports a medium effect size of 0.53 for change in NRRS scores (~50% reduction) following a lingual strengthening intervention in post-stroke dysphagic patients.71 With an alpha= .025 experimentwise alpha=.05, Bonferroni-adjusted for the two primary comparisons), a sample size of 60 subjects in total (15 per treatment combination) will provide 80% power to detect a 50% reduction in NRRS scores, based on standard deviation estimates from the same prior study. These sample size calculations are based on a simple two-sample test for change in means and are likely conservative estimates of the true power using our model. We plan to enroll 240 inviduals (120 participants and 120 caregivers enrolled as a dyad) total over 4 years. Based on our preliminary data examining prevalence of comorbid dysphagia and dementia at the University of Wisconsin Hospitals and Clinics (UWHC), approximately 70% of patients who meet criteria for dementia will be found to have dysphagia on the videofluoroscopic swallow study. This will result in a sample of 84 dyads with dementia and dysphagia (21 dyads in each arm of the factorial design; 21 dyads with lingual strengthening and 21 dyads without lingual strengthening; 21 dyads with saliva substitute and 21 dyads without saliva substitute) to allow for expected attrition of 30% from the intervention trial, consistent with prior studies.

Aim 1: To determine the impact of two novel interventions (lingual strengthening and saliva substitute) versus usual care on proximal swallowing outcomes in patients with mild-moderate ADRD.

HA: Patients who receive lingual strengthening plus saliva substitute will experience the greatest decrease in post-swallow oropharyngeal residue as compared to the other groups.

Mixed effects ordinal logistic regression models will be used to determine the effects of the two interventions, saliva substitute and lingual strengthening, on the primary outcome, the Normalized Residue Ratio Scale (NRRS) score. The regression model will include the main effect for visit and the interactions between visit and indicator variables for each of the interventions. The two primary comparisons of interest are the Wald tests for each interaction term. Subjects will be included in the model as a random effect to account for dependence in the repeated measures within the same subject over time. Potential interactions between the two interventions will be evaluated in an exploratory analysis in additional models that expand the primary model to include the relevant interaction term. Similar analyses will be performed for the other outcomes; where appropriate (e.g. lingual strength), linear mixed effects models will be used instead of mixed effect ordinal logistic models. All analyses will be performed on an intention-to-treat, or as-randomized, basis. A nominal two-sided p-value of 0.025 (Bonferroni adjusted for the two primary comparisons) will be regarded as statistically significant. Analyses will be conducted in R[52] using the ordinal package.[53]

Aim 2: To identify subgroups most likely to benefit from treatment by examining associations amongst key mechanistic variables for patients with ADRD in relation to treatment response (including swallowing physiology, saliva, and cognition).

HA: Those patients with mild ADRD, severe swallowing impairment [oropharyngeal residue and airway invasion], and altered salivation [quantity and viscosity] will experience the greatest decrease in oropharyngeal residue and increase in quality of life the following treatment.

Partial least squares (PLS) ordinal logistic regression models will be used to identify combinations of cognition, swallowing biomechanics and salivation variables at baseline that are predictive of Normalized Residue Ratio Scale (NRRS) scores at follow-up. Models will be adjusted for baseline NRRS scores and assigned treatment. PLS regression is a data reduction technique that identifies orthogonal linear combinations of the input variables (cognition, swallowing biomechanics and salivation) that maximize the correlation with the outcome (residue). The optimal number of orthogonal components will be selected based using BIC. Inference (confidence intervals and significance tests) will be performed using the bootstrap. Analyses will be repeated using SWAL-QoL total scores as the outcome. Associations between the identified orthogonal components and secondary outcome variables will be assessed by using the identified variables as additional predictors in mixed effects regression models used for Aim 1. Analyses will be conducted in R using the plsRglm package.[54]

Aim 3: Characterize associations among lingual pressures, saliva production, and dysphagia status on videofluoroscopy in patients with ADRD.

H_A: Patients with dysphagia will have lower lingual pressures and altered salivation (quantity and viscosity) as compared to those without dysphagia on videofluoroscopy.

For primary analysis of Aim 3, we will assess the associations among baseline dysphagia status (MBSimP total scores), maximum expiratory pressures, voluntary cough, salivary function (quantity and quality), and baseline lingual pressures. All participants will be included in this analysis, those with dysphagia on videofluoroscopy at baseline and those without. ROC characteristics will be examined (sensitivity, specificity, AUC) for dysphagia status on saliva characteristics, expiratory measures, and lingual pressures. Exploratory analyses will assess associations among MEPs, voluntary cough, other dysphagia measures (PAS scores), symptom parameters, and rehospitalization and pneumonia rates at 6 months.

Aim 4: Determine the oral microbiota profiles, saliva characteristics, oral health status, and swallowing function in ADRD dementia and test the extent to which swallowing impacts the composition of oral microbiota.

H_A: Those with lower oral microbial diversity and greater salivary alterations will show greater swallowing impairment.

Comparisons between samples will be performed using a Bray-Curtis dissimilarity analysis (60), which quantifies the compositional dissimilarity between microbial communities in terms of total diversity, allowing for visualization as a principal component analysis (PCA). A downstream correlation analysis will be performed on total community structure (Bray-Curtis dissimilarity and relative abundance) and composition using analysis of similarity (ANOSIM) in R (61). These analyses will allow for comparison of oral microbial differences and specific OTUs that contribute to these differences between those with and without dysphagia. An independent samples t-test will be used to compare the Bray-Curtis indices between the groups (dysphagia versus no/minimal dysphagia). To estimate the relationship between the change in oral microbial diversity, salivary components, swallowing function, and oral health, separate mixed effects ordinal logistic regression models will be fit to the data for each measured outcome.

Aim 5: Determine the relationships among oral microbial diversity, saliva characteristics, and incidence of pneumonia.

H_A: Persons with ADRD with less oral microbial diversity and greater salivary alterations will have a higher incidence of.

Partial least squares (PLS) regression models will be used to identify combinations of variables (saliva, oral health, swallowing, oral health) that predict microbial diversity and pneumonia incidence.

Aim 6: Conduct semi-structured interviews with participants to understand barriers and facilitators to the interventions used in the RCT and to following swallowing recommendations provided to those in the usual care arm.

H_A: Relevant themes, facilitators, and barriers regarding utilization of swallowing interventions and swallowing recommendations will be abstracted from interviews through use of directed content analysis.

In collaboration with Qualitative Health Research Consultants (QHRC), the study team will develop a qualitative codebook containing relevant themes, ideas, and emotions found in the transcripts of interviews conducted with participants. Using this codebook, members of the OHRC and the study team will complete open coding in NVIVO of all deidentified transcripts to identify the most valuable themes surrounding swallowing intervention and swallowing recommendations. Following the open coding process, the study team will complete directed content analysis of the coded transcripts to identify relevant themes, facilitators, and barriers to use of the swallowing interventions or swallowing recommendations that are part of the RCT or usual care arms.

14.0 RECORDS TO BE KEPT

14.1 Data Management

14.1.1 Participant registration, appointment tracking, and study-related billing will be managed through the ICTR OnCore database. Additionally, all data will be maintained in REDCap, an electronic data management system application managed by the UW-Madison Department of Medicine.

14.1.2 The PI and study coordinator will be responsible for monitoring data quality.

14.1.3 Data entry will be an ongoing process throughout data collection with records from individual participants added to the study database as they complete the baseline and follow-up assessments.

14.1.4 The statistical team will regularly check data for values that are out of range or logical inconsistencies. All data will be checked by at least one member of the research team after it has been entered to ensure that no erroneous entries have been made and to ascertain that no falsification has occurred.

14.1.5 Reports will be generated and reviewed monthly at research team meetings to show the status of all subjects on study and to bring to light any problems with data completeness and adherence to the protocol.

14.2 Study Records

14.2.1 Data collected from this study will come from questionnaires and from participant's medical records collected during the study.

14.2.2 Questionnaire data will be provided directly to study staff, and medical record data will be abstracted by study staff from the participant's electronic medical record.

14.2.3 The combined HIPAA authorization forms and consent forms (original and copies), questionnaires, and study data will be stored and protected in the locked Swallowing and Salivary Bioscience Laboratory (D5245) in the Geriatric Research Education Clinical Center in the VA Hospital or the Lab space in the

ADRC Mezzanine in UWHC. They will be stored in a locked filing cabinet within the space. Only appropriate members of the research staff will have keys.

14.2.4 Electronic data files will be stored on the REDCap system's secure server which is managed by the UW Department of Medicine. Access is restricted to those that have been granted access by the software administers via a password.

14.2.5 All breaches in data integrity will be reported by the PI to the UW-Madison Health Sciences IRB and to the appropriate NIH branch within 24 hours and immediate action will be taken to correct any problems.

14.3 Confidentiality Protections

14.3.1 Only research staff will have access to individually identifiable private information about human subjects.

14.3.2 For data collection and analysis procedures, all participants will be assigned an identification codes. This numeric code, not a name, will be used to label all electronic collection forms. All data will be coded and entered in a password protected electronic data management system application and only accessible by persons directly involved in the project. A document linking ID codes with names of participants will be kept in a separate file on the electronic data management system. Only the PI and project staff will have access to the relevant linking file. Data will be reported as group data so that no individual could ever be identified.

14.3.3 All members of the research team and study staff will complete HIPAA and research ethics training and have certification thereof. Any member of the research team who knows or has a personal relationship with any participants will recuse himself or herself from further study activity with the identified participants, and will not have access to identifiers that can link those participants with their data.

14.3.4 Additionally, it has been confirmed that a Certificate of Confidentiality (CoC) will apply to this study, and the study will abide by the requirements of the CoC.

14.4 Sharing Data and Specimens with Other Entities

14.4.1 A member of the study team will confirm that the study has proper IRB approval before releasing any specimen information with approved entities.

14.4.2 De-identified videofluoroscopic swallow study images may be shared with other entities for training purposes and student research projects, per a Data Transfer and Use Agreement. These images will not contain any Protected Health Information and all videos will be labeled with a code that includes the an ID number unrelated to the study ID, bolus volume, and bolus type (e.g. 123-5ml thin via spoon).

15.0 PATIENT CONSENT AND PEER JUDGMENT

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

16.0 DATA AND SAFETY MONITORING

All research team members will be involved in safety monitoring. Although not expected, research staff will inquire about adverse events during each follow-up phone call. Any negative

reactions that arise during the course of this study will be discussed in weekly research team meetings, entered into OnCore. All adverse events will be reviewed to determine whether a change in protocol is necessary. If a serious adverse event related to study activities occurs, it will be reported to the funding agency at NIH and the University of Wisconsin IRB within 24 hours. The chair of the IRB will review the report.

16.1 Potential Risks

16.1.1 One potential risk is an unintentional breach of confidentiality: patient private information, interviews, and transcripts could become known to persons not involved with the research. Patient data from the electronic health record include no sensitive information and will be securely stored by the researchers (described above). Direct identifiers will be removed from data used for day-to-day analysis and thus, we believe the risk of breach of confidentiality is low. The information collected does not include sensitive or potentially incriminating information. The data protection practices utilized by the research team (password protection; secure file servers; locked file cabinets for transcripts and other documents) minimize the likelihood of inadvertent breaches of confidentiality. Protection against the risk of loss of confidentiality is described in section 14.3.

16.1.2 Participants may experience frustration or fatigue with questionnaires. To minimize this risk, participants will be advised that they may choose to skip any questions that they do not want to answer. If caregiver participants become upset or appear distressed during completion of questionnaires, research staff will refer to resources for dementia caregiving support. Patients may experience some anxiety at being voice recorded during semi-structured interviews, but this risk is minimal. Additionally, caregivers may feel concerned that they are being judged by others who are reviewing the audio data. To avoid this, subsequent communication of findings from this study with will only include group findings and data that could potentially identify a patient or caregiver will not be shared outside of the research team. This will be explicitly addressed in the consent form. Additionally, no original data will be shared with anyone outside of the research team.

16.1.3 Although patients who cannot provide consent will have a legally authorized representative, it is possible that they will dissent to be involved in the study but may find it challenging to communicate their dissent. To mitigate this risk, the study team will utilize established procedures to attempt to obtain assent/dissent from persons with dementia. These procedures will ensure that, even if unable to provide legal informed consent, persons with dementia will be involved in the consent process to the extent possible. Research study staff will attempt to obtain assent from each participant whose legally authorized representative informed consent which will involve explaining the research study in very basic terms and assessing for an affirmative agreement, either verbal or non-verbal that indicates willingness to be involved in the study procedures. Study participants who indicate unwillingness to be involved in the study procedures will not be enrolled and will be asked whether it is acceptable to ask them about the project on a different day. Those who indicate unwillingness to participate in

study procedures at any time in the future will not be approached again. We realize consent/assent is an ongoing process. If a study participant expresses discomfort with study participation at any point in time, their consent/assent to participate will be re-visited discontinued if the study participant indicates unwillingness to participate in study procedures.

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

16.1.5 *Videofluoscopic Swallow Study Radiation Exposure (when performed as a research procedure):* During the VFSS, participants will be exposed to an estimated effective radiation dose of approximately 0.44 mSV with 174 seconds of mean fluoro time, which is equivalent to 52 days of natural background radiation.

16.2 Data Safety Monitoring Board

16.2.1 In providing oversight for the conduct of this study and at the request of the National Institute on Aging, we have constructed a Data Safety Monitoring Board, (DSMB) a formally constituted committee independent of the study team and University of Wisconsin that will meet every 6 months during the 5-year study period. Additional meetings may be scheduled as determined by the DSMB or as requested by Dr. Rogus-Pulia and her team. The DSMB members will review protocol-specific reports created by statisticians that serve a non-voting member role on the DSMB using data pulled from ICTR OnCore and REDCap. These standard reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of patient demographics for balance of randomization, and a summary of the number and seriousness of adverse events. An interim analysis of study results may be performed and source documents may be reviewed to allow the DSMB to independently judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by them to Dr. Rogus-Pulia and her team. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the UW-Madison Health Sciences IRB. A brief summary of these meetings will be included in yearly grant progress reports to NIA.

16.2.2 We have been instructed by the NIA Program Officer, Dr. Kristina McLinden, to construct our own Data Safety and Monitoring Board independent of this institution. The DSMB will include three members who are all independent of the sponsors/researchers. Please see a list of members with expertise below:

Theodore T. Suh, MD, PhD, MHS, AGSF
Medical Director, Turner Geriatric Clinic at East Ann Arbor
University of Michigan Geriatric Center

Dr. Theodore (Ted) Suh is the Medical Director for the Turner Geriatrics Clinic at the

University of Michigan East Ann Arbor Medical Campus. Previously, he served as the first Medical Director for Huron Valley PACE (Program for All-inclusive Care of the Elderly) in Ypsilanti, the Medical Director of the ACE Unit at Christus Santa Rosa Medical Center in San Antonio, and Medical Director of the outpatient Geriatric Assessment Program for Euclid Hospital of the Cleveland Clinic Health System. He has also served as a medical commentator for FOX News, has been an Epic electronic medical record Super user at 3 different healthcare institutions and was an expert medical witness for the U.S. Department of Justice. Dr. Suh received his M.D. and Ph.D. from the University of Cincinnati College of Medicine and his Master of Health Science degree from Duke University. He completed his internal medicine residency at Cleveland Clinic and fellowship training in geriatric medicine at Duke University and Durham VA Medical Center. Dr. Suh has been board-certified in internal medicine and geriatric medicine. In 2015, he became a Fellow of the American Geriatrics Society.

Stephanie Daniels, PhD, CCC-SLP
Professor, University of Houston
Department of Communication Sciences and Disorders

Stephanie K. Daniels, PhD, CCC-SLP is a Professor and Vice-Chair in the Department of Communication Sciences and Disorders at the University of Houston. Her primary area of research is stroke and dysphagia, and she has served as the PI on numerous federally funded studies. These studies have focused on neuroanatomical and neurocognitive predictors of dysphagia in stroke as well as validating screening procedures in this population. Her research endeavors have also involving the study of feeding and swallowing in individuals with dementia. She has established a body of work that relates directly to providing evidence-based practice to individuals with dysphagia. Dr. Daniels has published extensively in the field of dysphagia. She is an ASHA Fellow and Past-President of the Dysphagia Research Society.

Mark A. Espeland, PhD
Professor, Wake Forest School of Medicine
Department of Biostatistical Sciences
Alzheimer's Disease Core Center Faculty

I look forward to the opportunity to serve on the Data and Safety Monitoring Board for Dr. Rogus-Pulia. I feel I am well prepared to assume this role, which builds on my decades of work studying cognitive function and my extensive experience in leading clinical trials. My formal training is in statistics. I am founding Chair of the Department of Biostatistical Sciences at the Wake Forest School of Medicine and a Fellow of the American Statistical Association (1996) for my formative work in missing data and misclassification methods and the Society for Clinical Trials (2011) for my work in the design and conduct of multi-center studies. Later in my career, my primary research has shifted from methodology to have greater concentration on identifying approaches to preserve function and well-being as we age. I have held leadership roles in dozens of coordinating centers for major clinical trials, with outcomes spanning many age-related chronic diseases including cardiovascular disease, hypertension, physical function, cognitive function, diabetes, cancer, depression, osteoporosis, health care utilization, and quality of life. I have growing experience with research on aging and age-related conditions I have co-authored since 2010 are focused on

this area and the Modan Award I received from the American Diabetes Association in 2012 was based on my work examining trajectories of cognitive decline among older women with diabetes. I currently head the Data Management and Data Analytics Core of the Wake Forest Alzheimer's Disease Center. I also have considerable prior experience in cardiovascular disease: the Remington Award I received from the American Heart Association in 1996 was based on my work towards developing and introducing missing data methods for use in clinical trials with atherosclerotic outcomes. My induction in the American Association for the Advancement of Science last year drew from my biomedical and biostatistical work spanning several research fields. I am well-qualified to participate and lead multidisciplinary research teams. I have held leadership roles in dozens of coordinating centers. I am a frequent consultant to the NIH and industry, a member of the NIA Clinical Trials Advisory Panel, and statistical editor for the Journal of Gerontology. I have served on or chaired dozens of DSMBs for NIH and industry. I was a member of the National Academy of Science Panel on Preventing Dementia and Cognitive Impairment and have served on an NIH consensus conference panel on gestational diabetes. I have authored/co-authored 311 papers on statistical methodology and biomedical research (and 74 additional consortium publications).

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