
**STUDY PROTOCOL**

# The Pathophysiology of Swallowing Impairment in People recovering from COVID-19 Infection

**NCT 04537650**

**PI: Catriona M. Steele, Ph.D.**

**Swallowing Rehabilitation Research Laboratory**

**KITE Research Institute, Toronto Rehabilitation Institute, University Health Network**



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## LIST OF ABBREVIATIONS

| | |
|---|---|
| PrC-19 | People recovering from COVID-19 |
| VFSS | Videofluoroscopic Swallowing Study |
| LVC | Laryngeal Vestibule Closure |

# PROTOCOL SUMMARY

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| **Full Title** | The Pathophysiology of Swallowing Impairment in People Recovering from COVID-19 Infection. |
| **Short Title** | Swallowing impairment after COVID-19. |
| **Sample Size** | N=100 (approximately 25 at each collaborating site and 50 at the University Health Network) |
| **Study Population** | Patients who are recovering from COVID-19 infection. |
| **Accrual Period** | October 15, 2020 to January 31, 2022 |
| **Study Design** | This is an observational study, in which people recovering from COVID-19 infection will attend two outpatient clinic visits for a comprehensive swallowing assessment. The assessment will include a videofluoroscopy, measurement of respiratory-swallow coordination using a digital stethoscope, measures of tongue and cough strength and patient reported measures that will help us to understand the presence and impact of swallowing impairment (dysphagia) in this population. |
| **Study Duration** | October 15, 2020 to January 31, 2022 |
| **Procedure** | Participants will be asked to attend two 60 minute visits where we will capture a videofluoroscopy, measurement of respiratory-swallow coordination using a digital stethoscope, measures of tongue and cough strength and patient reported measures that will help us to understand the presence and impact of swallowing impairment (dysphagia) in this population. If requested, it may be possible to arrange for both visits to take place on the same day. |
| **Primary Outcomes** | • Frequency of boluses (per consistency) on which the participant displays unsafe swallows, defined as scores of 3 or higher on the Penetration-Aspiration Scale (Rosenbek et al., 1996).<br>• Frequency of boluses (per consistency) on which the participant displays inefficient swallows, defined as swallows with pharyngeal residue measured to fill 1% or more of an anatomical reference scalar [$(C2\text{-}4)^2$] on a lateral view x-ray. |
| **Secondary Outcomes** | • Frequency of boluses (per consistency) on which the participant displays time-to-laryngeal-vestibule-closure more than 1 standard deviation above the healthy reference mean (Steele et al.,2019).<br>• Frequency of boluses (per consistency) on which the participant displays laryngeal-vestibule-closure duration more than 1 standard deviation below the healthy reference mean (Steele et al., 2019).<br>• Pixel-based measurement of pharyngeal area at rest from a single a lateral view x-ray image, and classified as below or above 1 |

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|---|---|
| | standard deviation from the healthy reference mean (Steele et al., 2019).<br>• Frequency of boluses (per consistency) on which the participant displays pharyngeal area above the 75th percentile healthy reference value on the frame of maximum constriction (Steele et al., 2019).<br>• Frequency of boluses (per consistency) on which the participant displays multiple swallows, above the 75th percentile healthy reference value (Steele et al., 2019). |
| **Exploratory Outcomes** | • Frequency of boluses (per consistency) on which post-swallow inspiration is seen immediately following the swallow.<br>• Maximum value across 3 repetitions of a maximum tongue-palate press task, measured using the Iowa Oral Performance Instrument in an anterior position.<br>• Range of diet textures included in the participant's diet, measured using the International Dysphagia Diet Standardisation Initiative Functional Diet Scale.<br>• Total and individual question scores on the Sydney Swallow Questionnaire.<br>• Reported dyspnea using the Modified Medical Research Council Dyspnea Scale.<br>• Maximum peak voluntary cough flow across 3 repeated coughs through a peak-flow meter.<br>• Patient report of any changes (Yes/No) they have experienced in taste or smell associated with their COVID-19 infection. |
| **Endpoints of the study** | Recruitment and completed data collection in 100 patients across the 3 study sites. |

## 1.0 General Information

**Protocol title:** The Pathophysiology of Swallowing Impairment in People Recovering from COVID-19 Infection.

**Study principal investigator:**

**Dr. Catriona Steele**
The KITE Research Institute, Toronto Rehabilitation Institute, University Health Network
550 University Ave, 12th floor
Toronto, Ontario, Canada
M5G 2A2
Tel: 416-597-3422 x 7603

**Co-investigators for Toronto region:**

**Dr. Azadeh Yadollahi**
The KITE Research Institute, Toronto Rehabilitation Institute, University Health Network
550 University Ave, 12th floor
Toronto, Ontario, Canada
M5G 2A2
Tel: 416-597-3422 x 3659

**Dr. Steven Pong**
The KITE Research Institute, Toronto Rehabilitation Institute, University Health Network
550 University Ave, 12th floor
Toronto, Ontario, Canada
M5G 2A2
Tel: 416-597-3422 x 7896

**Dr. Mark Bayley**
Toronto Rehabilitation Institute, University Health Network
550 University Ave, 3rd floor
Toronto, Ontario, Canada
M5G 2A2

**Co-investigator for the Hamilton/Niagara region:**

**Dr. Ashwini Namasivayam-MacDonald**
McMaster University, Department of Rehabilitation Science
1400 Main St West, IAHS room 420
Hamilton, Ontario, Canada
L8S 1C7
Tel: 917-676-0772

**Co-investigator for the Florida region:**

**Dr. Emily Plowman**
University of Florida, Department of Speech and Hearing Science
1396 Center Drive, DG-130
Gainesville, Florida, United States
32611
Tel: 352-273-8632

## 2.0 Introduction

The recent spread of COVID-19 has led to an international pandemic, with >90 million confirmed cases to date worldwide, of which 22.5 million confirmed cases and >375,000 deaths have been reported in the USA. Infected individuals commonly experience severe respiratory difficulties and pneumonia, leading to hospital admission and the need for intensive care and mechanical ventilation. Emerging evidence suggests that impaired taste and smell may be early markers of the disease, and that in severe cases, there may be neurological damage in in the medulla, an important brainstem control site for both respiration and swallowing (Jean, 2001). Given the overlapping neuroanatomical regulation of breathing and swallowing, we hypothesize that dysphagia (swallowing impairment) will be common in People recovering from COVID-19 (PrC-19) and associated with poorer outcomes. Dysphagia involves impairments of swallowing safety and/or efficiency (Lovato and deFilippis, 2020). Impaired swallowing safety involves penetration or aspiration of material into the airway; impaired swallowing efficiency involves pharyngeal residue after the swallow, which, in turn, becomes a risk for secondary aspiration (Steele et al., 2020). Aspiration is considered a risk for pneumonia (Pikus et al., 2003; Arnold et al., 2016; Martino et al, 2005), which is a frequent reason for readmission to hospital (Prescott et al., 2015).

We will establish 3 regional research clinics that will offer comprehensive swallowing assessments to PrC-19 after initial recovery and a confirmed negative test for continuing COVID-19 infection. These research clinics will draw on established connections to clinicians in the Toronto area (PI Steele); the Hamilton-Niagara region to the west of Toronto (Co-I Namasivayam-MacDonald) and in Gainesville, Florida (Co-I Plowman). The assessments will include the collection of case history information, videofluoroscopy (i.e., a dynamic swallowing x-ray), use of a novel digital stethoscope to measure respiratory-swallow coordination, measures of other risk factors for dysphagia (e.g. bulbar muscle strength) and patient-reported outcomes. Detailed analyses of the videofluoroscopy swallowing studies (i.e. dynamic x-rays) will identify specific measures of swallowing that fall outside the range of normal variation based on comparison to healthy reference values established through our research program exploring swallowing physiology on liquids of different consistencies.

## 3.0 Study Objectives and Hypothesis

*3. 1 Purpose*

The proposed studies will be an extension of our current work exploring swallowing physiology in healthy adults and patients with dysphagia of various etiologies (Amyotrophic Lateral Sclerosis, traumatic Spinal Cord Injury, oropharyngeal cancer treated with radiation, Chronic Obstructive Pulmonary Disease, and Parkinson Disease). This work has resulted in the development and dissemination of a novel, evidenced based and standardized method for the analysis of videofluoroscopic swallowing studies (VFSS) known as the ASPEKT Method (Analysis of Swallowing Physiology: Events, Kinematics and Timing). Using this method, we have determined and published the first comprehensive set of normative reference values for swallowing physiology in a sex-balanced sample of healthy adults up to the age of 60 (Steele, Peladeau-Pigeon et al., 2019; Steele Swallowing Lab, 2019) across all liquid consistencies of the International Dysphagia Diet Standardisation Initiative

framework (Cichero et al., 2017; Cichero et al., 2017). Importantly, this work has afforded clinicians and researchers the ability to understand mechanisms of swallowing impairment in their patients, by providing a normative reference framework to index and identify specific measures of swallowing that fall outside the range of normal variation. We have recently extended this work by completing the analysis of a dataset collected in a sex-balanced sample of healthy older adults (> age 60) (in progress), which now enables us to account for age related changes when using reference data to identify swallowing pathophysiology in older patients.

Systematic methods for analyzing these data have enabled us to identify abnormalities in swallowing that most commonly explain penetration-aspiration and pharyngeal residue. In the proposed study, we will use the ASPEKT Method to identify pathophysiological mechanisms of impaired swallowing in PrC-19. Findings from the proposed study will provide foundational evidence for treatment recommendations in PrC-19 with dysphagia.

In healthy individuals, the swallow is usually positioned partway through an outward breath, such that the respiratory pause associated with swallowing is bracketed on either side by expiration (Brodsky et al., 2010; Martin-Harris, 2008; Martin-Harris et al., 2005; Butler et al, 2007). This positioning of swallowing in the respiratory cycle is considered optimal for airway protection, so that any remaining material in the laryngeal vestibule may be expelled by exhalation immediately after the swallow. Post-swallow inspiration has been observed as an abnormal respiratory-swallow coordination pattern in some clinical populations and is thought to represent a risk for aspiration of material into the airway (Brodsky et al, 2018; Brodsky et al., 2010; Butler et al, 2007; Martin-Harris et al., 2017). Incorporating measurements of respiratory-swallow phasing into clinical swallowing assessments has the potential to identify individuals at heightened risk of aspiration.

Historically, the combined measurement of breathing and swallowing has been a research activity using either nasal cannula methods or the measurement of chest wall movements via respiratory inductance plethysmography. There is a need for new, portable cost-effective methods that can reliably and validly measure respiratory-swallow dynamics during clinical assessment. As an exploratory objective, we will address this need with timely implementation of a novel digital stethoscope technology. Co-investigators Dr. Pong and Dr. Yadollahi have developed a novel digital stethoscope (the “E-Steth”) for use in telehealth community monitoring of cardio-respiratory function in PrSC-19. This innovative device uses a microphone mounted inside a stethoscope head to record physiological sounds into the Voice-Memo application on a smart phone. The recording can easily be sent to a clinician, who can run diagnostic signal processing algorithms. In this study, we will adapt the E-Steth technology to identify abnormalities in respiratory-swallow coordination, in the form of inspiratory airflow immediately after the swallow. Automatic signal processing algorithms previously validated for the measurement of airflow in sleep (Montazeri et al., under review) can be used to classify post-swallow airflow direction as expiratory (typical) or inspiratory (abnormal).

*3.2 Objectives*

Our objective is to understand the nature of swallowing impairment in PrC19, based on the following outcome measures:

Primary Outcomes:

- Frequency of boluses (per consistency) on which the participant displays unsafe swallows defined as scores of 3 or higher on the Penetration-Aspiration Scale (Rosenbek et al., 1996)
- Frequency of boluses (per consistency) on which the participant displays inefficient swallows defined as swallows with pharyngeal residue measured to fill 1% or more of an anatomical reference scalar [%(C2-4)squared] on a lateral view x-ray (Steele, 2020).

Secondary Outcomes:

- Frequency of boluses (per consistency) on which the participant displays time-to-laryngeal vestibule-closure more than 1 standard deviation above the healthy reference mean (Steele et al.,2019)
- Binary classification of a single pixel-based measure of pharyngeal area at rest, traced from a lateral view x-ray, and classified as below or above 1 standard deviation from the healthy reference mean (Steele et al., 2019)
- Frequency of boluses (per consistency) on which the participant displays pharyngeal area above the 75th percentile healthy reference value on the frame of maximum constriction (Steele et al., 2019)
- Frequency of boluses (per consistency) on which the participant displays multiple swallows, above the 75th percentile healthy reference value (Steele et al., 2019)

Exploratory Outcomes:

- Frequency of boluses (per consistency) on which post-swallow inspiration is seen immediately following the swallow.
- Maximum value across 3 repetitions of a maximum tongue-palate press using the Iowa Oral Performance Instrument in an anterior position.
- Range of diet textures included in the participant's diet, measured using the International Dysphagia Diet Standardisation Initiative Functional Diet Scale
- Total and individual question scores on the Sydney Swallow Questionnaire
- Reported dyspnea using the Modified Medical Research Council Dyspnea Scale
- Maximum peak voluntary cough flow across 3 repeated coughs through a peak-flow meter
- Patient report of any changes (Yes/No) they have experienced in taste or smell associated with their COVID-19 infection

*3.3 Hypothesis*

Our current expectations are that PrC-19 will show differences in swallowing function and physiology compared to age- and sex-matched reference values (Steele, 2019), as listed in the following table:

| **Parameter** | **Prediction in PrC-19 (vs age-matched healthy reference values)** |
|---|---|
| Penetration-Aspiration | Higher frequency and more likely to be silent |
| Time-to-Laryngeal-Vestibule-Closure (LVC) | Later closure due to priority of respiration |
| LVC duration | Shorter due to underlying respiratory challenges |
| Pharyngeal Area at Rest | Larger due to muscle weakness and atrophy.<br>Note: reference values show significant sex difference with larger area in males. |
| Pharyngeal Area at Maximum Constriction | Larger (i.e. poor constriction)<br>due to muscle weakness and atrophy |
| Residue | Greater due to poor constriction |
| # of swallows per bolus | Higher due to poor bolus clearance |

We expect PrC-19 patient to report swallowing-related burden. We hypothesize that post-swallow inspiration (a sign of respiratory-swallow discoordination) will be seen more commonly in PrC-19 compared to healthy reference data (Valenzano et al, 2020), and will be particularly common in those who report dyspnea.

## 4.0 Study Design

This is an observational study, in which people recovering from COVID-19 infection will attend two outpatient clinic visits for a comprehensive swallowing assessment. The assessment will include a videofluoroscopy, measurement of respiratory-swallow coordination using a digital stethoscope, measures of tongue and cough strength, and patient-reported measures that will help us to understand the presence and impact of swallowing impairment (dysphagia) in this population, as compared to reference data from healthy adults that has previously been collected and published by our lab.

*Data Collection Procedure*

We expect study participation to involve an initial 30 minute telephone or video conference call to review the consent documents, a 60 minute session to capture non-radiographic data, and a 60 minute session to capture the radiographic data. If requested, it is possible to arrange for both of the data

collection appointments to take place on the same day, although it is not possible to guarantee back-to-back scheduling and a delay between the sessions is likely.

Infection Control and Safety Procedures for the Face to Face Appointments:

a. We will contact the participant 2 days prior to each study appointment and use the UHN COVID 19 screening questions to confirm that they do not have any current symptoms of COVID-19 that are not otherwise explained and are suggestive of possible active infection. This will also confirm that they have not, to their knowledge, been exposed to someone who has active COVID-19. Two hours prior to each appointment, we will ask them to complete the UHN COVID-19 screening app questions on their smart phone (at www.UHNScreen.ca), or, to arrive at the facility in time to undergo routine COVID-19 screening prior to entering the facility. If the participant is accompanied by a companion, the companion will also need to complete these routine COVID-19 screening procedures. Upon arrival, they will be issued with a procedure mask to wear at the hospital.
b. For the initial appointment scheduled in the Swallowing Rehabilitation Research Laboratory at Toronto Rehab, the participant and their companion will be met in the Elm Street waiting room area at Toronto Rehab and escorted by a study team member directly to the 12$^{th}$ floor Swallowing Lab.
c. For the x-ray appointment at Toronto General Hospital, the participants will be given instructions on how to enter the hospital at the Elizabeth Street entrance where COVID-19 screening is performed, and how to reach the Diagnostic Imaging department, and will be met there by a member of the study team.
d. The study team members present for data collection will follow IPAC rules for limiting potential spread of infection. All study team members who will be directly involved in data collection are licensed speech-language pathologists who will have been required to review the lab's standard operating procedures relating to infection control and safety. They will be required to wear procedure masks at all times and to maintain 2 meter distancing from the participant and the other team members present, whenever possible. Regular disinfection of surfaces in the lab using appropriate wipes will be part of the study protocol. For study staff members who will perform tasks that require close physical proximity to the participant with less than 2 meters distance, additional personal protective equipment (PPE) will be used in accordance with IPAC recommendations, including wearing laundered gowns, gloves, face shields, and, if appropriate, N95 masks. Regular hand washing and sanitizer use will also be required. There will always be a minimum of 2 study team members present, and a buddy system will be employed to observe donning and doffing of PPE and to prompt whenever necessary to ensure adherence to safe PPE practices. These procedures have been reviewed and approved by the KITE Research Restart team.

1. Review of study information and consent form:
    a. All participants who show an interest in participating will be provided with the study information and consent form ahead of time. These documents will be sent either by

email or by mail, according to the participant's preference for delivery method. A telephone or video-conference call will be scheduled to review these documents and answer any questions.

b. For participants who wish to proceed, we will obtain an initial verbal consent that they have understood all the information provided, and, after verifying that they have no more questions, we will move forward with scheduling the study appointments. If the participant wishes, the study questionnaire can be mailed to them for review in advance of their first appointment. However, completion of the questionnaire will not take place prior to the first appointment or prior to signing the consent form.
c. During the first appointment, we will review the study procedures and answer all their questions. If they wish to proceed, we will ask them to sign the consent form. A copy of the consent form will be provided to the participant. Data collection will proceed only after these steps have been completed.

2. Demographic and medical history information:
    e. Participants will be asked to complete a form capturing demographic, medical history and history of COVID-19 management. Those participants who answer yes to questions inquiring about current respiratory difficulties (shortness of breath) or swallowing difficulties will be asked to complete the section of the questionnaire incorporating the Modified Medical Research Council Dyspnea Scale and the Sydney Swallow Questionnaire to understand these symptoms in more detail. For those who report no current symptoms of respiratory or swallowing difficulty, this section may be left blank.

3. Non-radiographic data:
    a. Bulbar muscle strength will be measured using 3 repetitions of a maximum effort isometric tongue-to-palate press task, measured using the Iowa Oral Performance Instrument. The patient will be instructed to "squeeze the bulb as hard as you can between your tongue and the roof of your mouth". A clean, single-use, disposable tongue bulb will be used for each participant.
    b. Voluntary peak cough flow will be measured using a Mini-Wright analog peak flow meter fitted with a single-use, disposable expiratory one-way valve filter mouthpiece following the American Thoracic Society (ATS) standards. The patient will be instructed to "cough hard like there is something stuck in your throat" and will perform three trials.
    c. Respiratory-swallow coordination data will be collected using the E-Steth digital stethoscope during a water swallow screening task. The E-steth stethoscope housing will be sanitized with alcohol wipes prior to and after use. The housing itself will not come into direct contact with the participant's neck, because there will be medical adhesive tape between the participant's skin and the device housing. Nevertheless, we will use a fresh e-steth device for each participant and will dispose of the device after use with each participant. After sanitization, the E-Steth housing will be attached to the participant's neck using double sided tape, over the suprasternal notch. The E-Steth output will be connected to a dedicated lab cell phone/MP3, iPad or laptop computer running the Voice Memos application and recorded as .m4a files. The participant will be

provided with a cup containing 60 ml of chilled bottled water and asked to take a comfortable sip and swallow. This procedure will be repeated up to 4 times. If the patient completes all 4 sips in without any overt signs of aspiration, a new cup containing 90 ml of water will be provided, and the patient will be asked to drink the entire 90ml in a sequential fashion without stopping.
*Stopping rule:* If the patient demonstrates obvious signs of aspiration, including coughing post-swallow at any point in the water swallow screening task, further water screening will be discontinued.

d. Following completion of the first appointment, the participant will be given instructions for their second appointment at the Toronto General Hospital diagnostic imaging department for the x-ray component of the study. If requested, it is possible to arrange for both of the data collection appointments to take place on the same day, although it is not possible to guarantee back-to-back scheduling and a delay between the sessions is likely.

4. Radiographic data:

The standardized videofluoroscopic swallowing study will be performed in the Diagnostic Imaging Department at the Toronto General Hospital. Swallowing x-ray appointments are always scheduled during a Tuesday afternoon time-slot. Upon arrival at the Toronto General Hospital entrance, the participant (and any companion) will again need to pass through the routine COVID-19 screening procedures before entering the building.

The x-ray procedure will involve swallowing 3 boluses each of thin, mildly thick and extremely thick barium and 1 consecutive drinking task of thin liquid.

*Stimulus preparation:* Bracco E-Z-Paque® powdered barium will be prepared in 20% w/v concentration with water, and thickened to target consistency using Resource Thicken-Up™ Clear (a xanthan gum thickener developed by Nestlé Health Science). Target consistency will be defined using the International Dysphagia Diet Standardisation Initiative definitions and Flow Test. For the Toronto site, all stimuli will be prepared in the Swallowing Rehabilitation Research Laboratory not longer than 6 hours prior to scheduled use, according to a strict standard operating procedure. Barium stimuli will be transported to the radiology suite at Toronto General Hospital, as per routine clinical procedures. Similar procedures will be followed at the Hamilton and Florida sites.

*Procedure:* Three cups of each stimulus will be prepared for the experiment, each containing 40 ml and organized in a muffin tray placed in front of the participant. If the participant completes all 3 thin sips without any observation of aspiration or serious residue, a new cup containing 90 ml of thin liquid will be provided, and the participant will be asked to drink the entire 90ml in a sequential fashion without stopping. This is a routine clinical method for ruling out swallowing safety concerns in patients who do not show concerns on single sip tasks. Single-use plastic teaspoons will be placed in the extremely thick cups to facilitate serving. The participant will be asked to take a

comfortable sip (or spoonful) from each cup. The cups will be weighed on a digital balance at the conclusion of the session to derive estimates of sip volume. The order of testing will begin with thin liquids and proceed to mildly thick and then extremely thick stimuli.

*Recording:* The videofluoroscopic swallowing study will be captured in lateral projection using pulsed videofluoroscopy at a rate of 30 pulses per second, and recorded on a synchronized videocapture system at 30 frames per second. The recording system is a secure TIMS Dicom system with password access that is connected to the hospital's network, enabling secure saving of all recordings in a folder on our research server. Any identifiers visible on the x-ray image (such as the participant's MRN number or age) will be hidden with black electronic screen scrubbers during the first step of data processing and prior to assignment for review.

*Stopping rules:* Testing of each consistency will be discontinued after the second observation of aspiration or serious residue. The entire protocol will be terminated after the 4th observation of aspiration. The sequential thin drinking task will only be performed if the participant completes all 3 thin sips without any observation of aspiration or serious residue.

*Compensation*
Participants will receive a $50 e-gift card for participating in this study.

*File Transfer*
All data processing will take place at the KITE Research Institute - Toronto Rehabilitation Institute - University Health Network. Each institution will be required to sign a data transfer agreement prior sending any data. We will use secure file transfer procedures to transfer the necessary data from the collaborating sites to the Toronto lab.

*ClinicalTrials.gov Registration*
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law.

## 5.0 Selection of Subjects

*Participants*
We aim to conduct 100 assessments (approx. 25 per collaborating site involved in the study and approx. 50 at University Health Network) over a 14-month period.

*Recruitment*
We will adopt three strategies for recruiting participants to this study:

1) We have linked to the Ontario COVID-19 Prospective Cohort Study (OnCoP) study being conducted by the CANCOV study PIs Drs. Margaret Herridge and Angela Cheung at UHN. The CANCOV study team has agreed to notify their participants of the opportunity to participate in our study. They will use our

study information sheet and referral form for this purpose. They have also suggested that a Swallowing Team Member could attend their weekly clinic and speak directly to CANCOV participants who agree to consider the study.

2) We will work through the members of our clinician advisory group and a wider network of clinicians in the cities where data collection is happening to solicit referrals of patients who meet the study inclusion criteria. We will ask these clinicians to introduce the study opportunity to patients and request permission to complete a referral to the study team for future contact.

3) We will conduct a broad public advertising campaign through local newspapers, magazines, websites, mailings and posters at community centres, seniors' residences, places of worship, and around the university and hospital campuses of the study sites (University of Toronto, University Health Network Toronto, McMaster University, Hamilton Health Sciences Centre, University of Florida, Shands Medical Centre).

The clinical research coordinator will respond to all inquiries or referrals regarding potential participation, contacting the patient by phone or videoconference using Microsoft Teams to discuss the study further, obtain initial verbal consent and schedule the study appointments. A reminder call will take place 2 days before the scheduled study appointments.

*Inclusion Criteria*

- Adult (18 years of age or older)
- Positive (or presumed positive) diagnosis of COVID-19 infection not earlier than March 1, 2020
- At least 2 weeks post positive diagnosis and medical management of COVID-19 infection
- Currently free from fever or chills; new onset of cough; worsening of chronic cough; new onset of sore throat; new onset of nausea/vomiting, diarrhea, stomach pain; eye pain or conjunctivitis; unexplained headaches, fatigue, malaise or muscle aches. Individuals with continuing complaints of shortness of breath, difficulty breathing, swallowing difficulty or decrease/loss of sense of taste or smell will be included.
- Adequate comprehension of English (able to understand consent form and follow study instructions)

*Exclusion Criteria*

We will accept any participants who meet the inclusion criteria, regardless of prior medical history. As indicated under the inclusion criteria, children under the age of 18 years old will not be involved in this protocol due to the use of radiation. Additionally, pregnant women will be excluded due to the use of radiation.

## 6.0 Risks and Benefits

*Risks*

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

a) It is possible that 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.
b) It is possible that participants may experience some fatigue during the data collection sessions. Participants will be reminded that they should disclose any fatigue or discomfort to the study personnel, and that they are free to discontinue any particular session or to withdraw from the study at any time.
c) Participants will receive exposure to radiation during the videofluoroscopy. Based on our previous research, we estimate the total duration of exposure to be < 90 seconds, with an associated dose estimate of <0.27 milliSieverts. For comparison, a dose of 0.35mSv is reported by Moro and Cazzani (2006) to correspond to a risk of 1 in 39,000 of developing a radiation-induced stochastic effect from a videofluoroscopy. A study of videofluoroscopy radiation exposure in patients who completed an 11-task protocol showed that patients with neurological diagnoses received the highest exposure time (Mean: 3.1 minutes, 95% confidence interval: 2.9 to 3.2 minutes) (Bonilha et al., 2013). Extrapolating from this calculation to the 10-task protocol for the proposed study, we estimate that patients who complete the entire protocol could receive up to 3 minutes of radiation exposure. We will use a warning bell to alert the data collection team to exposure time above this limit, and will terminate the protocol at the first opportunity following the bell.
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 videofluoroscopic 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 for documenting its occurrence. The protocol will be terminated immediately after the 4th observation of aspiration. Any participant who experiences aspiration will be provided with a "Summary of Research Findings" report that they can share with their family doctor. If appropriate, they will be referred to appropriate follow-up services.
e) Participants may experience skin irritation due to the adhesive patches and medical tape used to attach the E-steth sensor to the neck. Individuals who report known skin sensitivity or allergies to adhesives will be given the option to decline the E-steth component of the study.

*Benefits*

Participants will benefit by receiving a comprehensive swallowing assessment that may not otherwise have been available to them.

*Incidental Findings*

In the unlikely event that the video x-ray reveals an unexpected medical finding, the team will generate a report and will facilitate referral to appropriate follow-up services.

## 7.0 Statistics

We will use the ASPEKT Method (Steele et al., 2019) to analyze available recordings of thin liquid, mildly thick liquid and extremely thick liquid swallows, and compare values to age matched reference data (Steele Swallowing Lab, 2019). Our goal is to develop an understanding of the prevalence of

abnormal values in PrC-19 taking comorbidities and other related factors into consideration. These potential covariate moderators include demographic factors (sex, age, gender, race, ethnicity), pre-existing or co-existing medical diagnoses, history of the COVID-19 hospitalization including details of any ventilator support required, medical history since discharge (including any occurrences of respiratory infection), dyspnea, changes in taste and/or smell associated with the COVID-19 infection, bulbar muscle strength, cough strength, and abnormal respiratory-swallow coordination. Additionally, the person's ability to tolerate the full range of diet textures and their swallowing-related quality of life may be affected by COVID-19 related swallowing difficulties.

Assuming 100 participants and 3 boluses per consistency, this will result in a dataset of 300 boluses per consistency. Our previous research suggests that swallowing can differ across repeated boluses of the same consistency within an individual. It is, therefore, reasonable to calculate statistical power at the bolus level. A power calculation in Study Size software suggests that a sample of 138 boluses for a given consistency will be needed to detect frequencies of abnormal values higher than those seen in the healthy reference sample with odds ratios ≥ 2.00 with 80% power. Therefore, the targeted sample size should be sufficient both to detect increased frequencies of abnormal values and to allow the bivariate exploration of the impact of single covariate moderators on abnormal value frequency. We will not have sufficient data to create a multivariate model exploring the relative impact of different moderators; however the findings from this analysis will be sufficient to inform future studies in larger cohorts.

## 8.0 Data Safety and Monitoring Plan

A clinician advisory panel comprising 9 speech-language pathologists who work in critical care has been established to guide this study. Additionally, 3 physicians have agreed to provide medical advice to the study team. The clinician advisory group will meet via video-conference every 4-6 weeks over the course of the study. Dr. Teresa Valenzano, PhD, SLP(C), Reg. CASLPO will act as chair. Progress reports will be provided for review 1 week ahead of these meetings, and presented to the meeting. These reports will document the numbers of participants accrued, preliminary trends in the data and any adverse events. After discussion, the principal investigator, co-investigators, collaborators and study coordinators will leave the call, to allow for further in camera discussion. In the event that any concerns about study continuation are raised during the in camera session, Dr. Valenzano will report these back to the study team.

## 9.0 Data Handling and Record Keeping

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 McMaster University and the University of Florida are similarly bound by a confidentiality agreement outlined by the ethics board at their institutions.

Participants will be assigned a non-identifying alphanumeric study code, and the master key for this code will be retained separately by the lead investigators at each site (Dr. Steele, Dr. Namasivayam-MacDonald, Dr. Plowman) on a secure, password-protected, encrypted research server. Paper-based

documents will be stored securely in a locked filing cabinet under the supervision of the lead investigators at each site.

De-identified hard copy data will be transcribed onto an electronic file and transferred to Dr. Steele's lab at the KITE Research Institute – Toronto Rehabilitation Institute - University Health Network. Routine daily back-up of this research server will be performed to protect against data loss.

All de-identified data will be transferred to Dr. Steele using an encrypted file transfer portal, for subsequent analysis. 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. Steele, Dr. Plowman and Dr. Namasivayam-MacDonald.

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. If applicable, the REB at McMaster University and the University of Florida IRB will be notified. Any recommended further actions will be taken.

## 10.0 Conflicts of interest

Professor 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. Professor 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.

## 11.0 Additional Ethics Reviews

Additional ethics approvals have been separately obtained for other sites involved in this study as follows:

- University of Florida
- McMaster University

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