Ethics Protocol

Title: Physiological Flow of Liquids Used in Dysphagia Management – Study 5(e)

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1. Title

Physiological Flow of Liquids Used in Dysphagia Management (Study 5e).

2. Investigators

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3. Abstract

For individuals with neurodegenerative diseases, swallowing impairment (i.e., dysphagia) is a common and serious symptom. Dysphagia places the affected individual at risk for secondary health consequences, including malnutrition and aspiration pneumonia, and negatively affects quality of life. In order to assess and manage dysphagia appropriately in these complex patients, clinicians must have a thorough understanding of the physiological mechanisms which contribute to impairment.

Videofluoroscopy (i.e., dynamic swallow x-ray) is widely considered to be the "gold standard" method for determining the nature, severity and functional consequences of abnormal swallowing physiology. Although observations from videofluoroscopy are frequently described in research literature, few studies have used objective measures to quantify the impairments and pathophysiological changes in swallowing. This makes it difficult to compare results directly across research studies, determine at what point physiological changes contribute to functional impairments in swallowing, and explore what factors lead to changes in swallowing physiology. Changes in liquid thickness, for example, have been shown to influence swallowing physiology in a predictable manner in healthy individuals and patients post-stroke; however we do not know how changes in liquid thickness modulate swallowing physiology in individuals with neurodegenerative diseases.

The purpose of this study is to conduct quantitative analysis of swallowing physiology, seen on videofluoroscopy (swallow x-ray), in order to:

1) Identify physiological parameters contributing to swallowing impairment; and
2) Determine how swallowing physiology and function differs across five levels of liquid thickness: thin, slightly-thick, mildly-thick, moderately-thick and extremely-thick.

4. Background

Dysphagia (i.e., swallowing impairment) is often characterized in terms of:

(1) Impaired safety (i.e., food and liquids entering the airway, known as aspiration), and;
(2) Impaired efficiency (e.g., food and liquids leaving residue in the throat after the swallow).

Impaired swallowing safety is linked to pneumonia while impaired efficiency has been indicated as a risk factor for malnutrition. Further, the accumulation of residue in the throat poses an independent risk factor for subsequent aspiration events. Dysphagia is highly prevalent in individuals with neurodegenerative diseases, such as Amyotrophic Lateral Sclerosis (ALS) and Parkinson's Disease (PD). As there is currently no cure for these complex diseases, symptomatic management of dysphagia is the current standard of care.

Research on dysphagia in neurodegenerative diseases to-date has focused primarily upon the presence of aspiration; however, there has been relatively little attention paid to the underlying physiological differences which predict or contribute to swallowing impairment. Understanding the key mechanisms behind impairment is critical for guiding clinical assessment, predicting disease progression and providing rationale for specific management options. Thickened liquids, for example, are commonly recommended to reduce the risk of aspiration; however, the accumulation of post-swallow residue has been shown to increase with liquid thickness, particularly in individuals with oropharyngeal weakness. Few studies have systematically investigated the efficacy of thickened liquids, or how changes in liquid thickness influence swallow physiology in patients with neurodegenerative diseases. Studies which have begun to explore these relationships have been limited to one or two levels of thickness at extreme ends of the continuum (e.g., thin versus pudding/paste). The purpose of the proposed cross-sectional study is to explore the pathophysiology of dysphagia through quantitative measurements of swallowing physiology. We aim to identify the key physiological parameters of swallowing which contribute to impaired swallow safety and efficiency, and to determine how swallowing physiology and function differs across five levels of liquid thickness: thin, slightly-thick, mildly-thick, moderately-thick and extremely-thick.

This protocol outlines a subproject of a larger project entitled *Physiological Flow of Liquids Used in Dysphagia Management*. The larger project (i.e., parent grant) has been reviewed and funded by the National Institutes of Health as a 5-year R01 grant awarded to the PI (Catriona Steele, Ph.D).

The overall goal of the parent grant is to collect measurements of liquid flow through the oropharynx (i.e., mouth and throat) during swallowing. The factors that are expected to influence liquid flow include the liquid consistency (i.e., thin, slightly-thick, mildly-thick, moderately-thick, extremely-thick) and the forces applied during swallowing (i.e., tongue pressures and swallowing muscle contraction). The overarching objective is to determine how these factors interact to influence the flow of a liquid through the oropharynx in healthy swallowing, and various clinical populations. The goal of this subproject is to explore this question in adults with neurodegenerative diseases,

Work on the parent grant to date has included the development and testing of liquid stimuli to be used in the current project, as well as the characterization of liquid flow and swallowing physiology in healthy individuals. For the current study, measures of liquid flow and swallowing behaviour will be collected in patients with neurodegenerative diseases. Data collection for this proposed study will take place at the Swallow Systems Core laboratory at the University of Florida (Gainesville), in collaboration with Dr. Emily Plowman (Co-PI). Data processing and the primary data analysis will be conducted by members of Swallowing Rehabilitation Research at the Toronto Rehabilitation Institute, supervised by Dr. Catriona Steele (PI). Additionally, some aspects of data analysis and results dissemination will be conducted collaboratively between Dr. Steele's lab and Dr. Plowman's lab, and will be covered by a data sharing and transfer agreement.

5. Specific Aims

This study aims to address two primary research questions:

Aim 1: To identify the key physiological parameters of swallowing which are associated with impaired swallowing safety (i.e., penetration-aspiration) and efficiency (i.e., post-swallow residue). To address this research aim, we will collect x-ray videos of swallowing (known as videofluoroscopy). We will then perform blinded quantitative analysis of swallowing kinematics and events, following a series of standard operating procedures developed in the Steele Swallowing Lab. This procedure will yield measures of swallowing physiology, which we can link to measures of swallowing safety and efficiency. We will also collect a series of measures regarding non-swallowing factors (e.g., oral-motor strength/function, liquid sip size) which may influence the analysis results. *Significance:* This analysis will reveal the most clinically relevant parameters for dysphagia assessment, and highlight the specific physiological mechanisms which predict or contribute to impairments in swallowing safety and efficiency.

Aim 2: To explore how factors related to liquid thickness impact swallowing physiology and function. Throughout the videofluoroscopy, participants will swallow sips of liquids ranging in thickness (from thin to extremely thick). The liquids will be mixed with a contrast agent (barium sulfate) so they are visible on x-ray. Liquid thickness will be explored in terms of its influence on swallowing safety and efficiency, and as a covariate upon swallowing physiology. *Significance:* This research aim will provide insight into the efficacy of thickened liquids to reduce instances of aspiration in individuals with neurodegenerative

diseases, and will allow us to determine what constitutes an optimal level of thickness for therapeutic intervention.

6. Research Plan

Protocol Review

The parent grant of which this project is a subproject has undergone scientific review by the MFSR Study Section of the National Institutes of Health (USA). The current protocol will be reviewed by the IRB at the University of Florida, where participant recruitment and data collection will take place, as well as the REB at the University Health Network, where data analysis will take place.

Funding

All costs for this study will be covered by the grant received from the National Institutes of Health (National Institute on Deafness and Other Communication Disorders, USA, Grant #: 5 R01 DC011020-05).

Participants

The protocol will involve a single sample of 40 adults aged 18 or older with a confirmed diagnosis of Amyotrophic Lateral Sclerosis (ALS) or Parkinson's disease, who are at risk for swallowing problems. Patients who rely on enteral feeding (e.g., PEG-tube, NG tube) for all nutrition will be excluded.

Participants will be asked to attend a single appointment required to complete all data collection described in this protocol. Participation involves an intake questionnaire to confirm eligibility and document demographic information, tongue-strength measurement, and a dynamic swallowing x-ray (known as videofluoroscopy).

Sample Size & Statistical Power:

Sample size calculations have been performed using the data from the Dr. Steele's previous grant, in which ultrasound measures of the duration of hyoid movement differed by 200-400 ms between age groups and tongue-pressure amplitudes varied by 10-35 mm Hg depending on the liquid studied. Our goal is to detect differences in bolus flow measures ≥200 ms in this experiment with a medium effect size (Cohen's $d \geq 0.5$)(96). A power calculation shows that 36 participants will be needed to detect this difference with 80% power ($\alpha=0.05$); we will plan for n=40. This sample size will also be adequately powered to detect differences ≥10 mm Hg in tongue-pressure amplitudes.

Exclusion Criteria:

- Medical history of cancer, surgery or radiation in the head and neck region, which may impose structural and neurological differences in the region of interest.
- Clinical history of dysphagia or neuromuscular disorder unrelated to the primary diagnosis, which may impose physiological differences that are not directly resulting from pathology of interest.

- Severe cognitive impairment that would impair a participant's ability to follow necessary instructions during the assessment procedures.
- Significant respiratory compromise (e.g., reliance on mechanical ventilation, diaphragmatic pacer, or forced vital capacity below 65%) which could place an individual at significant risk for adverse events.
- Due to the inclusion of stimuli containing starch-based thickeners, which carry a significant carbohydrate load, individuals with Type 1 Diabetes will be excluded.
- Children and pregnant women will be excluded from the study due to the use of radiation.
- Individuals who are completely dependent on enteral nutrition will be excluded.

These exclusion criteria will be confirmed through medical chart review and using a self-report questionnaire form at the time of intake into the study. Any uncertainty will be clarified through discussion with the research assistant responsible for participant intake, and, where necessary with the PI and Co-PI.

Recruitment:

Participants with ALS will be recruited from the multidisciplinary ALS clinic at the University of Florida during regularly scheduled care visits. Participants with Parkinson's disease will be recruited from the University of Florida Center for Movement Disorders. Potential participants with either diagnosis will also be identified via approved flyers that will be posted within the University of Florida campus and surround areas of Gainesville. All evaluations, however, will occur in Dr. Plowman's research laboratory at the University of Florida, Gainesville, FL.

Potential participants will be identified by the Co-Investigators and Neurologists seeing patients in these clinics who will initially inform the patient of the study. Further information regarding the specific study aims, procedures, involvement and potential risks and benefits will be thoroughly described by either the Primary Investigator/Co-Investigator/study coordinator and/or the Research Assistants and written information in the form of the Informed Consent will be provided for the patient to review at their leisure. The patient and their caregiver will be encouraged to ask questions regarding the study and be offered time to think about their potential involvement. They will be provided with Dr. Plowman's business card stapled to the informed consent and told to contact Dr. Plowman if they would like to participate. If a patient decides they would like to participate at this initial point of contact, they will be asked to sign an informed consent form and be assigned a study subject identification number and enrolled in the study at this time. If a patient informs the study staff that they do not want to participate in the study they will receive no further information or contact from study personnel.

Informed Consent:

Only after confirming they have understood all the information that is provided, and after verifying they have no more questions, will eligible participants sign the consent form. A copy of the consent form will be provided to them. If the ability to comprehend the study is in question, the participant will be

excluded from participating. Speech, language and reading/writing difficulties will be accommodated, as needed; we will request a third-party witness (e.g., family member) to be present if accommodations are made, or if the individual is unable to physically sign the consent from, independently.

Data to be collected from each participant:

Once informed consent has been obtained, the following types of data will be collected from participants, or recorded from chart review:

a) Demographic information:
    a. Year of birth;
    b. Sex;
    c. Relevant medical history, medications (i.e., which may affect saliva production, dry mouth, taste), and ongoing treatments (e.g., presence/location of a Deep Brain Stimulator);
    d. Race/ethnicity (required for NIH grant-reporting).
    e. Primary diagnosis (i.e., ALS or Parkinson's disease)
    f. Location of onset (i.e., bulbar/spinal/mixed, if applicable);
    g. Time post-onset of symptoms (initial and swallowing-specific);
    h. Extent of disease severity (e.g., ALS Functional Rating Scale – Revised; Unified Parkinson's Disease Rating Scale; Hoehn and Yahr Scale).
b) Measures of tongue strength, taken at the start and end of the session to obtain baseline and post-experimental measures.
c) A videofluoroscopy recording of swallowing collected at a pulse rate of 30 pulses per second and video capture set to 30 frames per second.

Data Collection Procedures:

This study will consist of an intake questionnaire, measures of tongue strength, and a videofluoroscopy (swallow x-ray). Total time for data collection is not expected to exceed 1 hour.

Intake Questionnaire (5 minutes):

Demographic information will be obtained from participants during an intake interview, and recorded on the Intake Form. If a recent estimate of disease severity is not available on record, participants will be asked to complete the appropriate functional rating scale, according to the diagnosis (e.g., ALS Functional Rating Scale – Revised).

Tongue Strength Measurement (10 minutes):

Baseline and post-experimental measures of tongue strength on maximum isometric tasks and saliva swallows will be collected using the Iowa Oral Performance Instrument. This will enable us to understand the impact of weakness or fatigue on measures of swallowing physiology and liquid flow.

With the participant seated comfortably, a small air-filled disposable bulb will be placed in the mouth, behind the front teeth, and the participant will be instructed to press as hard as they can with the front and back of the tongue, three times in each position, with 30 seconds of rest between each trial. Next, participants will be asked to swallow their saliva with the bulb at the front of their tongue, three times, with 60 seconds between each swallow. Measures will be recorded on the Tongue Strength Measurement form.

Videofluoroscopy (30 minutes):

A videofluoroscopy (i.e., swallowing x-ray) will be conducted by a speech-language pathologist and a radiology technician, at the Swallow Systems Core laboratory in Gainesville, Florida. Dr. Plowman and the co-director of the Swallowing Systems Core lab own a C-Arm fluoroscopy unit that is housed in their secure research space. This C-Arm will be used to conduct all swallowing studies. This procedure will take approximately 30 minutes of the participant's time (including set-up, instructions) and will include up to 21 liquid bolus trials.

An array of barium stimuli has been developed for this study. These stimuli include thin, slightly-thick, mildly-thick, moderately- and extremely-thick liquids, defined by the International Dysphagia Diet Standardisation Initiative (IDDSI) framework. The barium stimuli used for videofluoroscopy will be prepared using E-Z-Paque® barium in 20% w/v barium concentration with starch and gum-based thickening agents (Nestlé Resource® ThickenUp® and ThickenUp Clear®). All stimuli will be prepared at the Swallowing Systems Core Laboratory, within 3 hours of the scheduled videofluoroscopy, according to a strict standard operating procedure. Following preparation, stimuli will be stored in the lab until needed.

Boluses will be presented in the following order:

a) Three (3) swallows of Level 0 thin liquid (Bracco E-Z-Paque powdered barium, prepared in a 20% weight-to-volume concentration);
b) Six (6) swallows of Level 1 slightly thick liquid (20% weight-to-volume barium concentration):
    - Three (3) boluses thickened with a xanthan-gum thickener (Nestlé Thicken Up Clear),
    - Three (3) boluses thickened with a starch thickener (Nestlé Thicken Up);
c) Three (3) swallows of Level 2 thick liquid (20% weight-to-volume barium concentration, thickened with a xanthan-gum thickener (Nestlé Thicken Up Clear);
d) Six (6) swallows of Level 3 moderately thick liquid (20% weight-to-volume barium concentration):
    - Three (3) boluses thickened with Nestlé Thicken Up Clear,
    - Three (3) boluses thickened with Nestlé Thicken Up;
e) Three (3) swallows of Level 4 extremely thick liquid (20% weight-to-volume barium concentration), thickened with Nestlé Thicken Up Clear.

Presentation of thickener type (i.e., xantham-gum vs. starch) will be randomized by participant, using a blocked design. Videofluoroscopies will be performed at maximum temporal resolution (i.e., 30 pulses per second), and recorded at 30 frames per second.

Participants will be asked to take comfortable sips of all sippable liquids (IDDSI Levels 0-2) and a comfortably sized spoonful using a teaspoon for levels 3 and 4. To control for the potential influence of variations in bolus volume on swallowing physiology, each cup will be weighed before and after the videofluoroscopy.

Ashley Waito, a visiting doctoral student and delegate of Dr. Catriona Steele (Co-I) at the collaborating site, will be involved as an onsite observer for a portion of this study. Ashley is approved by the UF Privacy Office as an observer with limited access to PHI for the purposes of this research study, and is approved for data analysis by the University Health Network Research Ethics Board.

Safety Precautions:

Throughout the study, steps will be taken to ensure participant safety and minimize risk of adverse events. We anticipate that comprehensive examinations of the full continuum of liquid consistencies may not be possible for all patients in this study, and we will adhere to strict rules to terminate the protocol, if necessary. If aspiration or penetration leaving residue in the laryngeal vestibule is observed on two trials of the same stimulus, the remaining trial(s) of that stimulus will be skipped and the examiner will move on to the next IDDSI level. If a participant displays 3 instances of aspiration (PAS ≥ 6), the swallowing x-ray will be stopped and data collection will discontinue for that participant. The protocol will be terminated after 3 observations of penetration-aspiration. If severe levels of pharyngeal residue are observed in an individual (i.e., either the valleculae or pyriform sinuses are judged to be 75% full or more, with risk of overflowing) and persist despite compensatory maneuvers, the swallowing x-ray will be terminated and the participant's dysphagia will be managed according to best practice standards of care.

After the initial swallow of each bolus is collected for research purposes, the attending speech-language pathologist may instruct the patient to perform additional tasks (such as coughing) or clearing swallows using compensatory maneuvers (e.g. chin down position) to manage instances of aspiration or residue, as deemed clinically necessary. These subsequent swallows using compensatory maneuvers will be noted on the appropriate Videofluoroscopy Clinical Reporting Form and will not be included in the data analysis. The attending clinician may terminate the protocol at any time if he or she deems the patient to be at significant risk for adverse events.

In the event of an unanticipated adverse response, the participant's neurologist will be immediately notified and the patient will be seen for a complete evaluation. Data, adverse events, and individual subject safety are monitored throughout each subject's evaluation as well as during weekly laboratory meetings with the PI and study team.

Data Processing and Analysis

All data processing will take place at the University Health Network, Toronto Rehabilitation Institute. Full-length videofluoroscopies will be transferred from the University of Florida to the Swallowing Rehabilitation Research Lab at the Toronto Rehabilitation Institute through a secure file transfer protocol.

An engineer from Dr. Steele's research team will segment each videofluoroscopy into individual bolus clips (i.e., one video clip, per bolus). Bolus-level videos will be de-identified to the highest possible degree and randomized for blinded analysis. Videofluoroscopy rating will follow a standard operating procedure, developed in the Swallowing Rehabilitation Research Lab. A minimum of twenty-five percent (25%) of the videos will be rated in duplicate to obtain measures of inter- and intra-rater agreement.

Planned Statistical Analysis

Once the videofluoroscopy ratings have been completed, statistical analysis will be completed either in Dr. Steele's laboratory or in Dr. Plowman's laboratory. Transfer of anonymized excel data sheets containing the information needed for these analyses will be covered by a data transfer and sharing agreement.

Statistical analysis will be conducted in a stepwise fashion, to address the research questions and identify trends within the data. We will begin by exploring correlations between measures of interest, to identify and appropriately address potential non-independence and collinearity. If two or more measures are found to be highly correlated with one another, we will retain the measure(s) which show the least variability and remove the remaining measures from the analysis. Further, because we are obtaining multiple bolus trials from the same participants, we will also calculate within-subject variance for each parameter of swallowing physiology and function.

We will explore how parameters of swallowing physiology vary based on swallowing function status (i.e., swallowing safety or efficiency) through a series of repeated measures ANOVAs, Spearman's Rho and Pearson's correlation coefficients, and logistic regression (statistical tests will be defined by the type of data). Following this, we will explore how liquid thickness modulates the relationships between parameters of swallowing physiology and function, as a covariate, using a path analysis.

Privacy and Confidentiality

Routine practices for ensuring the confidentiality and privacy of all participants will be followed in this study. All research personnel at the Toronto Rehabilitation Institute are required to sign a confidentiality agreement at the time of hire. Research personnel at the University of Florida are similarly bound by a confidentiality agreement outlined by the ethics board at their institution.

Participants will be assigned a non-identifying alphanumeric study code, and the master key for this code will be retained separately by the PI in a password-protected file on a secure, password-protected,

encrypted research server. Daily back-up of this research server is performed centrally at the Toronto Rehabilitation Institute to protect against data loss.

All videofluoroscopic data will be stored electronically on a secure, password-protected, encrypted research laptop (owned and operated by UHN), and transferred to the Swallowing Rehabilitation Research Team using an encrypted file transfer portal, for subsequent analysis. Any hard copy data will be transcribed into an electronic file (stored on the secured UHN server, accessed remotely), and the hard copy records will be stored in a locked filing cabinet in the Swallow Systems Core Laboratory. Only the participant's alphanumeric study code number will appear on the data collection sheets and in the data collection files.

Access to participant information and experimental raw data will be restricted to the study personnel named in this application. All records will be destroyed after 10 years under the supervision of Dr. 9

In the event of inappropriate release of personal health information, further release of information will be stopped, any information that can be retrieved will be retrieved, the UHN Privacy Office and REB will be notified, as well as the University of Florida IRB. Any recommended further actions will be taken.

7. Possible Discomforts and Risks

The following risks will be disclosed to all participants prior to obtaining their consent to participate:

a) Participants will receive exposure to radiation during the videofluoroscopy. The radiation exposure that participants will receive is about 50 millirem. This radiation exposure is equivalent to 60 days of natural background radiation to which people in the United States receive each year. The risk from this radiation exposure is considered to be very minor when compared with other everyday risks. As repeated exposure to radiation may increase risks of injury or disease, participants will be encouraged to consider previous and future potential exposures prior to deciding to volunteer for the study. Further, participants will be provided with a contact person if they want to learn more about radiation.
b) Participants may dislike the taste or texture of some of the thickened liquid stimuli in the study. Participants will be reminded that they are free to discontinue participation at any time.
c) Participants may experience some fatigue during the videofluoroscopy data collection session. Participants will be reminded that they should disclose any fatigue or discomfort to the research team, and that they are free to discontinue or withdraw from the study at any time.
d) Aspiration (entry of material into the airway) is a possible risk during the videofluoroscopic swallowing study that will be performed. This risk is always present for videofluorscopic swallowing studies, which are intended to document the presence and severity of swallowing abnormalities, including (but not limited to) aspiration. When aspiration is observed, standard procedures will be followed to encourage coughing and throat clearing to expel the aspirated material. If we observe severe or repeated instances of aspiration, we will discontinue data

collection, and the participant will be counseled regarding aspiration prevention strategies and aspiration-risk following the videofluoroscopy.

e) Choking is an extremely unlikely event. However, in the event of choking, routine emergency procedures will be followed.

f) Participants may be asked for information about sensitive issues, such as their mood, thoughts of suicide, and substance use, which may make them feel uncomfortable. They can choose not to answer any of the questions and they may discontinue participation in the study at any time. Some people, when asked such questions, experience strong emotional reactions that may require counseling. If a participant does, he/she will be strongly encouraged to tell the Principal Investigator, who can make an appropriate referral to the UF Counseling & Wellness Center at (352) 392-1575. If study personnel find that a participant is suicidal, he/she will be excluded from further participation in the study and an appropriate referral will be made. If study personnel should discover, based on the questionnaires or formal clinical interview, that a participant experience marked depression or suffer from another psychiatric condition, they will offer to make an appropriate medical, psychiatric, and/or psychological referral.

8. Possible Benefits

Although there are no anticipated direct benefits to participants in this study, the information obtained from this study will serve to guide future clinical practice and dysphagia management for individuals with neurodegenerative diseases.

Compensation

Data collection for each participant will involve: a) intake measures; b) videofluoroscopy. The total time commitment will be approximately 2 hours. An honorarium of $50 (USD) will be provided per participant to cover expenses associated with participation in the study. A voucher will be provided to cover onsite parking. This will be paid following the videofluoroscopy.

9. Conflicts of Interest

Dr. Steele, the principal investigator, holds current and prior research contracts with Bracco Canada and Nestlé Health Science, who are manufacturers of the barium products and thickening agents that will be used in this study. She has also served in an advisory capacity on expert panels for Nestlé Health Science. These relationships will be disclosed to participants in the study information sheet. All products for use in the study will be purchased. Neither Bracco Canada nor Nestlé Health Science will have any role as sponsors of this study. Dr. Steele will not receive any financial payment, either personally or to the lab, related to the use of Nestlé or Bracco products in this study.