Clinical Impact of Respiratory-Swallow Training on Refractory Dysphagia in OP HNC

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Abstract

Despite important advancements in medical and surgical cancer treatments that prolong survival, Veterans and non-Veterans with head and neck cancer (HNC) are faced with chronic, intractable dysphagia resulting in persistent drastic alterations in diet, the need for feeding tubes, and increased risk for aspiration pneumonia – a life threatening infection. We must devote research and clinical efforts to mitigate these devastating impairments because currently our rehabilitative intervention options are severely limited. As such, and in keeping with the VHA's Blueprint for Excellence Transformative Actions, the need for the development of effective swallowing interventions that show potential for ***rapid translation to clinical practice*** is imperative. Respiratory-swallow coordination is an essential element of airway protection during swallowing and facilitates many key aspects of swallowing physiology. This key coordinative event is significantly disrupted in patients who are dysphagic following medical and surgical treatments for HNC. Our preliminary trial tested an innovative swallowing treatment approach developed in our clinical laboratory, respiratory-swallow training (RST), that targets respiratory-swallow coordination directly and resulted in compelling improvements in physiologic swallowing outcomes in Veterans and non-Veterans suffering from dysphagia that persisted long after traditional behavioral swallowing intervention(s). The goal of this proposed trial is to extend our preliminary study using a rigorous, randomized cross over design and determine the impact and durability of RST on ***clinical outcomes*** essential for eating, drinking, health, and quality-of-life in patients with HNC. As such, positive results from the proposed trial have high significance and clinical relevance for patients' health and well-being.

A total of 51 participants will be recruited with the goal of 40 participants enrolled. Participants will be randomly assigned 1:1 to either RST (intervention arm) or no active treatment (control arm), which is considered standard of care in this patient population. The participants in the control arm will have no active treatment for 4 weeks and will then participate in RST as a cross-over design. Data obtained will be used to evaluate clinical efficacy and durability The primary efficacy endpoint is physiologic function metrics of the oropharyngeal swallow, and the secondary endpoint will be respiratory-swallow phase patterning. We will also elaborate on the impact of RST by detailing the physiological, airway protective, and morphometric changes that occur. We will use reproducible, reliable, and validated metrics that include the Modified Barium Swallow Impairment Profile, Penetration-Aspiration Scale, and Computational Analysis of Swallowing Mechanics to distinguish the mechanistic effects of RST. Further, adherence to a novel HP component using self-guided practice will be introduced and tested for feasibility and contribution to the degree and durability of the RST intervention effect.

Our overarching goal is to provide two parallel tracks of knowledge generation: 1) provide immediate clinical translation of experimental findings to improve the lives of Veterans and non-Veterans, and 2) drive model generation on fundamental mechanisms of motor coordination. Basic knowledge will drive clinical application and vice-a-versa. As such, this is an ideal experimental and clinical context that will fuel knowledge generation in this highly significant area of science and clinical practice.

Specific Aim 1. Directly train optimal respiratory-swallow phase patterning using RST and test the clinical efficacy and durability of the effect measured by change in physiologic metrics of the oropharyngeal swallow. Hypothesis: RST will improve swallow physiology, oral intake status and liquid/food texture tolerances. Primary Outcome: Physiologic metrics of the oropharyngeal swallow as measured by the Modified Barium Swallow Impairment Profile (MBSImP) scores,[13,14,19]; Secondary Outcome: Functional Oral Intake Scale (FOIS).[17,18]

Specific Aim 2. Elaborate the intervention impact of RST on swallowing physiology and airway protection. Hypothesis: RST will improve tongue base retraction, laryngeal vestibular closure, pharyngeal shortening, and pharyngeal clearance. Primary Outcome Measures: MBSImP scores,[13,14,19] Penetration-Aspiration Scale scores,[20] and morphometric canonical variate measurements.

List of Abbreviations

AB – Abdomen

A-P – Anterior-posterior

ALARA – As low as reasonably achievable

ANCOVA – Analysis of covariance

ANOVA – Analysis of variance

BMH – Bonnie Martin-Harris

CASM – Computational analysis of swallowing mechanics

CBOC – Community based outpatient clinic

CDE – Common Data Elements

CHEMO-XRT – Combined chemotherapy and radiation treatment

COPD – Chronic obstructive pulmonary disease

CPRS – Computerized Patient Record System

CS – Charlie Strange

E-E – Expiratory-expiratory

E-I – Expiratory-inspiratory

FDA – Food and Drug Administration

FEV1 – Forced expiratory volume in 1 second

FOIS – Functional Oral Intake Scale

FVC – Forced vital capacity

GEE – Generalized estimating equations

GOLD – Global Initiative for Obstructive Lung Disease

HIPAA – Health Insurance Portability and Accountability Act

HNC – Head and neck cancer

HP – Home practice

HPV – Human papilloma virus

I-E – Inspiratory-expiratory

I-I – Inspiratory-inspiratory

IRB – Internal Review Board

ITT – Intention-to-treat

MBSImP – Modified Barium Swallow Impairment Profile

MBSS – Modified barium swallow study

MDADI – M.D. Anderson Dysphagia Inventory

MoCA – Montreal Cognitive Assessment

NU – Northwestern University

OI – Overall Impression

OP – Oropharyngeal

PAS – Penetration-Aspiration Scale

PESO – Pharyngoesophageal segment

PFT – Pulmonary function testing

RC – Rib cage

RIP – Respiratory inductance plethysmography

RST – Respiratory-Swallow Training

SD – Standard deviation

SLP – Speech-Language Pathologist

SPiRE – Small Projects in Rehabilitation Research

SS – Swallow-by-swallow

SURG-XRT – Surgical resection followed by radiation treatment

TDRS – TIMS DICOM Review Software

TV – Tidal volume

US – United States

VA – Veteran Affairs

VAMC – Veteran Affairs Medical Center

WP – William Pearson

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Protocol Title: Clinical Impact of Respiratory-Swallow Training on Refractory Dysphagia in OP HNC

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2.0 Introduction

Swallowing Impairment in Head and Neck Cancer (HNC). Veterans are approximately twice as likely to incur HNC when compared to the general population and may suffer life-long inability to eat, drink, and swallow normally.[1-4] It is hypothesized that the increased incidence of cancer in veterans may be related to unique risk factors, such as exposure to toxic materials during military service, maladaptive behaviors to manage stress (e.g., smoking and alcohol abuse), or an increasing number of aging veterans who are more likely to manifest the disease later in life.[24] Comorbidities of veterans, such as chronic pulmonary disorders, may further complicate recovery from cancer treatment.[2]

In a 26-year follow-up study of approximately 250,000 United States (US) Veterans that evaluated the risks of cigarette smoking, a strong dose-response effect between smoking and a large number of cancer sites was revealed, including the oropharynx.[25] Worldwide, 350,000-400,000 people are diagnosed with oropharyngeal (OP) HNC each year – nearly 10% in the US alone.[26] *Of particular relevance to the current proposal is that swallowing impairment represents* ***the highest functional morbidity*** *in Veterans with OP HNC treated either with surgical approaches followed by radiation or with more recent organ-preservation protocols, such as combined chemotherapy and radiation*.[28-30] Although some recent data suggest these new organ sparing protocols are potentially less perturbing to swallowing function than surgery followed by radiation, toxicity from organ preserving treatments often results in devastating swallowing impairments.[28-50] Therefore, regardless of the cancer treatment modality, swallowing impairments are highly significant and are potentially long-lasting medical and functional concerns for HNC patients and the Veterans Health Administration.

Further, unlike many cancer types, the incidence of OP HNC is moving in the wrong direction. OP HNC incidence has increased by 1.3% from 2007 to 2011, likely related to increases in tumors incited by the human papilloma virus (HPV-positive).[4,51] This is particularly troubling since oropharyngeal tumors have high propensity to impair swallowing function because the tumor site and medical/surgical treatments directed toward cure or local control in the oropharyngeal region, include critical structures involved in airway protection and clearance of ingested material through the upper aerodigestive tract. Specifically, disruption of the structure and function of the *base of tongue* reduces its force-generating capacity to clear ingested material (bolus) from the oropharynx and its airway protection capacity that normally occurs by

shielding the laryngeal inlet as it retracts during swallowing.[52] Restrictions in the contractility of the pharyngeal constrictor muscles decreases their ability to shorten and compress anteriorly against the base of tongue and bolus tail, contributing to incomplete pharyngeal clearance with large amounts of *pharyngeal residue*, and limitations to elevation of the larynx and *closure of the laryngeal vestibule*.[10,52,53] Further, sensory end organs involved in the complex coordinative process of swallowing initiation and safety, including respiratory-swallow coordination, may be disrupted consequent to toxicities associated with the common treatments for HNC. Relevant to the current proposal, the mechanisms of swallowing impairment described herein are precisely those that were shown to improve when applying our respiratory-swallow training (RST) – the intervention focus in the current proposal.[8]

Along with the increase in OP HNC occurrence, the death rates associated with the disease have decreased and the five-year survival has increased. Five-year survival rates have been reported to be as high as 66% for OP HNC, and HPV-positive HNC survivors have a 54% better overall survival compared to those with HPV-negative tumors.[3,54,55] These promising increased survival rates are in part related to improved surgical and nonsurgical options for cure, and yet the degree of toxicity associated with these treatments options is often high and leads to immediate and/or delayed profound inability to swallow. These swallow impairments remain chronic, are often resistant to traditional swallowing therapy, and have devastating effects on health and well-being. Increased survival with poor health and quality-of-life associated to HNC-related dysphagia speaks to the need for focused attention on the development of innovative and rapidly translatable rehabilitation methods to improve the lives of Veteran and non-Veteran survivors. *Cancer survivorship has been described as traumatic, increasing an already* ***high risk of emotional and psychological distress in the Veteran population.*** This likely contributes to the refractory nature of dysphagia following treatment, especially for those with continued tobacco and alcohol use and chronic symptoms.[56]

Refinement and modification of traditional swallowing therapy paradigms are emerging at a slow pace but do show promise toward reversing some of the toxic effects associated with radiation and chemotherapy.[57-61] The respiratory-swallow cross-system approach that is the focus of the proposed study extends beyond traditional swallowing intervention that typically targets muscles and structures alone, and instead, is directed toward recalibration of respiratory-swallow phase patterning. This approach has been shown to have a significant impact on improving the physiologic mechanisms that are fundamental for safe and efficient swallowing. Based on our previous work and exciting preliminary results, we propose that persistent swallowing impairment may **not only** be related to disordered physiological processes within the oropharyngeal system, but **also** to the coordination of the swallow with respiration.[8,62] The nature of the swallowing impairment may predispose patients to disruptions in the otherwise highly stable phase relationship in respiratory-swallow coupling observed in normal, non-dysphagic individuals.[9]

Collectively, these data speak to the high significance of this proposal – a natural progression of our previous work – designed to further test a novel swallowing intervention that not only improves key elements of swallowing physiology, but also has shown potential for functional recovery. ***Our goal is to expand on the rigor of our preliminary trial and includes a randomized controlled clinical trial with cross-over that provide patients with a respiratory-swallow recalibration strategy to minimize the coordinative demands between breathing and swallowing and optimize airway protection and swallowing mechanics***. As such, the current application matches well the objectives of the VA Merit funding mechanism by providing definitive clinical evidence for a new therapy that shows high

promise to benefit a vastly underserved, Veteran and civilian population with chronic dysphagia. If clinical efficacy is determined, the intervention program will be easily disseminated to the VA clinical community and beyond through open access publications, and face-to-face and online web training instruction. Lastly, the current initiative will provide detailed information regarding the physiologic characteristics, i.e., "active ingredients" of changes in swallowing impairment throughout the intervention using innovative and well-tested, *reproducible* measurement approaches. Our eventual goal is to use this information to combine our RST protocol with other evidence-based interventions to target underlying swallowing impairments and optimize clinical outcomes in patients with dysphagia in both the late and acute phases of recovery.

Respiratory-Swallow Coordination. A substantial body of literature, including work from our labs, using a variety of measurement techniques including respiratory flow, chest wall movements, and motion imaging of the upper aerodigestive tract has shown that there is a highly stable, coordinative relationship between respiration and oropharyngeal swallowing in healthy adults.[4,12,15,16,53,62-78] Swallows have been shown to occur most frequently during a pause (respiratory inhibition) in the expiratory phase of the breathing cycle between middle and low, quiet breathing expiratory lung volumes.[4,12,15,16,52,62-80] This coordinative phase relationship appears to serve two related functions. First, it is vital to airway protection and secondly, it facilitates key, advantageous swallowing mechanical functions, such as laryngeal elevation and closure, pharyngeal shortening and pressure generation with consequent bolus clearance, and pharyngoesophageal segment (PES) opening.[12,15,52,68] Therefore, swallowing within this range of expiratory lung volumes may be a clinical marker for both the integrity of neural control mechanisms coordinating breathing and swallowing, and of airflow and mechanical events that are essential for safe and efficient swallowing.[62,63]

Precise respiratory-swallow coordination is vital for airway protection. Respiration is inhibited before and during pharyngeal swallowing in all species, including human infants and adults.[11,15,16,52,63-68,80] The exact timing of this pause or obligatory inhibition (sometimes referred to as deglutition apnea) differs slightly for liquid swallows, most likely due to differences in experimental procedures (e.g., differences in delivery of the bolus into the oral cavity for swallowing), measurement devices (e.g., nasal flow vs. chest wall measurements) and analysis procedures (e.g., looking at flow events vs. categorizing respiratory phase and volumes). [62-66,68-71,75] Swallowing at mid-to-low expiratory volumes during the expiratory limb of the quiet breathing cycle (optimal phase pattern), provides important mechanical advantages. The diaphragm continues to be active during the early expiratory phase and this places traction of the trachea and larynx limiting laryngeal elevation and cricopharyngeal opening. At mid-to-low expiratory volumes, the diaphragm is relaxed and traction on the trachea is minimal.[15,78,80] Although we are beginning to have a clearer understanding of normal respiratory-swallow coordination, our understanding of the potential impact of various medical conditions on this synergy is far from complete. Non-optimal respiratory-swallow phase patterning (swallowing at high lung volume during the inspiratory phase) has been found in HNC patients with dysphagia and in several neurologic conditions both in the absence and presence of significant respiratory disease.[9] Particularly relevant to the present study are our previous findings that partial surgical ablation of the oropharynx and/or various combinations of radiation and chemotherapy negatively impacted normal respiratory-swallow phase stability.[9] This may be due to: 1) impairments within the oropharyngeal swallowing system, such as delayed pharyngeal swallow due to sensory loss, *incomplete tongue base retraction*, and *impaired shortening and elevation of the larynx and pharynx* leading to *incomplete laryngeal vestibular closure* and opening of the PES[9] – all of which may impact coordination with breathing; 2) impairments within the respiratory system that may impact coordination with swallowing; and/or 3) disruptions in the

coordination of breathing and swallowing that exceed these systems and are related to neural control impairments. This creates, therefore, the important theoretical context for the necessity of examining both "within" and "across" swallow system impairment.[80] Our previous study supports the notion that this cross-system impairment can be trained or normalized.[8] Consistent with other areas of motor performance, we suggest that RST recalibrates the "sensory percept (perceived lung volume) specific to the domain of perturbation" (airway protection and pharyngeal clearance during swallowing performance).[82]

Our previous research findings have established an ideal backdrop for exploring the presence and effect of cross-system respiratory-swallow impairments on "within" swallowing system impairment (Figure 1). Further, we are ideally positioned to test interventions that minimize the impact of cross-system impairment on swallowing function (disordered physiology and aspiration) in our target population –Veterans and non-Veterans with chronic dysphagia treated for HNC.

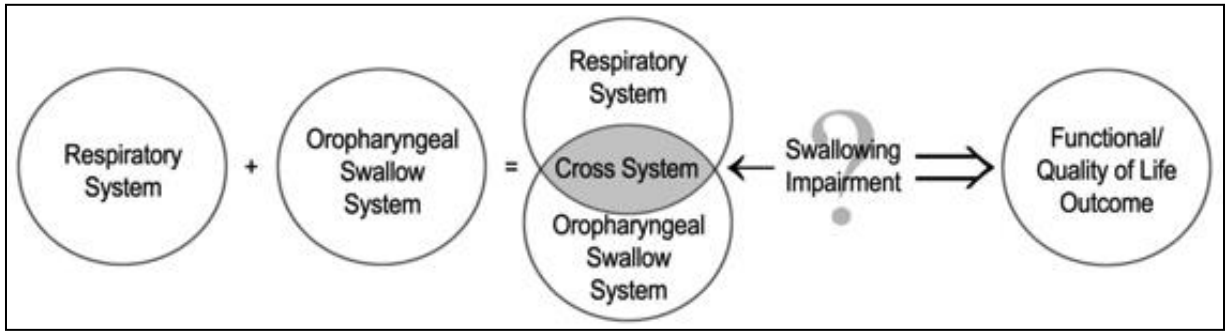


Figure 1 Theoretical model of cross-system, respiratory-swallow impairment.

PRELIMINARY STUDIES

Specific Aim 1. Understanding normal versus disordered aspects of swallowing, including respiratory-swallow coordinative processes, has been the focus of the principal and affiliated investigator's research for over 20 years. Additionally, the principal investigator (BMH) has extensive clinical experience and expertise in swallowing impairments consequent to HNC. Our team's expertise, experiences and laboratories provide the ideal scientific and clinical background for the proposed clinical study that is a natural progression of our previous successful trial.[8] We will focus our review on three areas of our previous work looking at respiratory-swallow coordination and discuss the impact of this work as it relates to the rationale for the methodology proposed in the current study.

Respiratory-Swallow Coordination and Phasing – Healthy, Adults without Dysphagia. Work unique to the laboratories of the current investigators has led to the development of a normative model of temporally integrated breathing and swallowing patterns using simultaneous respiratory flow and kinematic data time-linked to videonasoendoscopic and videofluoroscopic imaging of oropharyngeal swallowing.[12,52,62,68,78,83] These simultaneous recordings permit timing measures of a variety of key swallowing events, such as lingual and hyolaryngeal motion, laryngeal vestibular closure, tongue base retraction, pharyngeal contraction, and extent and duration of PES opening as they occur at various points along the respiratory signal (Figure 2). The broad objective of this line of research has been to establish normative temporal and respiratory phase pattern relationships between breathing and liquid swallowing in healthy, adult humans across the aging continuum. The significance of this work is deviations from normal

timing relationships may represent hazardous consequences during otherwise airway protective and bolus clearing mechanical swallowing events.

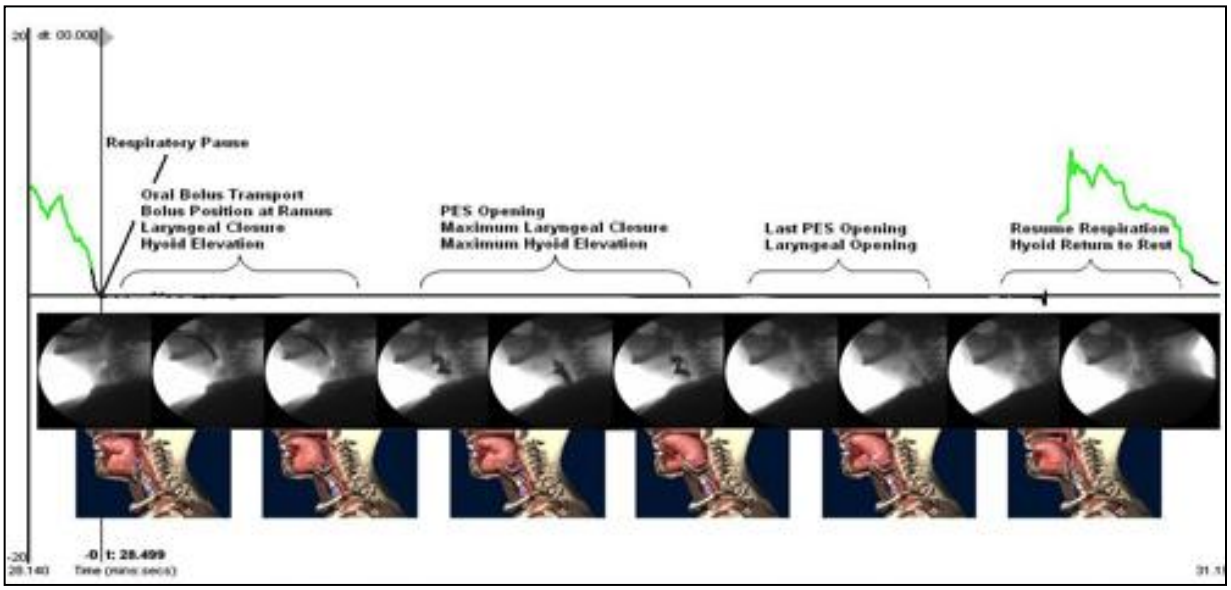
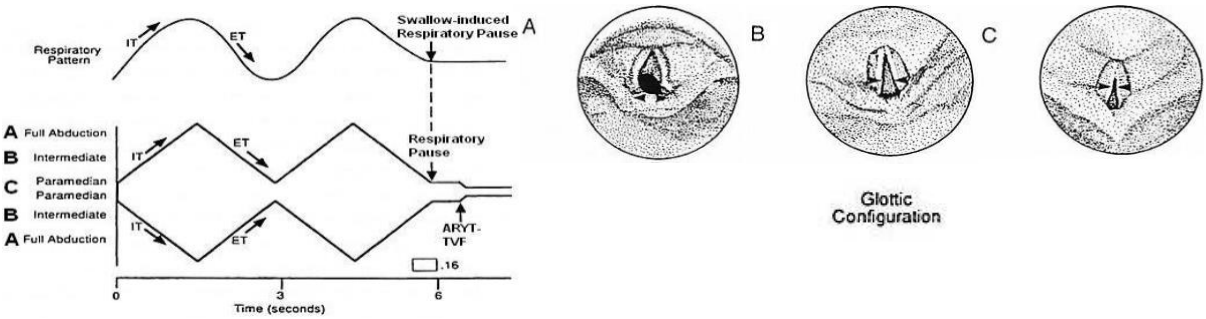


Figure 2 The timeline derived from simultaneous videofluorographic and nasal airflow recordings illustrating the phases of respiration surrounding swallowing and the temporal relationships between the respiratory pause and functional groupings of swallowing events (Figure adapted).[52]

Our early work (and that of others) has provided a clear description of respiratory-swallow coordination in normal, healthy individuals.[11,15,16,52,63-68,80] We have found that the respiratory pause to accommodate swallowing was most frequently and consistently preceded and followed by expiratory airflow. This **"optimal" phase** pattern has been termed expiratory-expiratory (**E-E)** to describe the respiratory events that bracket the swallow (Figure 3), which represented 75% of the observed respiratory-swallow phase relationships in one of our previous study of 76 healthy adults across the age spectrum.[8,52,77] This pattern was followed in frequency of occurrence when swallowing was immediately preceded by inspiratory and followed by expiratory (**I-E**) flow (20%). The two least frequently occurring patterns were when swallowing was preceded by expiratory activity but immediately followed by inspiratory flow **(E-I) (4%)**, and when swallowing interrupted inspiratory flow **(I-I**) (1%). None of the healthy individuals in the few cases of the non-optimal pattern demonstrated swallowing impairment or aspiration. However, swallows immediately preceded or followed by inspiratory flow (**E-I**, **I-E**, **I-I**) could potentially expose the passing bolus during the swallow or residual bolus after the swallow to negative, inspiratory pressures, thus increasing risk of aspiration that could pose problems in non-healthy populations with swallowing disorders.



The preferential segment of the expiratory limb during which swallowing occurs has implications for the influence of *lung volume* on airway protection and swallowing function which will be measured and studied directly in the current project. It has been shown that the manipulation of lung volume under experimental conditions (i.e., inspiring to total lung capacity, or expiring to functional residual capacity) prior to swallow modulates the timing of the swallow.[81,84] Exhaling to residual volume resulted in slower swallows compared to those swallows performed at functional residual capacity or total lung capacity.[83] However, given that healthy individuals do not typically initiate swallows at these lung volumes[11,12,15,16,51,62-67] and because it has been shown that single bolus swallows, regardless of bolus type, occur within a restricted range of mid-to-low quiet breathing lung volumes,[85] the relevance of lung volume on swallow safety and efficiency has not been entirely clear. In the proposed study, participants will be trained to swallow at mid-to-low, quiet breathing lung volumes to match the airway protective benefits of E-E phasing with the mechanical and airway benefits of this restricted range of quiet breathing lung volumes.

A final example of the airway protective and mechanical advantages of swallowing during mid-to-late expiratory phase during quiet breathing, hence mid-to-low lung volume, have been shown from another early study that examined the glottic configuration associated with respiratory phasing surrounding liquid swallowing.[62] The mid-to-late expiratory phase of the respiratory cycle was coincident with medialization (partially adducted) of the true vocal fold-arytenoid complex. This expiratory laryngeal posture promoted an advantageous set point for further glottic closure that is required at the height of the swallow to aid in the prevention of aspiration (Figure 3).[12,68] This medial glottic position was also observed during laryngeal descent in the late stage of the swallow and was associated with a brief expiration depicted in the flow and kinematic data. It has been stated that the positive pressure associated with post-swallow expiration may be assistive to bolus clearance.[52,63,68,70]

<u>Respiratory-Swallow Coordination and Swallowing Impairment – Patients Treated for OP HNC.</u>
Against this backdrop and based on our extensive research and clinical experience with the target patient population, we had reason to believe that respiratory-swallow coordination as described above is impaired and should be considered an appropriate target of clinical intervention. Patients who had been treated for OP HNC presented with non-optimal and potentially hazardous and inefficient respiratory-swallow coordinative patterns that contributed to their overall swallowing impairment. Our first preliminary investigation in patients treated for HNC investigated whether non-optimal respiratory-swallow phase patterning was present and if so, what are the implications for swallowing impairment. The early investigation was the first to examine the potential relationship between “within system” swallowing impairments (aspiration

and impairment in swallowing physiology) and "cross-system" alterations, such as respiratory-swallow phasing.[9] Twenty medically stable and chronically dysphagic OP HNC patients 12 months post-cancer treatment and traditional swallowing intervention were compared to 20 healthy, age-matched controls. Nine of the cancer patients were treated with surgical resection followed by radiation treatment (SURG-XRT), and 11 were treated with combined chemotherapy and radiation treatment (CHEMO-XRT).

As presented in Table 1, our preliminary data [from an early study that in part motivated our first training trial, revealed that only 35% of cancer patients (n = 7) used the optimal pattern (**E-E**) (65% used non-optimal) during single liquid swallows as compared to 75% (n = 15) of the normal controls (p = .04). The cancer patients used **E-I** (n = 3) and **I-E** (n = 10). None of the cancer patients in this sample produced the **I-I** pattern.

Table 1 Respiratory-swallow patterns during single liquid swallow in OP HNC patients.

	Respiratory Phase Pattern	
	E-E	Not E-E
Age-matched controls	**75%**	**25%**
Cancer	**35%**	**65%**

We also explored the relationship between respiratory-swallow phase pattern and Penetration-Aspiration Scale (PAS) scores. Of the 13 OP HNC patients (65%) presenting with the non-optimal phase patterns, 30% (n = 4) demonstrated varying degrees of penetration (PAS = 3-5) and 30% (n = 4) aspirated (PAS = 6-8). Patients with non-optimal phase patterns had statistically significantly greater (worse) PAS scores than patients with optimal phase patterns (p = 0.004). There were no differences between cancer treatment groups. Given the occurrence of non-optimal phase patterning and the higher PAS scores in these patients, we hypothesize that OP HNC patients may be swallowing at less than ideal and potentially hazardous moments in the respiratory cycle placing this group, or at least a subgroup of these patients, at increased risk of aspiration and physiologic swallowing impairment.[9] Further, the patients with non-optimal respiratory-swallow phase patterning also demonstrated higher (worse) scores relative to swallowing physiology. Patients with inconsistent phase patterns (some optimal, some non-optimal) across trials had significantly higher (worse) physiologic impairment indicated by higher Modified Barium Swallow Impairment Profile (MBSImP™) scores when compared to patients who produced consistent phase pattern across trials (T1: F = 3.597, p = 0.039; T2: F = 3.427, p = 0.045). The findings from this preliminary data set indicate that not only does the phase pattern play a role in the severity of swallowing dysfunction, but the consistency or stability of phase pattern may also impact severity of swallowing impairment. These preliminary data lead us to consider that respiratory-swallow phasing issues are important factors underlying chronic swallowing impairments and the presence of aspiration in patients with chronic dysphagia following OP HNC treatments.

Respiratory-Swallow Training Intervention: Preliminary Trial. In contrast to previous intervention approaches to swallowing rehabilitation, we designed a trial that targeted the coordinative relationships between respiration and swallowing directly using a recalibration approach that included visuallydirected, respiratory-swallow feedback. We minimized the coordinative requirements and trained consistent and optimal respiratory phase relationships shown to be ideal for airway protection and other mechanical aspects of liquid swallowing.

Our primary aims were three-fold: 1) use a novel, well-established hierarchy of motor skill acquisition,[62-64]and respiratory-related feedback protocol to train optimal respiratory-swallow coordinative phase patterns;[63-65] 2) determine the effect(s) of training on respiratory-swallow

phasing and physiologic swallowing measures; and 3) test the stability of the training effect one-month post-intervention. We hypothesized that more optimal respiratory-swallow coordination could be learned, sustained, and have a beneficial impact on swallowing function in chronically dysphagic patients treated for HNC. Our *current goal is to provide a context through RST that goes beyond improvements in swallow physiology alone and extends the clinical impact to achievement of increases in food and liquid options with minimized risk of laryngeal penetration and/or aspiration.*

Using visual feedback similar to our previous study, patients in our previous study were trained to initiate swallows during the expiratory phase of quiet breathing between mid-low lung volume and to continue to expire after swallowing. *Patients were instructed to not use any other previous swallowing maneuvers or compensations, nor did they demonstrate implementation of such.* Patient implementation of the optimal phase patterning increased significantly after the RST intervention ($p < 0.0001$) regardless of bolus viscosity (Table 2). That is, all patients learned to recalibrate their respiratory-swallow phasing and produced the optimal pattern (E-E).

Table 2 Optimal phase pattern rates by bolus viscosity and volume for all study patients.

Viscosity	Volume	Pre-intervention	Post-intervention	p-value
Thin liquid	5ml	53.3	93.3	<0.0001
	15ml	18.6	78.3	<0.0001
	Cup sip	27.1	86.7	<0.0001
Nectar	5ml	51.7	90.0	0.0001
	15ml	43.1	80.0	0.0009
	Cup sip	41.7	89.7	<0.0001
Honey	5ml	50.0	84.7	0.0013
	15ml	53.4	86.4	0.0018
	Cup sip	48.3	84.5	0.001

Specific Aim 2. Physiologic changes to the swallowing mechanism were demonstrated using one metric approach (MBSImP) in our preliminary study. The investigators explored the physiologic changes expected to occur following RST using innovative analysis methods that clarified the nature of these changes.

Computational Analysis of Swallowing Mechanics (CASM) is a multivariate morphometric analysis of coordinates mapping the functional anatomy of swallowing using modified barium swallow study (MBSS) imaging. As muscle groups underlie changes in coordinates, so then shape change characterizes swallowing mechanics (Figure 4).[22,86] CASM provides statistical analysis and visualization of covariant swallowing mechanics including hyolaryngeal movement, tongue base retraction, and pharyngeal contraction and shortening associated with any independent variable or outcome variable of interest.

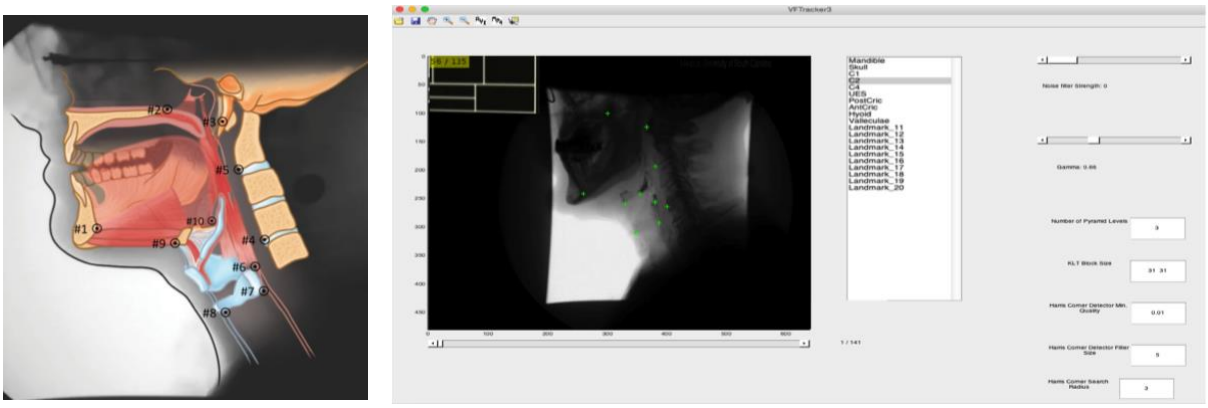


Figure 4 Example of landmark coordinates and automated tracker tool designed specifically for coordinate mapping of swallowing structures.

In a preliminary study using 192 pre- and post-RST swallows from 9 participants, CASM showed statistically significant differences in pharyngeal swallowing mechanics between pre- and post-RST groups (mean patient specific analysis, D = 3.33 ± 0.90, p <0.0001; aggregate data analysis, D = 0.80, p <0.0001). Regression analysis indicated that pharyngeal swallowing mechanics associated with RST was predictive of mechanics associated with laryngeal vestibular closure in the aggregate (R^2 = 0.25, p <0.0001), whereas pharyngeal swallowing mechanics associated with bolus changes from a large thin liquid bolus to a small thick bolus (pudding) was less predictive of mechanics associated with laryngeal vestibular closure in the aggregate (R^2 = 0.07, p <0.0001). Based on the demonstrated feasibility and outcome when using the morphometric analysis in this pilot study, *this approach will be a primary method to detail physiologic change associated with RST*.

The Modified Barium Swallow Impairment Profile© (MBSImP™). The MBSImP, which has been developed and tested over the past 10 years, is a valid and reliable standardized approach for the training and measurement of swallowing physiology, data collection, data analysis, and reporting results from a MBSS.[13,14,19] The objectives of the approach, including clinical validation of the physiologic metrics, achievement of inter-rater reliability, practicality in execution of the protocol and scoring, and linking to clinical action (intervention planning), have been translated to clinical practice throughout the US, Canada, Europe, and Asia.[13] This metric was used to quantify observations of changes in swallowing physiology that occurred following RST in our preliminary study. Achievement of optimal respiratory-swallow phase pattern was found to be associated with improvements in three MBSImP component scores: laryngeal vestibular closure (p = 0.0004), tongue base retraction (p <0.0001), and pharyngeal residue (p = 0.01). Significant improvements were also seen in PAS scores (p <0.0001). Relative to pre-intervention values, patients participating in one-month follow-up had: increased optimal phase patterning (p <0.0001); improved laryngeal vestibular closure (p = 0.01), tongue base retraction (p = 0.003), and pharyngeal residue (p = 0.006) MBSImP scores; and improved PAS scores (p <0.0001). These results led us to conclude that improvements in respiratory-swallow phase patterns can be trained using a systematic training protocol, and the respiratory phase-lung volume related visual feedback approach has favorable effects on airway protection and bolus clearance in patients with chronic dysphagia following HNC treatment.

Table 3 Pre- and post-intervention rates (respiratory-swallow phase pattern, PAS, and MBSImP), and average MDADI scores.

Outcome Measure	Pre-intervention	Post-intervention	*p*-value

Optimal respiratory-swallow phase	43.0	86.0	<0.0001
PAS ≥3	78.0	38.3	<0.0001
Lip closure ≥2	5.7	9.3	0.17
Tongue control during bolus hold	58.7	53.8	0.14
Bolus transport/lingual motion	37.3	50.2	0.07
Oral residue ≥2	77.3	76.4	0.80
Initiation of pharyngeal swallow	90.4	90.8	0.87
Soft palate elevation	19.8	31.0	0.03
Laryngeal elevation	76.6	70.8	0.43
Anterior hyoid excursion	94.7	90.5	0.10
Epiglottic movement	71.9	68.3	0.31
Laryngeal vestibular closure	78.2	55.5	0.0004
Pharyngeal stripping wave	59.3	67.6	0.27
Pharyngoesophageal segment opening	80.6	80.5	0.99
Tongue base retraction ≥2	96.0	88.6	<0.0001
Pharyngeal residue ≥2	96.1	88.4	0.01
MDADI (mean ± SD)	60.4 ± 14.8	65.3 ± 16.7	0.003

INNOVATION

Although the previously demonstrated positive effects of RST on swallowing physiology are promising, the clinical efficacy remains unknown until we determine if the training results in physiologic changes in of the oropharyngeal swallow leading to changes in what and how the patient is able to drink and eat. Thus, these questions and our preliminary results motivate the current study that will *not only test the clinical effect and durability of the training, but also serve to test the feasibility and added benefit of home practice using a refined approach for automated cueing and tracking respiratory-swallow phase and volume.*

As with our preliminary trial, our prediction is that these innovative intervention methods will not only improve swallowing physiology and quality-of-life, but will also result in functional improvements in every day eating and drinking in Veterans and non-Veterans with chronic, severe swallowing impairment that have been otherwise refractory to traditional swallowing interventions. The benefit of this training is that its simple, straightforward, and easy to learn methods facilitate patient compliance and maintenance of intervention effects include rationale for including or excluding certain populations – in particular vulnerable populations.

Inclusion of Women, Minorities and/or Children. *No participants will be excluded based on sex or race/ethnic origin.* Sex, ethnic, and racial information will be collected as part of the demographic information. Participants will be selected based on the inclusion criteria identified above.

Ethnicity (i.e., Hispanic/Latino, Non-Hispanic/Latino) will be recorded separately from race. All applicable racial categories (i.e., American Indian/Alaskan Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American, White) will be recorded for each participant by study personnel. All ethnic and racial totals will be reported, including specific categories for those Veterans and non-Veterans who report mixed racial descent (any combinations recorded by study personnel).

No outreach program to recruit minorities is planned because all individuals both within and outside of the VA healthcare system, regardless of race or ethnic origin, will be invited to participate. Every attempt will be made to recruit all racial and ethnic categories. No subjects will be excluded based on race or ethnicity. Though it is difficult to predict the sex, racial, and ethnic composition of the study sample, admission data reveals that there is a disproportionate composition between males and females for outpatient visits of Veterans and non-Veterans with OP HNC, with males have a substantially higher rate of outpatient visits. Historic data indicates men are twice as likely to have OP HNC compared to women.[4] Recent studies from three countries (United States, United Kingdom, and Romania) suggest there is a 2:1 ratio of males to females diagnosed with HNC and make up 80% Caucasian, 11% Black/African American, 4% Hispanic, and 5% other racial/ethnic categories.[122-124] It is anticipated that the sex, ethnic and racial mix of this study sample will roughly parallel these demographic data.

3.0 Objectives

Our previous trial in patients with severe and resistant dysphagia after cancer treatment and traditional swallowing therapy showed that targeting and recalibrating respiratory-swallow phase patterning directly through an innovative respiratory-swallow training (RST) method significantly improved aspects of swallowing *physiology* crucial for airway protection and clearance of ingested materials through the pharynx.[8,16] As with our preliminary trial, our prediction is that these innovative intervention methods will not only improve swallowing physiology and quality-of-life but will also result in significant functional improvements in every day eating and drinking in Veterans and non-Veterans with chronic, severe dysphagia that has been otherwise refractory to traditional swallowing intervention(s). The benefit of RST training is that it is a simple, straightforward method for patients to easily learn. . We are also using commercially available and simple to use recording and analysis hardware and software that can easily be expanded to mobile technology for more widespread application to the many thousands of patients with dysphagia consequent to HNC.

The goal of this current study is to extend our preliminary trial that yielded compelling physiologic changes with potential to improve the impact and durability of RST on *clinical outcomes* essential for eating, drinking, health, and quality-of-life.

Specific Aim 1. Directly train optimal respiratory-swallow phase patterning using RST and test the clinical efficacy and durability of the effect measured by change in physiologic metrics of the oropharyngeal swallow. Hypothesis: RST will improve oral intake status and liquid/food texture tolerances. Primary Outcome: Physiologic metrics of the oropharyngeal swallow as measured by the Modified Barium Swallow Impairment Profile (MBSImP) scores,[13,14,19]; Secondary Outcome: Functional Oral Intake Scale (FOIS).[17,18]

Specific Aim 2. Elaborate the intervention impact of RST on swallowing physiology and airway protection. Hypothesis: RST will improve tongue base retraction, laryngeal vestibular closure, pharyngeal shortening, and pharyngeal clearance. Primary Outcome Measures: MBSImP scores,[13,14,19] Penetration-Aspiration Scale scores,[20] and morphometric canonical variate measurements.

4.0 Resources and Personnel

Approved study personnel, including PI, clinical and research SLPs, and the Project Coordinator will be responsible for recruiting subjects, and consenting subjects; thus, they will have access to proteced health information. Additionally, the PI and clinicial/research SLP will also be responsible for administering study procedures.

The **PI**, Dr. Martin-Harris, will be responsible for and will supervise all aspects and coordination of all phases of the research project including the recruitment of study participants, completion of patient examinations, execution of the modified barium swallow studies (MBSSs), examination scoring, data entry, and data quality control. Furthermore, Dr. Martin-Harris will have primary responsibility for training study participants on the optimal respiratory-swallow pattern, conducting respiratory-swallow data analyses, preparation of manuscripts and scientific presentations, and dissemination of activities.

Dr. Kim, **Co-PI,** will assist in subject recruitment and monitoring respiratory function and will also assist interpretation of all study outcomes.

Research Assistant(s), will assist in participant accrual, data entry, database management, VA and IRB compliance and preliminary analysis. They will convert all MBSSs from TIMS DICOM System to .avi format for data analysis by the scoring SLPs and archive/backup the TIMS DICOM System study records week. They will coordinate and disseminate the examinations for scoring to the scoring SLPs. They will schedule pre- and post- intervention MBSS, pulmonary function screenings, and treatment intervention. They will maintain and update all subject files.

SLP Research Assistant, will assist the Research Assistants, including participant recruitment and scheduling, and IRB compliance, as well as SLP training and participant interventions. They will also assist in data analysis and interpretation.

Dr. McFarland, **Consultant**, will assume oversight for equipment calibration and respiratory data analyses.

VA SLPs, Anne Mary Lunkes and Rebecca Rogers, will assist in subject recruitment, completion of pre- and post-intervention MBSSs, and provide treatment intervention.

Scoring SLPs/Research Assistants, TBD, will be trained at the PI's lab at Northwestern University. Scoring SLPs will be responsible for completing all baseline and post-intervention scoring of swallowing physiology and respiratory patterning.

There is a **MOU** in place between Hines VA Hospital and Northwestern University for the PI, Dr. Martin-Harris for her 4/8ths effort.

5.0 Study Procedures

5.1 Study Design

Specific Aim 1 – Respiratory-Swallow Training (RST) In-Clinic.

Patient Sample. A total of 51 participants will be enrolled with the goal of 40 recruited if they meet inclusion criteria. Forty participants will be randomly assigned (1:1) to either RST (intervention arm) or no active treatment (control arm), which is considered standard of care in this patient population. Participants assigned to the control arm will cross-over after 4 weeks of no active treatment to undergo RST. All patients will participate in a pre-RST MBSS. The purpose of this pre-RST MBSS is to identify their baseline pre-RST respiratory-swallow phase patterning by specifying the respiratory phase and volume at time of swallowing initiation, assess swallowing physiology (MBSImP) and assess clinical swallowing status (FOIS). Participants will be included in the study if they are able to swallow at least one liquid consistency without visible tracheal residue (PAS ≤6) and without the use of a compensatory strategy or swallow maneuver. Participants will be excluded if they have known allergy or dietary restriction for contrast materials or liquids used during the MBSS or training, currently drinking greater than two drinks per day, severe COPD, are unable to swallow one liquid consistency without the use of a compensatory strategy or swallow maneuver without aspiration, or history of aspiration pneumonia within the past 12 months.

Clinician Examiners, Raters and Trainers. Expert speech-language pathologists (SLPs) will participate in this study to provide RST training, conduct the MBSSs, and perform blinded MBSImP and PAS scoring (i.e., without benefit of patient identifiers, randomization, clinical information, and performance during RST). The SLPs will not crossover study roles.

Spirometry. All Veteran and non-Veteran participants will undergo PFTs using spirometry performed by American Thoracic Society standards to stage COPD.[88] Participants will be characterized into Global Initiative for Obstructive Lung Disease (GOLD) spirometric groups on the basis of % predicted FEV1.[90] Any patient with severe stage COPD will be excluded from the study to protect against risk since experience in our clinic and previous study showed these patients could not consistently perform the proposed training tasks.

Modified Barium Swallowing Study (MBSS). MBSSs will be conducted in a routine fluoroscopy suite with a radiologist and examining SLP present. Fluoroscopy will be captured using a high-resolution imaging platform (TIMS 2000 SP DICOM System, Foresight Imaging, Chelmsford, MA). Participants will be seated upright and positioned in the lateral and anterior-posterior viewing planes. The visualization field will include the lips anteriorly, nasal cavity superiorly, cervical spinal column posteriorly, and the pharyngoesophageal segment (PES) inferiorly.[78,79,91-93] The MBSImP, a standardized, reliable, *reproducible*, and valid approach for the execution, assessment and interpretation of the MBSS, will be used to provide measures of swallowing physiology pre- and post-intervention. The MBSImP protocol includes 12 swallowing tasks via presentations of varying bolus consistencies, bolus volumes, and presentation methods. However, consistent with the MBSImP protocol, if a patient is unable to tolerate a swallow task because of safety (aspiration) concerns, that task is not included, and the component scores associated with the missing task are given the worst (highest) score in keeping with the statistical methods inherent in the tool. Standardized ready-to-use barium contrast (Varibar® E-Z-EM, 40% w/v, Bracco Inc.) will be presented. These swallowing tasks include: thin barium (two trials of 5ml via teaspoon, one cup sip, and sequential swallows from cup), nectar barium (one trial of 5ml via teaspoon, one cup sip, and sequential swallows from cup), thin-honey barium (one trial of 5ml via teaspoon), pudding barium (one trial of 5ml via teaspoon), a solid (one-half portion of a Lorna Doone shortbread cookie coated with 3ml pudding barium), and two additional tasks presented in the anterior-posterior viewing plane (one trial each of 5ml nectar and pudding barium). Participants will be asked to maintain a neutral

posture during the drinking tasks, since alteration of posture from the upright position may affect respiratory-swallow phasing.[93]

Respiratory-Swallow Phase Pattern Measures.

Respiratory Recording and Lung Volume Calibration. Respiratory movements of the rib cage (RC) and abdomen (AB) will be recorded using respiratory inductance plethysmography (RIP) (Inductotrace System; Ambulatory Monitoring, Inc., Ardsley, New York) coupled to a data acquisition system (BIPOAC Systems, Inc., Santa Barbara, CA, Model MP150).[95] The RC band will be placed around the rib cage at midsternal level, and the AB band will be placed around the abdomen below the lowest rib. The method developed by Banzett et al.[96] will be used to calibrate the summed RC and AB signals provided by the Inductotrace system to infer respiratory lung volume changes.[96] A standard ratio (RC to AB) of 2:1 will be used to weight the signals (originally recorded at equal gain) prior to being summed. The summed signal (in voltage) will then be calibrated using a known volume excursion to provide an estimate of lung volume. Each participant will be instructed to breathe in and out 3 times filling and emptying a Spirobag with a fixed 800 ml of air in the bag.

The optimal respiratory-swallow phase pattern targeted in RST is swallow initiation during the expiratory limb of the breathing cycle between mid-to-low quiet breathing lung volumes with resumption of expiration upon swallow completion. Respiratory data will be time synchronized with videofluoroscopic imaging data. Cycle detection and threshold algorithms programmed within AcqKnowledge software will be used to measure respiratory-swallow phase patterning for each subject during pre-intervention, post-intervention and follow-up.[95]

Functional Swallowing Measures.

Functional Oral Intake Scale (FOIS). The FOIS, a 7-point ordinal scale shown to associate with dysphagia severity, will be completed by the examining SLP to rate functional oral intake.[17] Level 1 implicates nothing by mouth, while a Level 7 indicates total oral diet without restrictions. Initial psychometric testing revealed high inter-rater reliability, validity, and sensitivity to change in oral intake status.[17] A clinical meaningful improvement on the FOIS has been defined as an improvement of ≥2 levels.[18]

Penetration-Aspiration Scale (PAS). The PAS is a widely used, standardized, valid, and reliable rating scale used to capture the presence and degree of penetration and aspiration during the MBSS exam.[20,97] The PAS is a multidimensional, 8-point ordinal scale. A score of 1 represents absence of aspiration or penetration, and a score of 8 represents the most severe degree of aspiration with no attempt made by the patient to react to or expectorate the aspirated material. A PAS score will be recorded by the scoring SLP for each swallowing task presented in the lateral viewing plane.

M.D. Anderson Dysphagia Inventory (MDADI). The MDADI is a self-administered questionnaire designed to evaluate the impact of dysphagia on the quality-of-life of patients with HNC.[98] The tool consists of 20 items across 4 subscales (global, emotional, functional, and physical). Each item is scored on a 5-point Likert scale. Two summary scores (global and composite) can be obtained. The composite score summarizes overall performing on 19 items as a weighted average of the subscales. Summary and subscale scores are normalized to range from 20 (extremely low-functioning) to 100 (high-functioning). A 10-point difference has been identified as a clinically meaningful difference in swallowing function.[99]

Performance Status Scale for Head & Neck Cancer Patients (PSS-HN). The PSS-HN is a scale administered by health professionals (e.g. physicians, speech-language pathologists, nurses, nutritionists) or other data managers (e.g. clerks, data managers) designed to evaluate the dysfunction and quality of life in patients with HNC.[131] Three subscales, (Normalcy of diet, Public Eating and Speech Intelligibility) each with 100 point rating scales and arranged in a hierarchically order from total incapacitation to normal functioning, are used to evaluate relevant parameters of functional status specifically for the HNC patient.

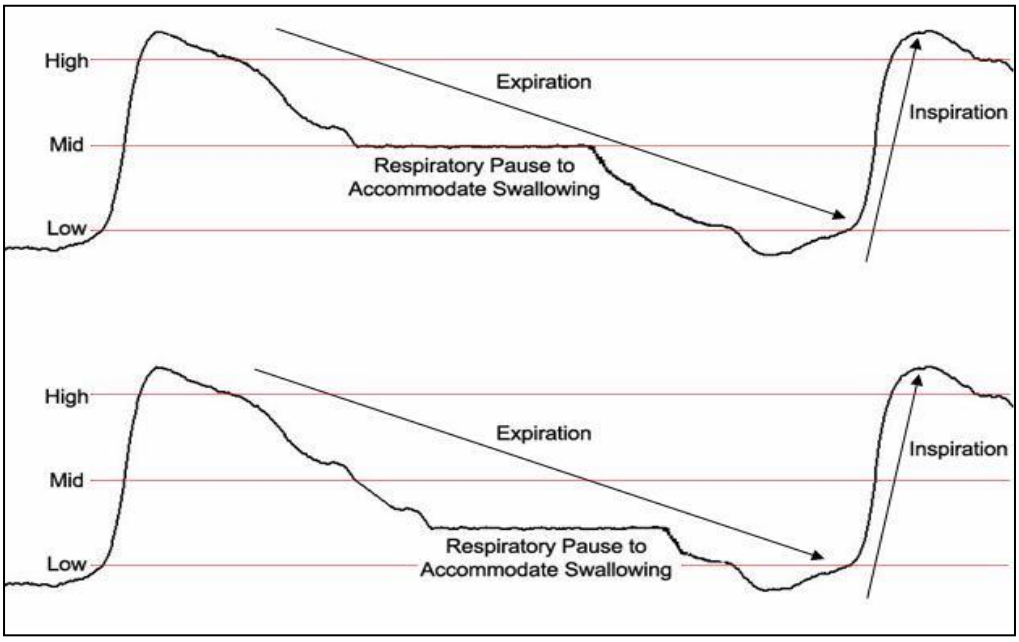
Respiratory-Swallow Training (RST). We will encourage optimal respiratory-swallow phase pattern in Veteran and non-Veteran participants using a protocol well supported by principles of motor learning and neural plasticity.[100-102] Participants will be given the option to complete RST at the Hines VA or Northwestern University.

Respiratory Tracking and Swallow Initiation Feedback. During the feedback portions of the training and using each participant's lung volume signals as described above, we will track and signal the appropriate moment of swallowing initiation using cycle detection and threshold algorithms programmed within *AcqKnowledge software* – an interactive software that allows for complex data acquisition, including simulation of model respiratory waveforms, respiratory cycle and threshold detection.[95] Respiration has a high degree of periodicity with relatively sharp-sloped waves and narrow peaks. During initial recordings with each participant, we will record at least two minutes of stable quiet breathing in the absence of experimental manipulation or other instrumentation. A peak detection algorithm steps through the respiratory waveforms (the cyclical changes in lung volume provided by the summed and calibrated Inductotrace signals) to find positive and negative peaks in a cycle and, from this, determines an average lung volume excursion from peak inspiration to peak expiration of each subject's quiet breathing lung volume change. From this, a threshold will be automatically determined as 50% of the expiratory lung volume change. During the training sessions in real time, the threshold detection algorithm will detect positive peaks in the respiratory volume change marking the end of inspiration and the beginning of expiration and will emit a visual and auditory feedback signal when 50% of the negative going lung volume change (expiration) has been reached. In this way, participants will be cued to produce their swallows beginning in the optimal range of lung volumes. These customizable programs to each participant's quiet breathing waveforms will track performance during RST. In this way, we can evaluate the achievement of criteria and performance for each of our training modules. In the RST modules, a visual and audio signal will be provided when the participant's tracked lung volume is within the optimal range and this feedback will eventually be removed as they move to the mastery module of training. A contact microphone (BIPOAC Systems, Inc., Santa Barbara, CA, Model TSD108) will be connected to the MP150 (in-clinic) units. The microphone signal will be used as a reliable indicator of the presence of swallows. The percentage of trials that each participant swallows within the target mid-to-low quiet breathing expiratory lung volume will be used to advance participants to subsequent modules of training.

AcqKnowledge software used during in-clinic RST is accessible via the desktop upon logging in to the computer. Templates are pre-programmed and once opened, the software only requires the participant to select the appropriate template and click "start" for data collection to begin. In addition to remote assistance by the treating speech-language pathologist (SLP), written and video, step-by-step tutorials will be provided to the participant for at home set-up, calibration, and training. Calibration is defined as 2 minutes of at-rest breathing and will be part of the step-

by-step guides provided to the participant. The participant must demonstrate independence in set-up and use of equipment and software within clinic under the supervision of the treating SLP prior to use at home. All signals acquired during RST sessions will be recorded on the laptop and analyzed offline.

Based on a well-established hierarchy of motor skill acquisition and consistent with our preliminary study,[100-102] the RST training protocol will be divided into 3 learning modules for a total of 21 goals: identification, acquisition (performance), and mastery (Figure 5). For each goal within the identification and acquisition modules, a minimum of 8 of 10 trials will be required for the goal to be met. A minimum of 9 of 10 trials will be required during the mastery module. If the participant does not meet the goal, reinstruction will be provided. Liquids will be standardized for all patients, but participants will be trained only on liquid consistencies with PAS scores ≤6 identified on the pre-RST MBSS.



During the Identification Module, samples from recordings of each participant's quite breathing cycle will be printed onto 8½" x 11" cards and used to train participants to accurately identify inspiratory and expiratory phases of the respiratory cycle. Their up-going trace will represent inspiration and down-going trace will represent expiration. Participants will be instructed to identify the mid-to-late portion of the expiratory phase of the respiratory cycle (latter ½ of the expiratory phase) (Figure 5).

Figure 6. Cue cards for training participants on lung volume and phase

Once participants can identify the phases of respiration during rest breathing and the target respiratory-swallow phase pattern (swallow initiation during expiration at mid-to-low lung volume with resumption of respiration in the expiratory limb) on the printed tracings, they will learn to identify these targets during actual breathing using the Inductotrace/MP150 system (described above). Participants will progress from demonstrating the optimal phase pattern during respiratory-swallow recording with visually assisted feedback to independently producing the targeted respiratory-swallow phase pattern. The training SLP will monitor the participant's respiratory-swallow phase patterns on the visual monitor, but the participant will not be permitted to view their performance in these later stages of training.

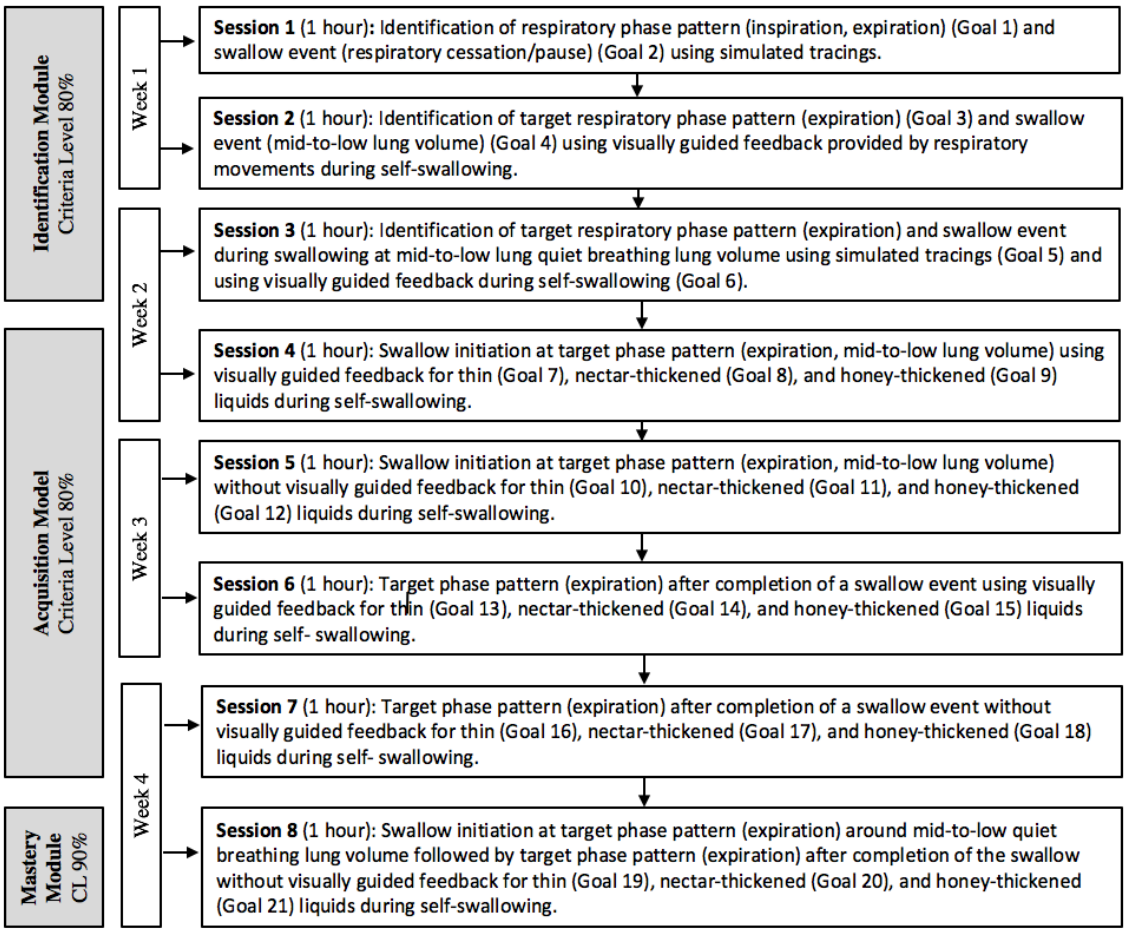


Figure 6 Depiction of goals for each training module and intervention timeline.

Each RST session lasts approximately one hour, with two sessions completed weekly. Based on previous clinical trial that demonstrated an average of six RST sessions to reach mastery.[8]

Thus, it is expected for participants to complete all goals and reach mastery within 4 weeks of RST (see Figure 6).

During the in-clinic RST training sessions, the computer videorecorder will be taking front-facing video of each patient's training sessions. These recordings will be compared to the physiologic signals received via the BIOPAC to better understand/learn/become informed about how the patients learn during intervention training sessions. These recordings will also be used for teaching purposes for study staff.

At the completion of RST, the participants will be asked to complete the NASA Workload Index, a 7-point scale which estimates the participant's perceived effort in completing the training.

Data Management, Analysis, and Reporting System Overview. Study related data are stored on VA approved computers and the VA research shared drive (S:), including de-identified study-related data (videofluoroscopic images, respiratory traces). Identifiable data (VASA), including demographic data, questionnaire responses, and treatment results are stored on the VA REDCap behind the VA firewall. De-identified videofluoroscopic images and respiratory tracings will be transported via VA issued encrypted external hard drives for analysis by specially trained analytic experts to the PI's lab at Northwestern University, and then stored on and analyzed from a password protected, dedicated server. This server is managed by Northwestern Information Technology and accessible to only approved study personnel. We will update the data transfer and storage operations as we are provided additional guidance and requirements from the ORO, Office of Research Oversight.

Power and Sample Size Justification. A total of 40 subjects will be randomized 1:1 using stratified block randomization to either Respiratory-Swallow Training (RST, intervention arm) or no control arm, where the participants serve as their own control and then cross over into the intervention group. Strata will be defined by treatment type. Data obtained will be used to evaluate clinical efficacy and durability. The primary outcome measure will be MBSImP physiologic function metrics of the oropharyngeal swallow. Our previous preliminary trial that tested the safety and efficacy of the behavioral swallowing intervention in a small sample of Veteran and non-Veteran patient with head and neck cancer showed a positive change in the physiologic outcomes. Assuming a similar treatment effect in the current trial, 20 patients in each arm provides 95% power to detect a change in MBSImP physiologic function in at least one of three MBSImP components (laryngeal vestibular closure, tongue base retraction, and pharyngeal residue) based on a Cochran-Mantel-Haenszel test with two-sided $\alpha = 0.025$. Although dropouts have been rare in our prior studies, we nonetheless inflated our sample size by 10% to adjust for unanticipated attrition, and plan to recruit 20 participants per arm for a total sample size of 40 subjects to guarantee at least 80% power. Thus, our final sample size will be a total of 40 participants.

Analysis Populations. Participants in the intervention arm who withdraw consent prior to completing their first training session will be replaced. Those who have completed at least one RST session will contribute to the intent-to-treat (ITT) population. Participants in the control arm who withdraw consent prior to visit 1 will be replaced. All others in the control arm will contribute to the ITT population. The per-protocol population will be composed of participants who complete both visit 0 and visit 1 evaluations (both arms), and who complete all required training sessions (intervention arm). Efficacy will be evaluated based on the ITT population. Participants in the ITT population who withdraw prior to endpoint evaluation at 6-weeks will be treated as failures (no improvement) in the ITT analysis. The safety population is defined as all participants

who partake in any component of the proposed study and will be based on the intervention actually received.

Specific Aim 2 Design and Methods – Intervention Impact of RST on Swallowing Physiology. We will elaborate the treatment impact of RST by detailing the physiological, airway protective and morphometric changes that occur from the intervention. We will use MBSImP, PAS (described for Aim 1), and CASM.

MBSImP Scores. The MBSImP scores will provide a primary outcome measure of swallowing impairment. The MBSImP is a validated and reliable scoring system for the quantification of swallowing impairment from MBSS recordings.[13,14,19] This tool has an ordinal scoring schema that permits quantification of oral, pharyngeal, and esophageal components of swallowing physiology. The operational definitions for the component scores represent a unique and unambiguous observation of structural movement and bolus flow. Seventeen physiologic components will be scored on a previously validated, rank order scale from least to most impaired. The scale for components ranges from 0-2 to 0-4 for each physiologic component.[14] Years of field testing shows scores of 0 or 1 for the physiologic components of lip closure, oral residue, pharyngeal residue, and tongue base retraction are considered to be within normal limits.[112] For all other components, scores greater than 0 represent some level of impairment. Two methods will be used for MBSImP scoring: swallow-by-swallow (SS) and overall impression (OI). SS scoring assigns an MBSImP score for all applicable physiologic components for each of the 12 swallowing tasks given during the protocol. SS cores will be recorded for each participant. The highest (worst) score will be given during SS scoring when the participant's condition or performance on a previous swallowing task results in the withholding of a subsequent swallowing task for safety concerns.[9,52] Additionally, missing data in SS interpretation will result if a participant refuses a swallowing task.[52] As such, we will only include scores for swallowing tasks that are actually presented.

Computational Analysis of Swallowing Mechanics (CASM). Annotators who meet reliability criterion[109] will use a MATLAB (version R2015a, 8.5.0.197613, 64-bit) semi-automated tracker tool designed specifically for coordinate mapping of swallowing structures.[113,114] Coordinates are annotated in all frames during oral transit and pharyngeal swallowing. The tracker tool produces an .mp4 video file of annotated landmarks for review and a .csv file of coordinates with a unique identifier assigned to each row of coordinates. Once video files are reviewed by an expert head and neck anatomist (Co-Investigator, WP), coordinates for all swallows are concatenated and a second file of variables that match unique identifiers is compiled to include group (pre-intervention vs. post-intervention), swallowing domain (oral vs. pharyngeal), bolus volume (large [cup] vs. small [5ml]), bolus viscosity (thin vs. thick), sex (male vs. female), penetration-aspiration status (within functional limits [PAS = 1,2] vs. penetration-aspiration PAS = 3-8]), and MBSImP component scores. These files are uploaded into MorphoJ integrated software for analysis.[115]

Statistical Considerations. The primary endpoints for Specific Aim 2 are MBSImP scores, PAS scores, and morphometric canonical variate scores for participants enrolled in the clinical trial (Specific Aim 1). MBSImP component scores and PAS will be dichotomized as impaired versus not-impaired as previously described.[8] [Analyses of impairment rates, MBSImP composite (oral and pharyngeal total) scores, and time course data will be conducted using ANACOVA, GEEs

and Rao-Scott Chi-square tests as described in Specific Aim 1. To evaluate rater reliability for MBSImP and PAS measures, 20% of MBSSs will be re-scored by each rater. Intra-class correlations coefficients will be calculated to measure inter- and intra-rater reliability.

CASM will be applied to pre- and post-RST MBSSs to determine and visualize improvements in covariant swallowing mechanics resulting from RST and determine which of these treatments is predictive of swallowing improvement as measured by MBSImP and PAS scores. Following a Procrustes fit of coordinates to control for differences in size and image rotation, a canonical variate analysis with post hoc discriminant function analyses[21,22] will be performed to determine statistical differences in pre- and post-RST swallowing mechanics by phase of swallowing for each subject and the aggregate. Eigenvectors will be used to visualize differences in covariant swallowing associated with treatment effect. Morphometric regression analysis will be used to evaluate respiratory-swallow training as a predictor of improved swallowing outcomes as measured by MBSImP and PAS scores.

Potential Risks

Radiation Exposure. The MBSS is a videofluoroscopic examination that includes minimal exposure to radiation. Data collected during the study will be used solely for research. The amount of radiation is minimized because fluoroscopy requires no film and radiation is kept to a minimum by tight coning of the x-ray beam to include only the superior structures of the upper aerodigestive tract. A lead apron will be used to protect reproductive organs from radiation scatter in all participants. Involvement of a trained radiologist and use of dedicated fluoroscopy equipment are likely to minimize radiation exposure. The radiation of a swallow study is approximately 40 mrem of radiation for approximately 5 minutes of exposure, which is 0.8% of the annual maximum amount permitted by the Food and Drug Administration (FDA) for radioactive drug research.[125] A fluoroscopy timer will alert the examiners if and when the 5-minute time limit is met, and the study will be subsequently stopped at this point. The average duration for each participant during the MBSS, including set-up and positioning, is approximately 30 minutes. Published data from Dr. Martin-Harris' lab demonstrated the standardized MBSImP protocol increases efficiency and speed for MBSS completion.[125] It takes an average of 2.89 minutes of fluoroscopy exposure (95% confidence interval (CI) of 2.80 to 2.97 minutes), which is well under the reported 3-5 minutes encountered in an upper gastrointestinal series.[125] Interpolating from the relationship Moro et al. (2006) published, the mean of 170 seconds relates to an effective dose of approximately 0.44 mSv, while the mean in the literature of 240 seconds relates to an effective dose of approximately 0.67 mSv.[125,126] On average, the use of a standardized protocol decreased effective dose by 0.23 mSv.[125]

Aspiration. Aspiration occurs when ingested materials enter the airway below the level of the vocal folds. Because these participants have known dysphagia, there is a risk of aspiration occurring during the MBSS.[127] If the barium is aspirated, it is not expected to cause severe lung injury due to its relatively non-irritant matter. However, acute inflammation, and even death, has been reported, despite whether it was attributed to either high or low-density preparations of barium. Participation in this investigation will *not increase the risk* of aspiration. If a swallowing impairment is observed during the examination, a referral to the participant's attending physician will be made.

The risk of aspiration will be clearly stated on the informed consent and during the consenting process. Despite this potential, our collaborative speech pathology and medical teams plan to institute measures that optimize the participant's safety. These include: 1) inclusion of

participants with no history of aspiration pneumonia during the past 12 months; and 2) liquid consistencies that result in PAS scores of ≥7 during the baseline MBSS will not be given during intervention portion of the study.

Participants are not required to have participated in previous traditional swallowing therapy. If they have participated in traditional swallow therapy, they must be 6 months post last treatment session and still have swallow disorders.[127] Consistent with our past trial that showed no adverse events, participants will be encouraged to swallow naturally without employing any previously instructed maneuvers or strategies. If the participant cannot swallow without a maneuver or strategy and meet inclusion criteria, he/she will be excluded from the study.

Respiratory Monitoring and Training. Respiratory monitoring and phase training will be accomplished using Inductotrace (Ambulatory Monitoring, Inc.) data.[128] There are no known risks associated with the placement of loose elastic bands (Inductobands, Ambulatory Monitoring, Inc.)[128] around participants' chests and abdomens while data are collected on a data acquisition system (BIPOAC Systems, Inc., Santa Barbara, CA, Model MP150). There is the unlikely potential, though inconsistent with our preliminary observations, that manipulation of respiratory phase surrounding the swallow may make the participant's swallowing worse, either during the intervention or the post-intervention MBSS. If there is any clinical indication that the participant is experiencing coughing or discomfort with the task, the task will be discontinued, and the participant will be excluded from further treatment. No alternative procedures or treatments are available.

Patient Perceived Effort Associated with Training. All patients will be asked to complete the NASA Task Load Index survey. This survey contains 6 task load domains and asks the participant to indicate the mental, physical and temporal demand, performance success, effort and frustrations levels associated with the training using a visual analog rating scale.

Adequacy of Protection from Risk

Recruitment and Informed Consent

Designated approved study personnel will obtain informed consent, including PI, Study Coordinator, Research SLP (speech-language pathology), and clinical SLPs. All potential participants (volunteers) will be explained the study procedures, potential risks and benefits by the consenting study personnel. All eligible participants, regardless of race, ethnic origin, or sex, will be asked to participate as long as authorization and informed consent can be obtained. Any participant may withdraw from the study at any time without penalty or prejudice for treatment.

Protection against Risk

Recruitment and Informed Consent. Potential participant volunteers will be identified by the following methods of participant recruitment, all approved by the VA Institutional Review Board (IRB): 1) follow-up medical visits, such as the otolaryngology-head and neck clinics at the Hines VAMC, Loyola University Medical Center; 2) announcement of the study in the VA patient bulletins and monitors; 3) community based outpatient clinics (CBOCs); 4) review of patient medical charts (CPRS) at HVA to find patients that match the diagnosis of oropharyngeal cancer and dysphagia diagnoses and mailing informational letters to these potential patients; and 5) posting of recruitment flyers at Jesse Brown VA, Loyola University Medical Center, Northwestern Memorial Hospital, and Northwestern Medicine Healthcare Partners.

All potential eligible participant will sign a study consent form approved by the VA's IRB. The potential risks as described above will be clearly stated on the informed consent and during the consenting process (see above in Potential Risks). Veterans and non-Veterans who express interest in participating will be explained the study protocol, presented with a consent form to sign and date, and be given an opportunity to have any questions regarding the procedure or the research study addressed and answered to their satisfaction. Additionally, non-Veteran participants will sign a Notice of Privacy Practices (NoPP) form which will be sent to the appropriate privacy officer.

The study investigators will not treat the socially/economically disadvantaged participant volunteers differently from other participants in the study. This includes all study personnel ensuring there are no coercive behaviors undertaken during the study period. For this study, study personnel will not be obtaining data regarding the veterans' social and/or economic status. Therefore, study-related complications are not anticipated, and all participants will be treated identically and equally.

Radiation. This research study involves exposure to a small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 3.0 mSv each year.[125] The effective does from this study is about 0.44 mSv, which is estimated from a 3-minute exposure during a videofluoroscopic study.[125] This is equal to the average radiation all Americans receive in two months from natural background radiation, such as naturally occurring radioactivity in the soil.[126] Any risk from this small amount of radiation is too small to be measured directly and is small when compared to other every day risks.

Care should be taken to reduce the influence of all possible factors not related to improved diagnostic yield according to the as low as reasonably achievable (ALARA) principle.[125] This means that the radiation exposures resulting from the practice must be reduced to the lowest level possible considering the cost of such a reduction in dose. The amount of radiation each participant will be exposed to is relatively small since the X-ray machine is only turned on while he/she swallows. Although such doses of radiation may be potentially harmful, the risks are so small that they are difficult to measure. The potential long-term risk from the radiation doses is uncertain, but the risk to each participant is estimated to be slight. The barium that allows the liquid and food to show up on X-ray is not harmful and will stay in the body only for a relatively short period of time.

Examining SLPs will wear lead-lined, radiation shielding aprons around their chest and torso. SLPs will also wear lead-lined thyroid shields. A radiation dosimeter will also be worn to measure exposure levels that are monitored by the facility. A lead apron skirt will be provided to each participant to protect his/her reproductive organs from radiation scatter.

Female participants will not be allowed to participate if they are pregnant or if there is any possibility of being pregnant.

Based on the inclusion/exclusion criteria described above, potential Veteran and non-Veteran volunteers will be asked to participate in the study only after informed consent is obtained.

Termination. If a participant does not meet a single target goal following 3 sessions, the RST intervention will cease, and data will contribute to the intention-to-treat analysis as outlined in the research plan.

Non-participation. Each participant has the alternative to not participate in the study. If the participant chooses not to participate, it will not affect their current and/or future medical care or any benefits to which they are entitled.

Human Subjects Involvement and Characteristics

A total of 51 Veteran and non-Veteran volunteers will be recruited.

Inclusion of Women, Minorities and/or Children. *No participants will be excluded based on sex or race/ethnic origin.* Sex, ethnic, and racial information will be collected as part of the demographic information. Participants will be selected based on the inclusion criteria identified above.

Ethnicity (i.e., Hispanic/Latino, Non-Hispanic/Latino) will be recorded separately from race. All applicable racial categories (i.e., American Indian/Alaskan Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American, White) will be recorded for each participant by study personnel. All ethnic and racial totals will be reported, including specific categories for those participants who report mixed racial descent (any combinations recorded by study personnel). No outreach program to recruit minorities is planned because all eligible individuals, regardless of race or ethnic origin, will be invited to participate. Historic data indicates men are twice as likely to have OP HNC compared to women.[4] Recent studies from three countries (United States, United Kingdom, and Romania) suggest there is a 2:1 ratio of males to females diagnosed with HNC and make up 80% Caucasian, 11% Black/African American, 4% Hispanic, and 5% other racial/ethnic categories.[122-124] It is anticipated that the sex, ethnic and racial mix of this study sample will roughly parallel these demographic data.

ANTICIPATED TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex**		
	Females	**Males**	**Total**
Hispanic or Latino	0	3	3
Not Hispanic or Latino	2	35	37
Ethnic Category: Total of All Subjects *	2	38	40
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	6	6

White	2	32	34
Racial Categories: Total of All Subjects *	2	38	40

Children will not be eligible for enrollment in this project. Children do not commonly present with HNC. Further, respiratory-swallow phase patterns and training have not been systematically studied in dysphagic children. This supports their exclusion from this project that is based on preliminary data acquired in adults.

5.2 Recruitment Methods

A total of 51 Veteran and non-Veteran volunteers will be enrolled with the goal of 40 meeting inclusion criteria. Potential participant volunteers will be identified by the following methods of participant recruitment, all approved by the VA Institutional Review Board (IRB): 1) follow-up medical visits, particularly the otolaryngology-head and neck clinics; 2) announcement of the study in the VA patient bulletins and monitors (Appendix); 3) community-based outpatient clinics (CBOCs); and 4) review of patient medical charts (CPRS) at Hines VA to find patients that match the diagnosis of oropharyngeal cancer and dysphagia diagnoses (letters will be mailed to these potential patients with information in regards to the study. Also included will be a brief survey, along with a postage paid return envelope, which allows the patients to indicate if interested in participating or not); 5) posting of recruitment flyers at Jesse Brown VA, Loyola University Medical Center, Northwestern Memorial Hospital, University of Chicago Medical Center, and Northwestern Medicine Healthcare Partners.

Participants will be compensated for their participation in the study to assist support of their time and travel. Participants will receive $40 for each MBSS and $30 for each RST session. For participants randomized to immediately undergo the intervention, they have the potential maximum of earning $440. The participants randomized to the control group will undergo one additional MBSS procedure immediately prior to their cross-over to the intervention arm, for a potential maximum of $480. Participant payment will be made according to the current local fiscal office guidance and processes. Planned payments will be approved by appropriate study personnel for disbursement according to this schedule:

- Payment 1: after first study visit to determine eligibility for intervention (which includes first MBSS)
- Payment 2: after week 1 of intervention
- Payment 3: after week 2 of intervention
- Payment 4: after week 3 of intervention
- Payment 5: after week 4 (final) of intervention
- Payment 6: after post-intervention study procedures
- Payment 7: after 1-month follow-up study procedures
- Payment 8: after 3-months follow-up study procedures
- Payment 9: after 6-months follow-up study procedures
- One additional payment will be made to those participants assigned to the control arm. This payment will be dispersed immediately after the MBSS procedure immediately prior to starting RST treatment.

5.3 Informed Consent Procedures

Informed consent will be otained by all trained study personnel, including PI, Study Coordinator and SLP, using a VA IRB approved informed consent form. All participants will be explained the study procedures, potential risks, and benefits by consenting personnel.

5.4 Inclusion/Exclusion Criteria

Inclusion and Exclusion Criteria. ***Entry inclusion criteria:*** 1) ≥21 years of age; 2) signed informed consent; 3) at least 6 months post head and neck cancer treatment for oral cancer, oropharyngeal cancer, laryngeal cancer, or hypopharyngeal cancer; 4) consumes ≤2 alcoholic drinks daily and 5) English speaking. ***Entry exclusion criteria:*** 1) known allergy or dietary restriction for materials used during the exam; 2) severe chronic obstructive pulmonary disease (COPD); and 3) recent history of aspiration pneumonia (past 12 months). ***Intervention inclusion criteria:*** 1) pass Montreal Cognitive Assessment (MoCA) (≥26)[87]. ***Intervention exclusion criteria****:* 1) fails MoCA (<26); and 2) inability to tolerate at least one liquid consistency (PAS ≥7). Women of child-bearing age will be screened via questionnaire in accordance with VA Medical Center policy precautions. Women who are pregnant will be excluded from this trial given that five MBSSs are required and the risk of any radiation to the fetus exceeds the potential benefit of this study. Men will also be counseled regarding the risks of radiation exposure to their reproductive organs. Hospital policy precautions for radiation safety will be applied. Informed consent will be obtained by the examining speech-language pathologist (SLP). The study procedures, potential risks, and benefits will be explained to all participants, and caregivers when appropriate, by the examining SLP. It will be explained that participation in the study will not have any impact on the quality of his/her present and/or future care as a patient. Further, if a participant chooses not to participate or drops out of the study at any time, there will be no consequences of this action. There will be no additional study sites involved with this research.

Cognitive Criteria. There exists the possibility that study volunteers may experience co-existing cognitive problems that preclude the learning of a new motor task. Participants will be screened immediately following consent (prior to the baseline modified barium swallow study, MBSS) for cognitive impairment using the MoCA[87] – a cognitive screening test designed to assist health professionals for detection of mild cognitive impairment. The standardized procedure covers the following cognitive domains: visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation. Scores for each domain are summed and a total score is obtained that can be adjusted for educational level. MoCA scores <26 suggest cognitive impairment. Thus, participants with a total MoCA score of 25 or less will be excluded from further participation.

Pulmonary Criteria. There is some evidence indicating that pulmonary function status may impact respiratory-swallow phasing and swallowing impairment,[116-119] and many patients with HNC present with varying degrees of disordered pulmonary function. An important covariate of upper airway function is lower airway disease. Since smoking is a risk factor for both HNC and COPD, a number of patients have both diagnoses. Although we did not find an association between pulmonary function and the ability to train in our preliminary study, it remains unclear whether expiratory airflow obstruction changes expiratory time constants and potentially impacts swallowing timing or physiology. Consequently, all participants will be screened for the presence of pulmonary disease if they meet the cognitive screening criteria prior to the baseline MBSS. Pulmonary screening will include spirometry performed by a licensed pulmonary function technician and reviewed for compliance with the American Thoracic Society standards.[117,118] These data will permit further study of the impact of pulmonary function on respiratory-swallow

phasing and the outcome variables in the proposed trial. The best single objective measurement of COPD severity is the forced expiratory volume in 1 second (FEV1).[120,121] FEV1 will be analyzed as a covariate in analyses. Patients with severe COPD (FEV1<50% predicted) will be excluded from further study and will not receive the baseline MBSS.

5.5 Study Evaluations

All potential participants will be screened for eligibilty as described above for inclusion/exclusion criteria using medical charts and collection of general history information related to cancer diagnosis, treatment, dysphagia treatment, and current swallowing problems. Once deemed eligible, the participants will then undergo evaluation to determine eligibility for RST that includes an MBSS with simultaneous respiratory recordings, completion of cognitive screen (MoCA) (Appendix), and questionnaire (MDADI) (Appendix).

If participants meet eligibilityty criteria to participate in RST as outlined above, each participant will undergo in-clinic RST sessions with an SLP. After the RST is completed, participants will undergo an MBSS with simultaneous recordings, completion of MDADI, and information about oral intake/diet tolerance (FOIS) (Appendix) for post-treatment measurements. Further, the participant will undergo these same procedures at 1-month, 3-months, and 6-months after experimental portion is completed.

5.6 Data Analysis

Statistical Considerations. Specific Aim 1: Trial design. The primary objective of Specific Aim 1 is to demonstrate the clinical efficacy and durability of RST in participants with dysphagia with a history of OP HNC. A total of 88 participants will be [recruited and randomly assigned 1:1to either RST (intervention arm) or control arm, given the crossover design of the study.. We will use a stratified permuted block randomization scheme with random block sizes of 2 or 4 to balance important prognostic variables across the two trial arms. There will be 5 strata defined by treatment modality (radiation therapy alone, surgery alone, chemo-radiation therapy, surgery + post-operative radiation therapy, surgery + post-operative radiation therapy + adjuvant chemotherapy). The study statistician will maintain randomization lists and be responsible for randomizing consented participants. The study schema is depicted in Figure 8. The control arm will cross over to RST after visit 1 following data collection for evaluation of clinical efficacy.

Endpoint Definitions and Analysis Plans. The primary efficacy endpoint for Aim 1 is oropharyngeal swallowing physiologic metrics (MBSImP) and evaluated at: visit 0, defined as pre-RST for intervention subjects, and baseline for control subjects; and visit 1, defined as post-RST for intervention subjects or 4 weeks post-baseline evaluation for control subjects. We will compare changes in MBSImP physiologic function metrics in patients randomized to intervention versus control. Change in MBSImP physiologic function metrics will be compared using one-way analysis of covariance (ANACOVA), with trial arm as the main effect and adjustment for stratification variable of treatment type. If approximate normality is not satisfied, we will use generalized estimating equations (GEEs) with an identity link function and robust standard error estimator. Furthermore, the regression framework of GEEs will accommodate adjustment for stratification factor. Durability of response will be evaluated using ANACOVA or GEEs as described by comparing post-RST MBSImP physiologic function metrics to those obtained at 1-,3-, and 6-month follow-up visits. We will further evaluate the modifying and confounding effects of sex, age, smoking status, COPD status, and pulmonary function.

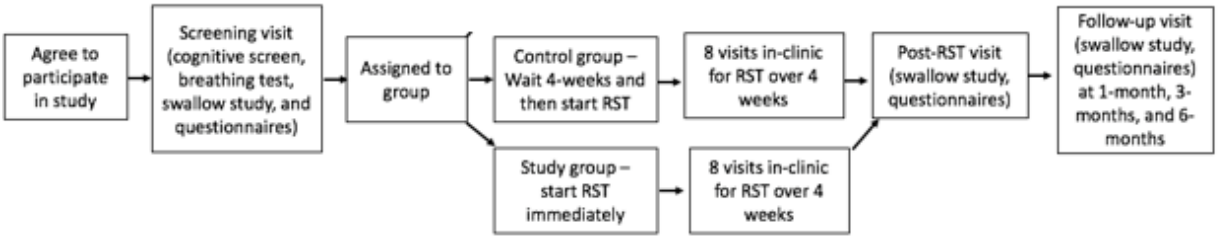


Figure 7 Study schema for current proposal.

Further, response durability will be evaluated using FOIS measures obtained at 1-, 3- and 6-months post-RST. Because control subjects cross over to RST at visit 1, FOIS measures collected at visit 1 for control subjects additionally will serve as their pre-RST FOIS measures (Figure 7). Clinical efficacy will be evaluated by comparing change in FOIS ($\Delta FOIS = FOIS_{visit1} - FOIS_{visit0}$) in patients randomized to intervention versus control. ΔFOIS comparisons will be conducted using one-way analysis of covariance (ANACOVA), with trial arm as the main effect and adjustment for stratification variables. If approximate normality is not satisfied, we will use generalized estimating equations (GEEs) with an identity link function and robust standard error estimator, which accommodates valid inference in the presence of misspecification.[103,104] Furthermore, the regression framework of GEEs will accommodate adjustment for stratification factors. Durability of response will be evaluated using ANACOVA or GEEs as described by comparing post-RST FOIS measurements to those obtained at the 1-, 3- and 6-months follow-up visits. In addition, we will model longitudinally collected FOIS scores as a function of time (measured as a categorical variable) using GEEs, with additional independent variables for stratification factors and pre-RST FOIS included in all models. Comparisons at individual time points will be performed using model-based linear contrasts with inference based on associated two-sided generalized score tests. We will further evaluate the modifying and confounding effects of sex, age, smoking status, COPD status, and pulmonary function. Secondary endpoints include MDADI summary scores, and respiratory-swallow phase patterns (binary measure classified as optimal versus non-optimal) collected at all time points. Analysis of MDADI scores will follow the approach used to analyze FOIS scores. Comparisons between visits 0 and 1 respiratory-swallow phase patterns will be performed using a Rao-Scott chi-square test, an approach that accommodates comparisons of proportions from paired data with Mantel-Haenszel-type adjustments for stratification factors.[105] GEE models of respiratory-swallow phase patterns will be similar to those described for FOIS measures but using instead a

logit or probit link function as appropriate for binary endpoints. Results for all endpoints will be summarized separately for males and females to assess differences by patient sex.

Statistical Considerations: Specific Aim 2 Design and Methods – Intervention Impact of RST on Swallowing Physiology. We will elaborate the treatment impact of RST by detailing the physiological, airway protective and morphometric changes that occur from the intervention. We will use MBSImP, PAS (described for Aim 1), and CASM.

MBSImP Scores. The MBSImP scores will provide a primary outcome measure of swallowing impairment. The MBSImP is a validated and reliable scoring system for the quantification of swallowing impairment from MBSS recordings.[13,14,19] This tool has an ordinal scoring schema that permits quantification of oral, pharyngeal, and esophageal components of swallowing physiology. The operational definitions for the component scores represent a unique and unambiguous observation of structural movement and bolus flow. Seventeen physiologic components will be scored on a previously validated, rank order scale from least to most impaired. The scale for components ranges from 0-2 to 0-4 for each physiologic component.[14] Years of field testing shows scores of 0 or 1 for the physiologic components of lip closure, oral residue, pharyngeal residue, and tongue base retraction are considered to be within normal limits.[112] For all other components, scores greater than 0 represent some level of impairment. Two methods will be used for MBSImP scoring: swallow-by-swallow (SS) and overall impression (OI). SS scoring assigns an MBSImP score for all applicable physiologic components for each of the 12 swallowing tasks given during the protocol. SS cores will be recorded for each participant. The highest (worst) score will be given during SS scoring when the participant's condition or performance on a previous swallowing task results in the withholding of a subsequent swallowing task for safety concerns.[9,52] Additionally, missing data in SS interpretation will result if a participant refuses a swallowing task.[52] As such, we will only include scores for swallowing tasks that are actually presented.

Computational Analysis of Swallowing Mechanics (CASM). Annotators who meet reliability criterion[109] will use a MATLAB (version R2015a, 8.5.0.197613, 64-bit) semi-automated tracker tool designed specifically for coordinate mapping of swallowing structures.[113,114] Coordinates are annotated in all frames during oral transit and pharyngeal swallowing. The tracker tool produces an .mp4 video file of annotated landmarks for review and a .csv file of coordinates with a unique identifier assigned to each row of coordinates. Once video files are reviewed by an expert head and neck anatomist (Co-Investigator, WP), coordinates for all swallows are concatenated and a second file of variables that match unique identifiers is compiled to include group (pre-intervention vs. post-intervention), swallowing domain (oral vs. pharyngeal), bolus volume (large [cup] vs. small [5ml]), bolus viscosity (thin vs. thick), sex (male vs. female), penetration-aspiration status (within functional limits [PAS = 1,2] vs. penetration-aspiration PAS = 3-8]), and MBSImP component scores. These files are uploaded into MorphoJ integrated software for analysis.[115]

Statistical Considerations. The primary endpoints for Specific Aim 2 are MBSImP scores, PAS scores, and morphometric canonical variate scores for participants enrolled in the clinical trial (Specific Aim 1). MBSImP component scores and PAS will be dichotomized as impaired versus not-impaired as previously described.[8] Analyses of impairment rates, MBSImP composite (oral and pharyngeal total) scores, and time course data will be conducted using ANACOVA, GEEs and Rao-Scott Chi-square tests as described in Specific Aim 1. To evaluate rater reliability for

MBSImP and PAS measures, 20% of MBSSs will be re-scored by each rater. Intra-class correlations coefficients will be calculated to measure inter- and intra-rater reliability.

CASM will be applied to pre- and post-RST MBSSs to determine and visualize improvements in covariant swallowing mechanics resulting from RST and determine which of these treatments is predictive of swallowing improvement as measured by MBSImP and PAS scores. Following a Procrustes fit of coordinates to control for differences in size and image rotation, a canonical variate analysis with post hoc discriminant function analyses[21,22] are performed to determine statistical differences in pre- and post-RST swallowing mechanics by phase of swallowing for each subject and the aggregate. Eigenvectors will be used to visualize differences in covariant swallowing associated with treatment effect. Morphometric regression analysis will be used to evaluate respiratory-swallow training as a predictor of improved swallowing outcomes as measured by MBSImP and PAS scores.

5.7 Withdrawal of Subjects

Participation is voluntary and the participant can withdraw from the study at anytime without penatly, consequences or loss of rights to which they are entitled. If the participant wishes to withdraw, they can contact study personnel at anytime. They will still receive compensation based on tasks completed as outlined previously. The investigator may withdrawal the participant from the study if they are unwilling or unable to follow study procedures or have worsening breathing problems, lung disease, or pneumonia.

6.0 Reporting

The PI (BMH) will be responsible for ensuring participant safety on a daily basis. An internal *Data and Safety Monitoring Board (DSMB)* - comprised of a radiation oncologist, medical oncologist, head and neck surgeon, pulmonologist, biostatistician, information technology specialist, and a speech-language pathologist - will act in an advisory capacity to monitor participant safety, evaluate the progress of the study, and to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses. The PI will be informed of serious adverse events as soon as they occur and will notify the IRB, DSMB, VA RR&D within 24 hours of notification. The *DSMB* will meet twice annually, either in-person or by teleconference call, to review study progress, data quality, and participant safety.

Safety reports will be sent to the PI twice a year and will include a detailed analysis of study progress, data and safety issues. *DSMB members* will have no direct involvement with the study investigators or intervention. Each DSMB member will sign a Conflict of Interest Statement regarding any relationship that could be perceived as a conflict of interest related to the study and/or associated with commercial interests pertinent to study objectives. Data will be presented in a blinded manner during the open sessions of the DSMB or in safety reports. Data and discussion will remain confidential during DSMB meetings and in safety reports. Participant identities will not be known to the DSMB members.

Any unanticipated problem, SAE, and/or protocol deviations will be immediately reported to the PI. All the SAE will be reported within Five working days of the Investigators Knowledge of the event to the Hines VA IRB. In the event when the PI is not able to continue to conduct the study, Dr. Kim (ENT) will take over the responsibilities as a PI.

7.0 Privacy and Confidentiality

This study will use subjects' Protected Health Information (PHI). Extensive efforts will be made by all study personnel to keep personal information and research records private and confidential. Each participant will be assigned an alphanumeric identifier (XX1, etc.), which will be used in lieu of other identifying information. All research related materials will be secure in a locked file cabinet at the Hines VA Hospital in Rm D326. Personal information will be given out as required by law. Only approved study personnel will be provided access, which requires appropriate VA and CITI training for research-related duties. A Certificate of Confidentiality will not be used for this study.

Study related data are stored on VA approved computers and the VA research shared drive (S:), including de-identified study-related data (videofluoroscopic images, respiratory traces). Identifiable data (VASA), including demographic data, questionnaire responses, and treatment results are stored on the VA REDCap behind the VA firewall. De-identified videofluoroscopic images and respiratory tracings will be transported via VA issued encrypted external hard drives for analysis by specially trained analytic experts to the PI's lab at Northwestern University, and then stored on and analyzed from a password protected, dedicated server. This server is managed by Northwestern Information Technology and accessible to only approved study personnel. We will update the data transfer and storage operations as we are provided additional guidance and requirements from the ORO, Office of Research Oversight.

Per VA regulations, research records, including identifiers will be destroyed 6 years after cutoff (at the end of the fiscal year) after completion of the research project, but may be retained longer if required by other federal regulations or sponsor archive requirement. Once a VA study personnel member leaves, his/her access to all data related to the study will be terminated. Prior to destruction of any research-related records, the PI will contact Records Management Officer for current policy.

8.0 Communication Plan

- Bi-monthly summary e-mail from Study Coordinator to review study progress and any items that need action.
- Routine monthly meetings via in person or via telephone conference call amongst all study personnel to discuss study progress and interpretation of study outcomes, as well as to identify and solve any barriers to study completion.
- Weekly bi-monthly meetings between Study Coordinator, Research SLP and PI, to discuss study progress and interpretation of study outcomes, with particular focus on study accrual, as well as to identify and solve any barriers to study completion.
- If there is a protocol deviation, serious adverse event, and/or unanticipated problem, the PI and IRB will be immediately notified. Additionally a summary of the event and solution with a plan to prevent future problems will also be communciated with all study personnel.
- Study Coordinator will routinely check for issues related to completion of IRB-approved study protocol, data collection and ensure the regulatory binder is up-to-date.

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