Investigation of Two Swallowing Therapy Models during Radiation Therapy for Head and Neck Cancer

Document History	Notes
Version 1 Date: 26 Mar 2019	Initial Approval
Version 2 Date: 01 Apr 2019	Revision includes: • Inclusion/ exclusion criteria (removed repeated criteria from the protocol, and pregnant women exclusion) • Removed AE/SAE reporting • Clarified randomization technique • Added demographic survey and INFO 25 • Modified paper logging form to include date and participation name and modified technology survey to include 2 additional questions.
Version 3 Date: 28 May 2019	Revision includes: • Formatting changes • Updated study calendar and measurement time points to clarify all discrepancies • Updated regulatory considerations such as site communication and data monitoring to include management of the various subsites.
Version 4 Date: 1 JUL 2019	Revision includes: • Updating study calendar to clarify procedure collection time window- 4 week +/- 2 days, 7 week +/- 2 days, 19 week +/- 1 month, 1 year +/- 1 month • Updated study calendar to allow for baseline MBSS to occur up to 2 days after start of radiation. • Updated section 11.3 to explain how data will be managed and stored. • Added pre-screening survey (appendix M) to allow researchers to ask eligibility questions prior to consent.
Version 5 Date: 10 JAN 2020	Revision includes: • Formatting Changes • Removed Appendix B (Patient Demographics) due to redundancy and clarified data points collected in demographic and medical history section of study calendar • Removed inconsistencies by adding DIGEST, PAS, and INFO 25 in the study calendar • Clarified wording of active study duration as being seven weeks • Removal of wording that had mistakenly been carried over from the previous feasibility study, such as the tracking of patient oral intake and some app feedback functionalities • Clarification that MBSS videos from all sites will be stored on Stanford Medicine Box until study conclusion

Version 6. Date 12 Oct 2020	Revision includes: • Added procedure to provide study patients with standard scale to measure MIO during video visits • Addition of list of participating centers (subsites)
Version 7 Date 9 Dec 2020	Revision Includes: • Change in sub-site Principle Investigator at Fox Chase Cancer center from Barbara Ebersole to Kathleen Donocoff
Version 8. Date 29 Mar 2021	Revision Includes; • Update to PI oversite plan for subsites.
Version 9. Date 8 June 2021	Revision Includes: • Change in Sub-site Principle investigator at Fox Chace Cancer Center from Kathleen Donocoff to Liane McCarroll.

Investigation of Two Swallowing Therapy Models during Radiation Therapy for Head and Neck Cancer

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Version 9 / Version Date: (8-Jun-2021)

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TABLE OF CONTENTS

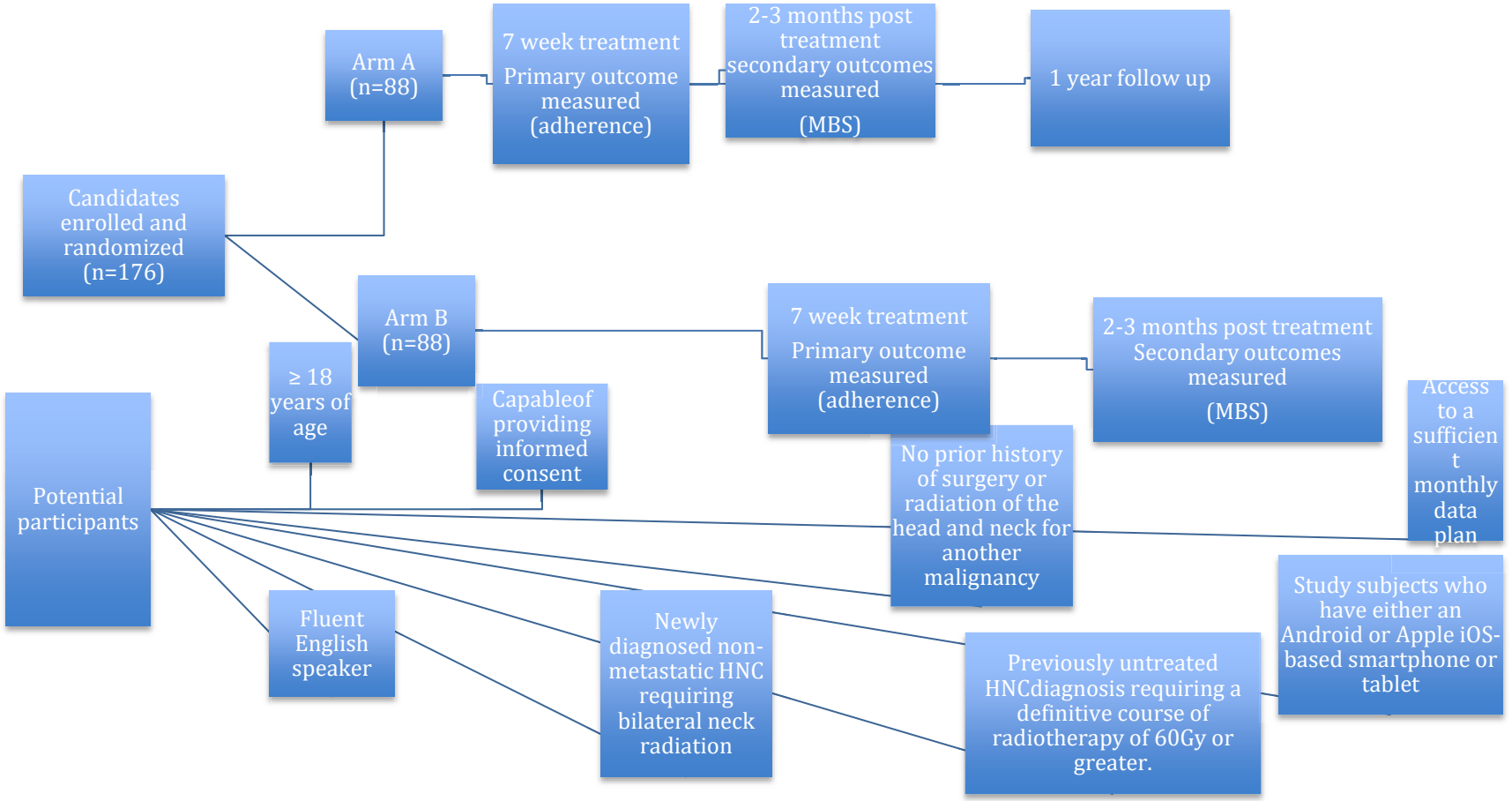
PROTOCOL SYNOPSIS

In the table below summarize the basic aspects of this research. This is to be used as a quick reference guide. Remove any section that is not relevant to the research.

TITLE	Using mobile health technology to enhance adherence and improve swallowing outcomes in patients undergoing radiation therapy for head and neck cancer
INVESTIGATIONAL PRODUCT OR PROCEDURE	Vibrent mobile application
PRIMARY OBJECTIVE(S)	To evaluate the impact of the "HNC Virtual Coach" mobile application on patient adherence to a prescribed swallowing therapy protocol.
SECONDARY OBJECTIVE(S)	To evaluate the impact of the "HNC Virtual Coach" program on the prevalence, characteristics, and severity of dysphagia three months post-treatment in patients undergoing radiation therapy for head and neck cancer.
TREATMENT SUMMARY	Participants in the experimental arm (Group A) will receive a comprehensive swallowing rehabilitation app ("HNC Virtual Coach"). The paper group (Group B) will be given paper exercise logs to fill out.
SAMPLE SIZE	176
STATISTICAL CONSIDERATIONS	88 patients will be enrolled in each arm. This number will provide 80% power to detect a 15 percentage point difference between groups. This calculation is made assuming 33% adherence in arm B and a standard deviation of 32 based on prior studies. This sample size includes the addition of 20% to account for anticipated drop out. The proposed research is a RCT with a primary aim of determining if a mobile application may enhance adherence to swallowing therapy in patients undergoing radiation for head and neck cancer thus improving swallowing

	outcomes. Analysis of the primary endpoint (adherence) will be carried out using logistic regression, comparing arms A and B. A secondary endpoint will be the average percent adherence per week. Analysis of the secondary adherence endpoint will be carried out using a linear mixed effect model with weekly adherence as a dependent variable, a patient-specific random intercept, treatment arm as the primary predictor, and week as a fixed (categorical) effect. We will also explore the impact of the mobile app on a variety of swallowing outcomes including diet level, patient perception, and physiological measures. Analysis of these endpoints will be carried out using logistic regression comparing arms A and B.

SCHEMA


Arm A (n=88)
7 week treatment Primary outcome measured (adherence)
2-3 months post treatment secondary outcomes measured (MBS)
1 year follow up
Candidates enrolled and randomized (n=176)
Arm B (n=88)
7 week treatment Primary outcome measured (adherence)
2-3 months post treatment Secondary outcomes measured (MBS)
≥ 18 years of age
Capableof providing informed consent
Potential participants
No prior history of surgery or radiation of the head and neck for another malignancy
Access to a sufficien t monthly data plan
Fluent English speaker
Newly diagnosed non-metastatic HNC requiring bilateral neck radiation
Previously untreated HNCdiagnosis requiring a definitive course of radiotherapy of 60Gy or greater.
Study subjects who have either an Android or Apple iOS-based smartphone or tablet

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Include additional abbreviations as needed. Remove any unnecessary abbreviations.

AE	Adverse events
DIGEST	Dynamic Imaging Grade of Swallowing Toxicity
DoD	Department of Defense
DSMC	Data Safety Monitoring Committee
EPHI	Electronic Protected Health Information
FEES	Fiberoptic endoscopic evaluation of swallowing
FOIS	Functional Oral Intake Score
GCP	Good clinical practice
Gy	Gray
HNC	Head and neck cancer
HPV	Human papilloma virus
IMRT	Intensity modulated radiation therapy
LHS	Learning Healthcare System
MASA	Mann Assessment of Swallowing Ability
MBS	Modified barium swallow
MBS-ImP	Modified barium swallow impairment profile
MDADI	MD Anderson Dysphagia Inventory
NIH	National Institutes of Health
PAS	Penetration Aspiration Scale
PHI	Protected Health Information
PI	Principal investigator
PSS-HN	Performance Status Scale Head and Neck
Reps	Repetitions
SLP	Speech language pathologist
SRC	Scientific review committee
TORS	Transoral robotic surgery
WHO	World Health Organization
UNK	Unknown
WBC	White blood cell
WHO	World Health Organization

1. OBJECTIVES

Primary Objective

Our objective is to conduct a randomized controlled trial to test the impact of the "HNC Virtual Coach" mobile application on adherence to prophylactic swallowing therapy during head and neck radiation. Prior studies have demonstrated the value of mobile health technologies in improving patient adherence in a variety of settings, including exercise programs (Guarino et al., 2016; Hui et al., 2016, Carter et al 2013). Preliminary feasibility data collected by our study team demonstrated the "HNC Virtual Coach" program could be easily integrated into standard care and lead to high levels of patient engagement in their swallowing exercise program. (Starmer 2017) Our central hypothesis is that patients randomized to use the "HNC Virtual Coach" application will demonstrate better adherence to swallowing exercises, translating to better functional swallowing outcomes, than patients receiving usual care. We propose to achieve our objective by pursuing the following specific aims.

Aim 1: To evaluate the impact of the "HNC Virtual Coach" mobile application on patient adherence to a prescribed swallowing therapy protocol.

1.2. Secondary Objectives

Aim 2: To evaluate the impact of the "HNC Virtual Coach" program on the prevalence, characteristics, and severity of dysphagia three months post-treatment in patients undergoing radiation therapy for head and neck cancer.

2. BACKGROUND

2.1 Study Disease

Head and neck cancer (HNC) is the 6th most common type of cancer in the world and has recently seen a dramatic rise in the United States secondary to oropharyngeal tumors related to the human papillomavirus (HPV) (Chaturvedi et al., 2008). Patients with HPV-associated HNC tend to be younger and healthier at diagnosis than patients with "traditional" head and neck cancer risk factors related to alcohol and tobacco consumption (Gillison et al., 2008). Hence, the majority of patients who will develop HNC in 2018 (and beyond) will have fewer competing morbidities than traditional patients and are expected to have long lifespans in which to develop potential toxicity of treatment. In addition, patients with HPV-associated HNC have markedly better oncologic outcomes, when matched with other variables, compared to traditional HNC (Fakhry et al., 2008). Overall, the need to providing effective cancer therapy, with minimal side effects, is especially important in this cohort of modern patients with HNC.
For patients with newly diagnosed HNC, treatment may include surgery, radiation, and/or chemotherapy, often delivered in combination. The majority of patients receive radiation therapy at some point in their treatment, either as definitive treatment or in the post-operative

setting. All of the modalities have their own distinct set of potential acute and long-term side effects, and the combination of therapies can also contribute to long-term toxicity (Rosenthal 2014; Gane et al 2017). Modern advancements in surgery (namely, transoral robotic surgery, TORS), radiation therapy (namely, intensity-modulated radiation therapy, IMRT), and chemotherapy (namely, the use of novel systemic agents) all have shared minimizing toxicity as a primary goal. However, treatment still has significant impact on quality of life as noted by multiple studies (Ringash 2015; Jones 2017; Achim 2017).

Dysphagia is one of the most common sequelae of HNC and its treatment. The increased use of definitive radiation-based treatment (without surgery) to allow for organ preservation has led to a growing awareness of the potential for dysphagia from this approach. This is likely related to radiation fibrosis and changes in innervation of the muscles of swallowing (King et al., 2016). The use of radiation and chemotherapy has been beneficial in sparing the consequences of surgery and removal of tissues involved in swallowing; however, the preservation of an organ when treating HNC does not necessarily equate to the preservation of function. A substantial body of evidence suggests that patients receiving non-surgical treatment for HNC are at risk for both acute toxicities and long-term alteration of swallow function (Starmer et al., 2014; Hutcheson et al., 2012; Eisbruch et al., 2002). Such alterations may contribute to long-term decrements in health status and quality of life (Daugaard et al., 2017; Silveira et al., 2015; Ringash 2015). It has become increasingly apparent that prevention of dysphagia through active participation in prophylactic swallowing therapy with speech-language pathologists (SLP) can positively affect these outcomes (Carroll 2008; Kotz 2012; Carnaby-Mann 2012).

The data supporting the use of prophylactic swallowing exercises includes multiple outcome measurements. Carroll and colleagues (2008) demonstrated that individuals performing swallowing exercises prior to and during chemoradiation demonstrated more normal tongue base apposition to the posterior pharyngeal wall during swallowing as well as more normal epiglottic inversion three months after treatment than did a matched group of patients who started exercises after completion of radiation suggesting the beneficial impact of preventative exercises on physiology. Further, Kotz and colleagues (2012) demonstrated more favorable diet levels 3-6 months following completion of treatment in patients completing preventative exercises. Carnaby-Mann (2012) used post-treatment muscle size/composition as measured by MRI as the primary outcome measure comparing preventative treatment with sham treatment and monitored care. In the active treatment arm in which patients performed swallowing exercises twice daily over the duration of treatment, there was less structural change in the genioglossus, hyoglossus, and myohyloid muscles than in the other two treatment groups. A composite measure was designed to designate a favorable swallowing-related outcome, and included weight loss <10%, maintenance of oral diet, and a change of <10 points on the Mann Assessment of Swallowing Ability (MASA). In the active treatment arm, 86% achieved this desirable outcome, while only 47% in the other groups achieved this. There was a 36% absolute risk reduction for loss of swallowing ability when participating in preventative exercise. These results serve as strong evidence that patients receiving non-operative HNC treatment should be engaged in swallowing therapy prior to the start of radiation.

Swallowing therapy may include a number of interventions, including compensatory strategies that work to impact bolus flow, as well as exercises which aim to influence swallowing

physiology. Swallowing exercises are typically selected by a SLP based on physiologic findings during an instrumental swallowing evaluation; modified barium swallow (MBS) or flexible fiberoptic endoscopic evaluation of swallowing (FEES). Exercises are designed to improve the safety and/or efficiency of the swallow and may target structures such as the tongue, pharyngeal constrictors, and suprahyoid musculature. Exercises such as the effortful swallow, Mendelsohn maneuver, and the Masako technique have been shown to be effective in improving the strength of the muscles of deglutition (Lazarus 2002, Hoffman 2012, Fujiu 1996). Additionally, in the case of patients undergoing radiation therapy, range of motion stretches may target structures within the field of radiation, such as the tongue and the masseter muscles (Logemann 1997). Dysphagia exercises are typically trained by the SLP with the patient doing the majority of exercises at home.

Patient adherence to treatment recommendations requires that patients be active participants in their care. Prior studies of adherence in the exercise literature show that adherence rates tend to be poorer in patients engaging in home exercise programs than those receiving clinical therapy (Forkan 2006, Hardage 2007). In addition, for patients with HNC, oncologic treatment itself may be cumbersome (including multiple daily appointments) and painful, and patient understanding of treatment recommendations can be lacking. Increasing patient comprehension of the importance of swallowing intervention is critical for improving adherence. Multiple recent reports have demonstrated that adherence to swallowing therapy recommendations is poor in patients with HNC (Table 1).

Table 1: Studies reporting adherence rates to swallowing therapy

Reference	Population	Adherence rate
Wall, 2017	Head and neck cancer radiation	27%
Cnossen, 2017	Head and neck cancer radiation	38-70%
Mortensen, 2015	Head and neck cancer radiation	33-53%
Shinn, 2013	Head and neck cancer radiation	13-45%
Kotz, 2012	Head and neck cancer radiation	31%

These studies repeatedly demonstrate that ~2/3 of patients do not follow through with recommended swallowing therapy protocols, demonstrating the critical need for head and neck care teams need to determine strategies that facilitate patient adherence. Prior work by our team has focused on clinical models and the inclusion of the SLP in the multidisciplinary care team as one strategy to help enhance patient understanding of the importance of prophylactic swallowing intervention (Starmer et al., 2011). In addition, through collaborations within the multidisciplinary team, our group is assessing strategies to minimize treatment toxicity, such as pain, using gabapentin to block nerve related pain and optimize functionality (Yang et al., 2016; Starmer et al., 2014). With this proposal, we further advance this initiative by using a mobile health application specifically designed to address these issues to assist in difficulty performing

the exercises, remembering the exercises, and understanding the rationale for the exercises. The World Health Organization (WHO) has classified factors that may impact patient adherence into five distinct groupings: patient-related, socio-economic, therapy-related, condition-related, and health care system related factors (Sabate 2003). While many of these factors cannot be regulated by the health care team, others such as therapy-related and health care system factors may be manipulated to optimize adherence. Mobile health technology has been proposed as a tool to influence such barriers to adherence. There are multiple studies that have shown the positive impact of mobile health technology, including use in methadone clinics and asthma management clinics (Guarino et al., 2016; Hui et al., 2016). With regard to exercise programs, use of mobile applications has been associated with higher levels of exercise in contrast to paper logging programs. Carter et al. (2013) reported nearly double the rates of exercise program retention at 6 months (93% versus 53%) and nearly triple the exercise logged (92 days versus 29 days) when a mobile health application was integrated into a weight loss program, leading to a greater degree of weight loss and BMI change.

2.2 Study Agent/Device/ProcedureThe "HNC Virtual Coach" program has been developed in conjunction with Vibrent Health (www.vibrenthealth.com), a cloud-based precision health platform for individual and population health. The Vibrent team has partnered with stakeholders across the healthcare ecosystem to advance disease prevention and treatment based on real-world evidence and scientific rigor. Vibrent has experience with leading edge technologies for both commercial contracts and academic grant projects including adaptive algorithms, wireless wearables and medical devices, passive sensing, predictive modeling, machine learning, adaptive tailored messaging, dynamic automated care planning, big health data system integration, genomics, and more. Vibrent was recently chosen by the National Institutes of Health (NIH) to provide the technology backbone for its historic Precision Medicine Initiative (www.joinallofus.org), engaging millions of Americans over the next ten years. This groundbreaking effort aims to engage more than one million participants to understand how genomics, lifestyle, behavioral, and environmental factors impact an individual's health. For the purpose of the current investigation, Vibrent Health will partner with head and neck cancer teams at a number of National Cancer Institute designated Comprehensive Cancer Centers to optimize and evaluate a precision health platform to facilitate patient adherence to swallowing exercises and optimize functional swallowing outcomes.

2.3 Rationale

This protocol seeks to address the issue of low adherence to swallowing exercises by implementing a customizable mobile application ("HNC Virtual Coach") as an adjunct to routine clinic visits and instruction from SLPs. Prior studies which have demonstrated improved adherence in the setting of weight loss and non-cancer medical management suggest that this approach is feasible; our hypothesis is that a mobile health application will improve adherence to swallowing exercises. However, performance of the exercises is not the only endpoint. Multiple studies have shown that improved exercise adherence results in notable benefits with regard to swallowing function. Our second hypothesis is that increased adherence to swallowing exercises will then lead to preservation of functional swallowing physiology and subsequently to increased swallowing safety, efficiency, and patient perceived quality of life.
The "HNC Virtual Coach" application, tailored to patients with HNC, will monitor patient progress while also providing a direct line of communication to health care providers should any

questions or concerns arise concerning their treatment. The mobile application will also feature instructional videos that describe the swallowing exercises in detail, providing patients with another resource to help improve their overall rehabilitation experience. Finally, home practice reminders and prompts will be used to help patients integrate the exercises into their daily routine. We seek to demonstrate that use of the "HNC Virtual Coach" program will be associated with greater adherence to home exercise protocols as measured by logged exercises completed. This hypothesis is based on our preliminary feasibility data and patient feedback regarding the value of the application to their treatment (Starmer et al 2017). Specific feedback from participants in the feasibility trial included:

Feasibility trial participant feedback
" I felt like my therapist was with me every day doing my exercises. All of my family and friends felt like they knew her."
"The app was good because it made me feel like if I didn't do the exercises, the teacher would yell at me."
"I knew when to do my exercises. Keeping everything in one place was very helpful."
"It is easy, you don't have to be computer literate to use it."

A feasibility study investigating the approach of using a mobile technology application (in general) and the "Swallow for Life" swallowing therapy application (specifically) in patients with HNC has recently been completed through a collaboration between Stanford University and Johns Hopkins University, under the guidance of PI Heather Starmer. A total of 36 patients were enrolled in this feasibility study in less than one year, demonstrating our ability to accrue the required number of patients to complete this investigation and the level of interest from the patients. The majority of patients were diagnosed with oropharyngeal squamous cell carcinoma (83%), and most received chemoradiation as their primary treatment (75%). Overall, there were 7004 entries into the mobile application, including exercise adherence data, weight, and quality of life surveys. At least two exercise sessions per day were entered by 25% of participants and at least one session per day was logged by 53% of participants. While a 53% partial adherence rate may seem meager, prior studies demonstrated adherence rates closer to 30-40% (Table 1). Thus, while not directly comparable, there is reason to believe that use of this mobile application may in fact be an effective tool to enhance adherence. Only 20% of participants did not meaningfully engage with the application (i.e. less than 10 logs total over study duration). The average number of exercise sessions logged was 44; however if those who did not engage with the application were excluded from analysis, this number rose to 60 sessions logged. On average, participants logged their weight 27 times and their pain 65 times over the course of the study. Intra-app surveys regarding failure to log exercises were completed 71 times by 23 unique patients. Entries revealed the majority of patients had completed the exercises but forgot to log them (70%) suggesting that actual adherence rates may have been underestimated in this series. Other reasons for failure to log included; time constraints (13%), fatigue (6%), pain (6%), app/internet issues (4%), and lack of understanding of the exercises (1%). Exit interviews of patients revealed overall satisfaction with the app. Features cited as most beneficial included: use of videos to reinforce exercise technique, reminders to keep on track with exercises, and a feeling of increased accountability. Based on the outcomes of this study and the feedback received from patients, our study team has worked extensively with the Vibrent program development team to optimize the mobile application for the purpose of this clinical trial.

Revisions include: simplification of the logging system, patient customization of reminders, reducing unnecessary notifications, and improving the user interface. While this feasibility trial was not designed to determine relative adherence between patients using the app and those receiving standard care, preliminary data suggest this intervention may be an effective adjunct to standard treatment, thus prompting the need for further investigation.

2.4 Study Design

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

State the primary purpose for the protocol from the following choices:
Supportive Care: protocol designed to evaluate one or more interventions where the primary intent is to maximize comfort, minimize side effects or mitigate against a decline in the subject's health or function. In general, supportive care interventions are not intended to cure a disease.

State the interventional model from these choices:
Parallel: one of two groups in parallel for duration of study.

State the number of intervention arms.
2

State whether the study will be masked (at least one party is unaware of the treatment)
Single Blind: one party is unaware of the intervention assignment,

State whether the study is randomized.
Participants will be randomized to treatment arms

State type of primary outcome or outcome that the protocol is designed to evaluate:
Efficacy

2.5 Correlative Studies Background

Provide background information on <u>each</u> planned correlative study including the biologic rationale and hypotheses as well as the relevant preclinical and clinical data.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix A.

3.1 Inclusion/ Exclusion Criteria We have decided not to duplicate the inclusion/exclusion criteria here, please refer to Appendix A.

3.2 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original

signed copy of the consent document must be retained in the medical record or research file.

3.3 Randomization Procedures

Following enrollment, randomization will be carried out using pre-printed lists with block size of 4 through OnCore. Clinical research coordinators will complete the randomization process after consent completed.

3.4 Study Timeline

Primary Completion:
The study will reach primary completion 24 months from the time the study opens to accrual.

Study Completion:
The study will reach study completion 36 months from the time the study opens to accrual.

4. TREATMENT PLAN

We propose a randomized control trial with two arms; the experimental "HNC Virtual Coach" app group (Group A, n=88), and a paper logging control group (Group B, n=88). In clinical practice, many patients would not even complete paper log forms, therefore the act of logging alone may inflate adherence values. However, the ability to measure adherence across study groups required some level of logging to minimize the potential for recall bias. As a result, inclusion of the paper logging groups appeared to be the best compromise for comparing our experimental intervention with usual care. We hypothesize that those participants in Group A will complete a higher percentage of prescribed exercises than those in group B. Additionally, we hypothesize that those individuals in Group A will have more favorable swallowing outcomes as defined below.

Participants in the experimental arm (Group A) will receive a comprehensive swallowing rehabilitation app ("HNC Virtual Coach"). The paper group (Group B) will be given paper exercise logs to fill out. All patients will consult with a SLP prior to the initiation of radiation therapy. At that time, baseline evaluations of swallowing function (outlined below) will be performed. All participants will be educated regarding potential radiation-related side effects and trained in the same series of swallowing exercises by the SLP. In order to ensure fidelity of the target interventions, each SLP involved in this study will complete training with the site PI to ensure exercises and logging are being instructed according to the protocol. SLPs will ensure that the patient is able to return demonstrate each exercise during their visit.

Patients with elevated risk for developing dysphagia post-radiation will be the target of this intervention. This includes individuals with primary head and neck tumors in the oral cavity, oropharynx, nasopharynx, larynx, and hypopharynx requiring bilateral neck radiation. Patients with recurrent disease will be excluded from participation. Detailed inclusion and exclusion criteria can be found in Appendix A. Patients will be screened for eligibility, consented, enrolled, and randomized prior to the initiation of radiation therapy. Eligibility screening will be conducted through weekly screening of radiation oncology clinics, new patient referrals and tumor board patient lists. Those individuals identified as candidates for the study will be contacted by study personnel and educated regarding the trial. Interested participants will

be consented using an IRB approved consent form. Informed consent will explain to participants that they will receive an intervention to support their swallowing therapy during radiation. Following enrollment, randomization will be carried out using pre-printed lists with random block size. Subjects will meet with a member of the research team for a baseline visit that will review details on how to download and use the application or how to complete paper exercise logs. Written instructions regarding the app will be provided for patient reference at home. Participants will then be instructed to use the "HNC Virtual Coach" app in order to log daily exercises over the course of their treatment. All study subjects will proceed to routine clinical care, consisting of standard fractionated radiotherapy with or without concurrent chemotherapy (based on standard clinical indications). Participants in the experimental arm will be asked to use the "HNC Virtual Coach" program as an adjunct to standard care during treatment. The active study duration for each participant will begin on the first day of radiation. All participants will receive standard care with the SLP with planned clinical visits scheduled at the beginning of radiation, mid-way through radiation, and at the conclusion of radiation.

We have developed a demographic information instrument to allow us to properly describe our cohort and to examine possible effects of these factors on adherence and functional outcome measures. (Appendix L) Variables of interest include age, sex, ethnicity, disease stage, disease site, HPV status, education level, marital status, distance from home to treatment center, and insurance status. Additionally, participants will be asked to rate their comfort level with smartphone technology using a visual analogue scale (Appendix C). These will be completed at the time of study enrollment, prior to randomization.

Participants will be asked to complete and log their swallow exercises using either the Vibrent application or paper forms throughout the duration of radiation therapy. The Vibrent application will time stamp the date and time of data entry for secondary analysis to determine whether logging occurs on a daily basis or in batch. Paper logs will be collected by study personnel and entered into a central Redcap database. Each patient's program will ask the patient to complete 3 sets of ten repetitions of four different exercises, twice each day: Jaw stretches, Effortful Swallow, Mendelsohn Maneuver, and the Masako Maneuver. These maneuvers have all been well described and validated in the literature for patients undergoing treatment for head and neck cancer (Pauloski 2008).

Participants in the experimental arm (Group A) will receive a notification reminder to complete target exercises as well as a link to a video workout twice each day through the mobile application. Additional educational videos will also be made available through the "HNC Virtual Coach" program to support the patient with treatment-related toxicities that may impact exercise adherence during radiation (such as pain, fatigue, and xerostomia). All of these exercises and additional information are within the normal standard of care and are simply facilitated outside of the clinical setting by the "HNC Virtual Coach" program. When two sequential exercise sessions in a row are not completed, the application will push a survey to the participant to ascertain the reason why the sessions were not completed. Available options will include: 1) Didn't have time, 2) Pain, 3) Not feeling well/no energy, 4) Don't know how to do them, 5) Don't think they are necessary, 6) Issues with technology, and 7) Other. Based on participant responses, the study team will have the option to push information to the participant to address cited issues. During the baseline visit, the patients will be instructed that this mode of

communication is not intended to substitute the standard modes of communication with their provider, or obviate the need for scheduled follow-up visits. The communication portal rather serves as a real-time feedback component on the patients "out of clinic" course of treatment. Instructions will be given regarding any emergencies, with directions to not communicate via the system and to call 911 or go to the emergency room. In addition to these features, the app will also collect data regarding pain on a scale of 1-10 daily, where 1=no pain and 10=severe pain. This will allow investigators to monitor pain as a variable that may impact adherence. Additionally, in order to evaluate the relative role of oral intake during treatment, participants will be asked to rate their oral intake for nutrition/hydration as "all", "some", or "none" on a daily basis.

Participants in the paper control group (Group B) will be asked to log exercises on provided logging sheets (Appendix D). Both groups will be asked to rate their pain on a scale of 1-10 daily when they log their exercises either on the control app or on their paper logging sheets. We acknowledge that there are limitations to relying on patient logging as a measure of adherence. Unfortunately, there is no gold standard for measuring exercise adherence. A number of patient reported surveys have been reported in the literature; however these have been shown to have limited reliability and validity (McLean 2017). In the absence of validated, reliable measures of adherence, patient logging remains the mainstay for measuring adherence in the majority of the exercise literature. The reliance on patient logging across treatment arms will minimize the risk for reporting bias in this study.

Aim 1: To evaluate the impact of the "HNC Virtual Coach" mobile application on patient adherence to a prescribed swallowing therapy protocol.

Primary outcome variable: Overall adherence to prescribed exercise protocol measured as percentage of prescribed exercises completed over a seven-week period. (i.e. if participants are asked to complete 6 sets of 10 reps of each exercise daily for 7 weeks, maximum potential would be 420 sets).

Aim 2: To evaluate the impact of the "HNC Virtual Coach" program on the prevalence, characteristics, and severity of dysphagia in patients undergoing radiation therapy for head and neck cancer.

Secondary outcome variables:
Patient reported:
MD Anderson Dysphagia Inventory (MDADI) (Appendix E)

Clinician reported:
Functional Oral Intake Score (FOIS) (Appendix F)
Performance Status Scale – Head and neck (PSS HN) (Appendix G)

Functional measures obtained during videofluoroscopic swallowing studies (VFSS):
Penetration Aspiration Scale (PAS) (Appendix H)
Individual item and composite scores of the Modified Barium Swallow Impairment Profile (MBS-ImP) (Appendix I)

Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) severity scores (Appendix J)
Maximal interincisor distance

See study calendar for when these outcome measures will be collected

Modified barium swallow procedure: All MBS studies will follow a standard protocol. Additional boluses or strategies may be employed by the treating clinician only after completion of the study trials outlined below. Examinations will be conducted using a minimum of 30 frames per second and recorded for review purposes. Studies will be saved in AVI or MPEG format. Patients will be evaluated while seated in lateral and frontal views with views to include the soft palate superiorly, the cricopharyngeus inferiorly, the lips anteriorly, and the cervical spine posteriorly. A penny will be taped to the participant's chin during the evaluation to provide calibration for measurements performed following the MBS. Varibar contrast will be used in trials as outlined below:

Lateral view: 5cc Varibar thin liquid X2
10cc Varibar thin liquid X1
20cc Varibar thin liquid X1
Ungraded cup sip Varibar thin liquid X2
5cc Varibar pudding X2
½ graham cracker coated with 3ml Varibar pudding X1
Frontal view: 20cc Varibar thin liquid bolus X1

MBS videos from all sites may be stored in Stanford Medicine Box until the study's completion. The modified barium swallow videos will then be reviewed by a Stanford MBS-ImP trained SLP blinded to treatment group.

The MD Anderson Dysphagia Inventory (MDADI) was selected to capture and quantify the patient perception of swallowing dysfunction. It is a 20-item patient reported survey that measures the impact of dysphagia on patients with HNC. Each item is rated on a scale of 1-5 with lower numbers indicating poorer function. Mean subscale scores are multiplied by 20 to provide a final score between 20-100. This scale has been validated as a reliable tool to measure the impact of dysphagia on head and neck cancer patients (Chen 2001).

In order to describe patient diet levels, the Functional Oral Intake Scale was selected. The FOIS is a 7-point ordinal scale used to describe oral intake where lower scores reflect more limited oral intake and higher scores reflect more normal diet levels. Originally validated in patients with dysphagia following stroke, the FOIS was found to have very good inter-rater reliability and validity (Crary 2005). It has been used extensively in studies of dysphagia in the head and neck cancer population.

The Performance Status Scale – Head and Neck (PSS-HN) was chosen to provide additional detail regarding diet and eating restrictions. This measure has been validated and shown to have good correlation with other measures of function in this population (List 1990).

In order to measure physiologic swallow function during MBS studies, three assessment

tools were chosen. The Penetration Aspiration Scale is an 8-point interval scale used to describe degree of bolus entry into the laryngeal vestibule and patient response to this material. Lower scores reflect more normal function. It has been shown to have favorable intra- and inter- judge reliability (Rosenbek 1996).

The Modified Barium Swallow Impairment Profile is a tool designed to quantify degree of impairment on 13 individual physiologic components visualized during a modified barium swallow where higher numbers reflect greater dysfunction. This tool correlates significantly with other measures of swallowing including penetration aspiration scores, diet scores, and quality of life (Martin-Harris 2008).

The Dynamic Imaging Grade of Swallowing Toxicity was established to rate the safety and efficiency of the pharyngeal swallow during modified barium swallow studies using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) framework. The scale has been shown to correlate with the MBSImp composite score, MDADI, and oral intake levels (Hutcheson 2017).

These measures, in combination, provide a comprehensive evaluation of swallowing physiology, its functional impact, and patient perception.

4.1 Criteria for Removal from Study

Treatment failure is not a study endpoint. Study subjects will be removed when requested by study subjects.Cessation of the research procedure will not affect the routine clinical care a study subject receives as the study subject will still be receiving standard of care through their regularly scheduled clinic appointments. The use of the Vibrent^{TM} mobile application will only serve as an adjunct to this standard of care.

4.2 Alternatives

The alternative to participation in this trial is standard clinical care.

5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Investigational Agent/Device/Procedure

The "HNC Virtual Coach" program has been developed in conjunction with Vibrent Health (www.vibrenthealth.com), a cloud-based precision health platform for individual and population health. The Vibrent team has partnered with stakeholders across the healthcare ecosystem to advance disease prevention and treatment based on real-world evidence and scientific rigor. Vibrent has experience with leading edge technologies for both commercial contracts and academic grant projects including adaptive algorithms, wireless wearables and medical devices, passive sensing, predictive modeling, machine learning, adaptive tailored messaging, dynamic automated care planning, big health data system integration, genomics, and more. Vibrent was recently chosen by the National Institutes of Health (NIH) to provide the technology backbone for its historic Precision Medicine Initiative (www.joinallofus.org), engaging millions of Americans over the next ten years. This groundbreaking effort aims to engage more than one million participants to understand how genomics, lifestyle, behavioral, and environmental factors impact an individual's health. For the purpose of the current investigation, Vibrent Health will partner with head and neck cancer teams at a number of National Cancer Institute designated

Comprehensive Cancer Centers to optimize and evaluate a precision health platform to facilitate patient adherence to swallowing exercises and optimize functional swallowing outcomes.

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

Intervention Description
Participants in the experimental arm (Group A) will receive a notification reminder to complete target exercises as well as a link to a video workout twice each day through the mobile application. Additional educational videos will also be made available through the "HNC Virtual Coach" program to support the patient with treatment-related toxicities that may impact exercise adherence during radiation (such as pain, fatigue, and xerostomia). All of these exercises and additional information are within the normal standard of care and are simply facilitated outside of the clinical setting by the "HNC Virtual Coach" program. When two sequential exercise sessions in a row are not completed, the application will push a survey to the participant to ascertain the reason why the sessions were not completed. Available options will include: 1) Didn't have time, 2) Pain, 3) Not feeling well/no energy, 4) Don't know how to do them, 5) Don't think they are necessary, 6) Issues with technology, and 7) Other. Based on participant responses, the study team will have the option to push information to the participant to address cited issues. During the baseline visit, the patients will be instructed that this mode of communication is not intended to substitute the standard modes of communication with their provider, or obviate the need for scheduled follow-up visits. The communication portal rather serves as a real-time feedback component on the patients "out of clinic" course of treatment.
Arms/Groups if arms or groups have been specified for the protocol, all arms must be described and have at least one intervention (unless arm type is "No Intervention") and each intervention must be assigned to at least one arm.

5.2 Availability

The mobile application will be provided by Vibrent Health.

5.3 Agent Ordering

The application will be downloaded from standard app stores with the assistance of the research coordinator.

6. ADVERSE EVENTS AND REPORTING PROCEDURES

6.1 Potential Adverse Events

No medical risks are expected to result from the use/implementation of the Vibrent^{TM} mobile application. The risk associated for all participants will not be greater than that of routine care for head and neck cancer patients receiving radiation therapy. No direct risk is anticipated for completion of questionnaires or use of mobile applications as patients already have familiarity with these devices throughout their daily lives.

6.2 Adverse Event Reporting

Since this is a low-risk study with no anticipated adverse events (AE) related to the intervention, we will not be collecting any AEs or SAEs.

7. STUDY CALENDAR

Schedules shown in the Study Calendar below are provided as an example and should be modified as appropriate.

	Pre-Study[1]	Wk 1	Wk 2	Wk 3	Wk 4[2]	Wk 5	Wk 6	Wk 7[3]	Wk 19[4]	1 Year[5]
Optimize mobile application[7]	X[7]									
Paper Logs[12]		X	X	X	X	X	X	X		
Informed consent	X									
Demographic Survey (Appendix L)[9]	X									
Medical history[10]	X									
Technology comfort scale (Appendix C)[8]	X									
MD Anderson Dysphagia Inventory (Appendix E)	X								X	X
INFO 25 (Appendix K)	X								X	
Functional oral intake score (Appendix F)	X				X			X	X	X
Performance status scale H&N (Appendix G)	X				X			X	X	X
Weight	X				X			X	X	X
Maximal inter-incisor distance (mm)[13]	X				X			X	X	X
Modified barium swallow[11]	X[6]								X	X

Footnote:

1. Procedures to be completed any time prior to start of radiation treatment. If SOC procedures are completed prior to consent, they can be included, and do not need to be repeated.
2. Procedures to be completed during Week 4 of radiation treatment (+/- 2 days).
3. Procedures to be completed during final week of radiation treatment (+/- 2 days).

4. Procedures to be completed 3 months after end of radiation, ideally within (+/- 2 weeks). However, if the procedures cannot be completed during that window (+/-) 1 month is acceptable.
5. Procedures to be completed 1 year after end of radiation (+/- 1 month).
6. Pre-study MBSS should occur prior to start of radiation treatment, but can also occur within 2 days after start of radiation.
7. For patients randomized in the app arm of the study.
8. Part of the technology survey questions (the first 2 questions) are in the "pre-screening survey." When the patient is completing the technology survey, the first 2 questions can be left blank if the participant has already answered them in the pre-screening survey (Appendix M).
9. In addition to Appendix L, the following demographic information will be collected from source documentation: date of birth, age at enrollment, miles from residence to treatment center
10. Medical History: tumor site, TNM staging (8^{th} edition), AJCC stage, HPV status, Primary treatment, Prescribed radiation dose (Gy), and Chemotherapy/Systemic Treatment
11. Modified Barium Swallow Study metrics (Appendix I) completed along with Penetration Aspiration Scale (Appendix H) and DIGEST scores (Appendix J)
12. For patients randomized to paper log arm of the study.
13. Provide patients with standard scale to measure MIO during video visits (via mail or during in-person visit)

8. MEASUREMENTS

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance
Primary Outcome Measure Definition: Overall adherence to prescribed exercise protocol measured as percentage of prescribed exercises completed over a seven-week period. (i.e. if participants are asked to complete 6 sets of 10 reps of each exercise daily for 7 weeks, maximum potential would be 420 reps).
* Title: Exercise adherence
* Time Frame: At the end of the 7 week treatment period
* Safety Issue: No

8.1 Primary Outcome Measure

Adherence to prescribed exercise protocol

(a) 8. 1.2 Measurement Definition

Overall adherence to prescribed exercise protocol measured as percentage of prescribed exercises completed over a seven-week period. (i.e. if participants are asked to complete 6 sets of 10 reps of each exercise daily for seven weeks, maximum potential would be 420 reps).

(b) 8.1.3 Measurement Methods

Participants will be asked to complete and log their swallow exercises using the either the Vibrent application or paper forms throughout the duration of radiation therapy and for 1 month after the completion of therapy. The Vibrent application will time stamp the date and time of data entry for secondary analysis to determine whether logging occurs on a daily basis or in batch. Paper logs will be collected by study personnel weekly and entered into a central Redcap database.

(c) 8.1.4 Measurement Time Points

Adherence measures will be obtained at the conclusion of the 7-week treatment period.

8.2a Secondary Outcome measures (These measures, in combination, provide a comprehensive evaluation of swallowing physiology, its functional impact, and patient perception.)

Patient reported:
MD Anderson Dysphagia Inventory (MDADI)

(d) 8.2a.2 Measurement Definition

The MD Anderson Dysphagia Inventory (MDADI) was selected to capture and quantify the patient perception of swallowing dysfunction. It is a 20-item patient reported survey that

measures the impact of dysphagia on patients with HNC. Each item is scored on a 5 point scale with 1=lower function and 5=higher function. Possible scores range from 20-100 with higher scores indicating more normal swallowing function. Mean scores will be assessed for each treatment group at the time of each assessment. Standard deviation and 95% CI will be reported.

(e) 8.2a.3 Measurement Methods

MDADI: Each item is rated on a scale of 1-5 with lower numbers indicating poorer function. Mean subscale scores are multiplied by 20 to provide a final score between 20-100. All participants will complete on paper forms.

(f) 8.2a.4 Measurement Time Points

Please see study schedule for the measurement time points.

8.2b Secondary Outcome measure

Functional Oral Intake Score (FOIS)

(g) 8.2b.2 Measurement Definition

In order to describe patient diet levels, the Functional Oral Intake Scale was selected. The FOIS is a 7-point ordinal scale used to describe oral intake where lower scores reflect more limited oral intake and higher scores reflect more normal diet levels. The mean group FOIS score will be reported as well as standard deviation and 95% CI at each assessment (see study calendar).

(h) 8.2b.3 Measurement Methods

FOIS score will be given by the treating clinician based on patient reported diet level.

(i) 8.2b.4 Measurement Time Points

Please see study schedule for the measurement time points.

8.2c Secondary Outcome measure

Performance Status Scale – Head and neck (PSS HN)

(j) 8.2c.2 Measurement Definition

The Performance Status Scale – Head and Neck (PSS-HN) was chosen to provide additional detail regarding diet and eating restrictions. The three items which will be administered include “eating in public”, “understandability of speech”, and “normalcy of diet”. Each item ranges from 0-100 with higher numbers reflecting more normal function. The mean group score will be reported as well as standard deviation and 95% CI at each assessment (see study calendar).

(k) 8.2c.3 Measurement Methods

PSS-HN will be completed by the treating clinician based on patient reports.

(l) 8.2c.4 Measurement Time Points

Please see study schedule for the measurement time points.

8.2d Secondary Outcome measure

Functional measures obtained during videofluoroscopic swallowing studies (VFSS)
Penetration Aspiration Scale (PAS)

(m)8.2d.2 Measurement Definition

In order to measure physiologic swallow function during MBS studies, three assessment tools were chosen. The Penetration Aspiration Scale is an 8-point interval scale used to describe degree of bolus entry into the laryngeal vestibule and patient response to this material. Higher numbers reflect more severe laryngeal penetration/aspiration. The mean group score for most severe PAS will be reported as well as standard deviation and 95% CI at each assessment (see study calendar).

(n) 8.2d.3 Measurement Methods

MBS ratings (PAS, MBS-Imp, DIGEST) will be rated by clinicians blinded to group assignment based on review of videotaped assessments.

8.2d.4 Measurement Time Points

Please see study schedule for the measurement time points.

8.2e Secondary Outcome measure

Functional measures obtained during videofluoroscopic swallowing studies (VFSS)
Individual item and composite scores of the Modified Barium Swallow Impairment Profile (MBS-ImP)

(o) 8.2e.2 Measurement Definition

The Modified Barium Swallow Impairment Profile is a tool designed to quantify degree of impairment on 13 individual physiologic components visualized during a modified barium swallow where higher numbers reflect greater dysfunction. The mean group score for the composite oral component and pharyngeal component will be reported as well as standard deviation and 95% CI at each assessment (see study calendar).

(p) 8.2e.3 Measurement Methods

MBS ratings (PAS, MBS-Imp, DIGEST) will be rated by clinicians blinded to group assignment based on review of videotaped assessments.

(q) 8.2e.4 Measurement Time Points

Please see study schedule for the measurement time points.

8.2f Secondary Outcome measure

Functional measures obtained during videofluoroscopic swallowing studies (VFSS)
Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) severity scores

(r) 8.2f.2 Measurement Definition

The Dynamic Imaging Grade of Swallowing Toxicity was established to rate the safety and efficiency of the pharyngeal swallow during modified barium swallow studies using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) framework. This scale provides a safety impairment score, an efficiency impairment score, and an overall score. Lower numbers on this scale are indicative of more normal function. The mean group impairment scores will be reported as well as standard deviation and 95% CI at each assessment (see study calendar).

(s) 8.2f.3 Measurement Methods

MBS ratings (PAS, MBS-Imp, DIGEST) will be rated by clinicians blinded to group assignment based on review of videotaped assessments.

(t) 8.2f.4 Measurement Time Points

Please see study schedule for the measurement time points.

8.2g Secondary Outcome measure

Maximal interincisal opening

(u) 8.2g.2 Measurement Definition

Maximal interincisor distance will be reported in mm as the space between the bottom of the upper incisor and the top of the lower incisor. In patients missing dentition, 10mm will be deducted from this value for each missing incisor to represent the average incisal height.

(v) 8.2g.3 Measurement Methods

Standard mm measuring tools will be used.

(w) 8.2g.4 Measurement Time Points

Please see study schedule for the measurement time points.

9. MULTISITE REGULATORY CONSIDERATIONS

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring board for this study, please refer to the Data and Safety Monitoring Committee SOP for more information.

11.1 Monitoring plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities approximately once per year to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review protocol deviations from all sites associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

The Stanford Cancer Institute research team will conduct bi-annual audits of sub-site enrollment and regulatory compliance. This will include a review of one subject enrolled in that time period including case report forms, eligibility checklists, source documents and regulatory binders. If no subjects have been enrolled in this time period, the audit will be skipped until the next cycle. The research team will also review protocol deviations and communicate findings with the DSMC and IRB as appropriate.

11.2 Protocol Review and Amendments

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment to all participating investigators. Investigators will be expected to obtain IRB approval within 90 days for all amendments.

11.3 Data management

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will be developed using the REDCap database system and will be maintained by study personnel under the direction of the protocol director. CRFs will be kept in a locked office, only accessible to the research team.

A chart with all of the relevant research patient information will be maintained for each patient at each institution, and the patient charts may be reviewed by Stanford for yearly audits.

Study data will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure, web application designed to support data capture for research studies. It provides user-friendly, web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-

institutional consortium which includes Stanford University and was initiated at Vanderbilt University. The database is hosted at the Stanford University School of Medicine secure data center. The system is protected by Secure Socket Layer (SSL) encryption and a strong web based authentication system. Data collection is customized for each study or clinical trial based on a study-specific data dictionary defined by the research team with guidance from the Stanford Center for Clinical Informatics REDCap administrator. Every personnel in the different sites is given access to only their specific site's "Data Access Group" and can only see and enter information for their patients. The Stanford research team will manage this access.

For patients randomized on the app arm of the study, some of their data will be captured via the VIbrent Health application. Vibrent Health has been deploying and managing solutions in highly regulated, highly secure, highly sensitive environments. Vibrent Health has supported and accredited solutions for the National Institute of Health (NIH), the US Army, commercial and military medical treatment facilities and hospitals. We understand the compliance requirements for these industries and the business requirements to protect the sensitive data that these businesses contain. Vibrent Health currently uses Cyber Secure Amazon AWS Cloud infrastructure to host the Vibrent Platform. Amazon AWS Cloud provides compliance with various Federal regulations that impact privacy and security requirements. AWS Cloud is FedRAMP and FISMA certified and provides many other compliances and certifications such as HIPAA, SOC 1/2/3, PCI DSS Level 1, ISO 27001 and others. AWS Data centers are housed in nondescript facilities and are not open to the public.

Vibrent Coaching Platform (VCP) App is based on a three-tier architecture consisting of web, application and data tiers. The data tier consists of an Amazon Web Services RDS Aurora Multi zone deployment. The database contains all data interactions with the patients. The data tier is deployed upon AWS Aurora product which is Amazon's custom MySQL offering.

11.4 Study Documentation

The Protocol Director and participating site investigators must maintain adequate and accurate participant case histories with observations and other data pertinent to the study. Original source documents should be transcribed to REDCap in a timely manner and used to communicate study data to the lead site. Source documents include hospital records, clinical charts, laboratory and pharmacy records, and recorded electronic data. Original source documents should be kept by each site, an must be provided to the lead site when requested.

Participating Center's PIs will be responsible for maintaining the clinical protocol and subjects' study charts, assuring that consent is obtained and documented, and reporting the status of the trial in continuing renewals submitted to their IRB and trial monitoring group(s) as per their facility protocol. Prior to a subsite's start of enrollment, each subsite will be required to attend a teleconference where relevant Stanford research SOPs and documentation will be reviewed as mentioned in the Investigator Initiated Multisite Trial SOP.

11.5 Site Communication

When all participating institutions have successfully received IRB approval *and* have started enrolling patients, teleconferences to discuss participants and study-related matters will be held at least every two months, although calls may occur more frequently if needed. Teleconferences will be coordinated by Research staff at a participating institution; PIs, Research Coordinators, Nurses, and Co-Investigators if needed will participate. Any issues with patient compliance, database entry, or other items will also be discussed in these calls. Calls may include review by PIs of subject data to assure validity as well as the safety of subjects; and the progress of the trial may also be discussed. At times of study renewal or more frequently if needed, PIs may review safety reports and clinical trial efficacy endpoints and confirm that the safety outcomes favor continuation of the study.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

The proposed research is a RCT with a primary aim of determining if a mobile application may enhance adherence to swallowing therapy in patients undergoing radiation for head and neck cancer thus improving swallowing outcomes. Analysis of the primary endpoint (adherence) will be carried out using logistic regression, comparing arms A and B. A secondary endpoint will be the average percent adherence per week. Analysis of the secondary adherence endpoint will be carried out using a linear mixed effect model with weekly adherence as a dependent variable, a patient-specific random intercept, treatment arm as the primary predictor, and week as a fixed (categorical) effect. We will also explore the impact of the mobile app on a variety of swallowing outcomes including diet level, patient perception, and physiological measures. Analysis of these endpoints will be carried out using logistic regression comparing arms A and B.

(x) Randomization

Randomization will be carried out using pre-printed lists with block size of 4.

10.4 Primary Analysis

Analysis of the primary endpoint (adherence) will be carried out using logistic regression, comparing arms A and B. Analysis of the secondary adherence endpoint will be carried out using a linear mixed effect model with weekly adherence as a dependent variable, a patient-specific random intercept, treatment arm as the primary predictor, and week as a fixed (categorical) effect.

(y) Analysis Population

Analysis will include all participants.

(z) Analysis Plan

As above

12.5 Secondary Analysis

We will also explore the impact of the mobile app on a variety of swallowing outcomes including diet level, patient perception, and physiological measures. Analysis of these endpoints will be carried out using logistic regression comparing arms A and B.

(aa) 12.5.1 Analysis Population

Analysis will include all participants.

(bb) 12.5.2 Analysis Plan

As above

12.6 Sample Size

(cc) 12.6.1 Accrual estimates

Accrual estimates are based upon average clinical volumes at three participating institutions over the past 3 years.

(dd) 12.6.2 Sample size justification

88 patients will be enrolled in each arm. This number will provide 80% power to detect a 15 percentage point difference between groups. This sample size includes the addition of 20% to account for anticipated drop out.

(ee) 12.6.3 Effect size justification

This calculation is made assuming 33% adherence in arm B and a standard deviation of 32 based on prior studies.

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APPENDICES

APPENDIX A: Participant Eligibility Checklist

Protocol Title:	**Investigation of Two Swallowing Therapy Models during Radiation Therapy for Head and Neck Cancer**
Protocol Number:	**IRB-48015**
Principal Investigator:	**Heather Starmer**

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☒ IRB Approved ☒ Contract signed ☒

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Age ≥ 18 years	☐	☐	
2. Fluent English speaking subject	☐	☐	
3. Study subject capable of providing informed consent	☐	☐	
4. Patient with newly diagnosed non-metastatic head and neck cancer such as cancer of the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx that require bilateral neck radiation. Individuals with unknown primary head and neck cancer with nodal disease necessitating bilateral radiation will also be included.	☐	☐	

5. No prior history of surgery and/ or radiation of the head and neck for another malignancy	☐	☐	
6. Study subject with a previously untreated head and neck cancer diagnosis requiring a definitive course of radiotherapy requiring a prescribed dose of 60Gy or greater.	☐	☐	
Exclusion Criteria (From IRB approved protocol)	**Yes**	**No**	
1. Lack of smartphone, tablet, or Internet connection.	☐	☐	
2. Patients with recurrent disease.	☐	☐	
3. Individuals with contraindications to radiation therapy.	☐	☐	

*****All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

Appendix C: Patient Comfort with Technology

1. **Do you own either an Android or Apple-iOS based smartphone or tablet?**

   ☐Yes ☐No

2. **Do you have access to an internet connection or a sufficient monthly data plan (~200MB/month) or greater?**

   ☐Yes ☐No

3. **Please mark on the line to indicate your comfort using technology.**

Very uncomfortable Very comfortable

4. **Please mark on the line to indicate your comfort using your smartphone.**

Very uncomfortable Very comfortable

5. **Please mark on the line to indicate your comfort using your tablet.**

Very uncomfortable Very comfortable

Appendix D: Paper logging form

Exercise logging form: Please indicate the number of sets of exercises prescribed you completed and denote your level of pain after completing the sets of exercises with 1 being no pain, and 10 extreme:

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date							
AM							
PM							
Pain Level (1-10)							

Participant Name: _____

Appendix E: MD Anderson Dysphagia Inventory

This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing.

The following statements have been made by people who have problems with their swallowing. Some of these statements may apply to you.

Please read each statement and circle the response which best reflects your experience in the past week.

E1. **My swallowing ability limits my day to day activities.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

E2. **I am embarrassed by my eating habits.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

F1. **People have difficulty cooking for me.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P2. **Swallowing is more difficult at the end of the day.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

E7. **I do not feel self-conscious when I eat.**

Strongly]Agree	Agree	No opinion	Disagree	Strongly Disagree

E4. **I am upset by my swallowing problem.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P6. **Swallowing takes great effort.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

E5. **I do not go out because of my swallowing problem.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

F5. **My swallowing difficulty has caused me to lose income.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P7. **It takes me longer to eat because of my swallowing problem.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P3. **People ask me, "Why can't you eat that?"**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

E3. **Other people are irritated by my eating problem.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P8. **I cough when I try to drink liquids.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

F3. **My swallowing problems limit my social and personal life.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

F2. **I feel free to go out to eat with my friends, neighbors, and relatives.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P5. **I limit my food intake because of my swallowing difficulty.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P1. **I cannot maintain my weight because of my swallowing problem.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

E6. **I have low self-esteem because of my swallowing problem.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P4. **I feel that I am swallowing a huge amount of food.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

F4. **I feel excluded because of my eating habits.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

Appendix F: Functional Oral Intake Scale (FOIS)

Level 1: Nothing by mouth

Level 2: Tube dependent with minimal attempts of food or liquid

Level 3: Tube dependent with consistent oral intake of food or liquid

Level 4: Total oral diet of a single consistency

Level 5: Total oral diet of multiple consistencies but requiring special preparation or compensations

Level 6: Total oral diet of multiple consistencies without special preparation but with specific food limitations

Level 7: Total oral intake without restrictions

Appendix G: Performance Status Scale – Head and Neck

Eating in Public

_____ No restriction of place, food, or companion (eats out at any opportunity) (100)

_____ No restriction of place but restricts diet when in public(eats anywhere but may limit intake to less “messy” foods, e.g. liquids) (75)

_____ Eats only in presence of selected persons in selected places (50)

_____ Eats only at home in presence of selected persons (25)

_____ Always eats alone (0)

Understandability of speech

_____ Always understandable (100)

_____ Understandable most of the time; occasional repetition necessary (75)

_____ Usually understandable; face to face contact necessary (50)

_____ Difficult to understand (25)

_____ Never understandable; may use written communication (0)

Normalcy of diet

_____ Full diet (no restrictions) (100)

_____ Peanuts (90)

_____ All meat (80)

_____ Carrots, celery (70)

_____ Dry bread and crackers (60)

_____ Soft, chewable foods (e.g. macaroni, canned/soft fruits, cooked vegetables, fish, hamburger, small pieces of meat) (50)

_____ Soft foods requiring no chewing (e.g. mashed potatoes, applesauce, pudding) (40)

_____ Pureed foods (in blender) (30)

_____ Warm liquids (20)

_____ Cold liquids (10)

_____ Nonoral feeding (tubefed) (0)

Appendix H: Penetration Aspiration Scale

Score	Characteristics
1	Does not enter airway
2	Enters airway, remains above cords, is ejected
3	Enters airway, remains above cords, not ejected
4	Enters airway, contacts cords, is ejected
5	Enters airway, contacts cords, not ejected
6	Enters airway, below cords, ejected out or into larynx
7	Enters airway, below cords, not ejected despite effort
8	Enters airway, below cords, no effort to eject

Appendix I: Modified Barium Swallow Impairment Profile (MBS-Imp)

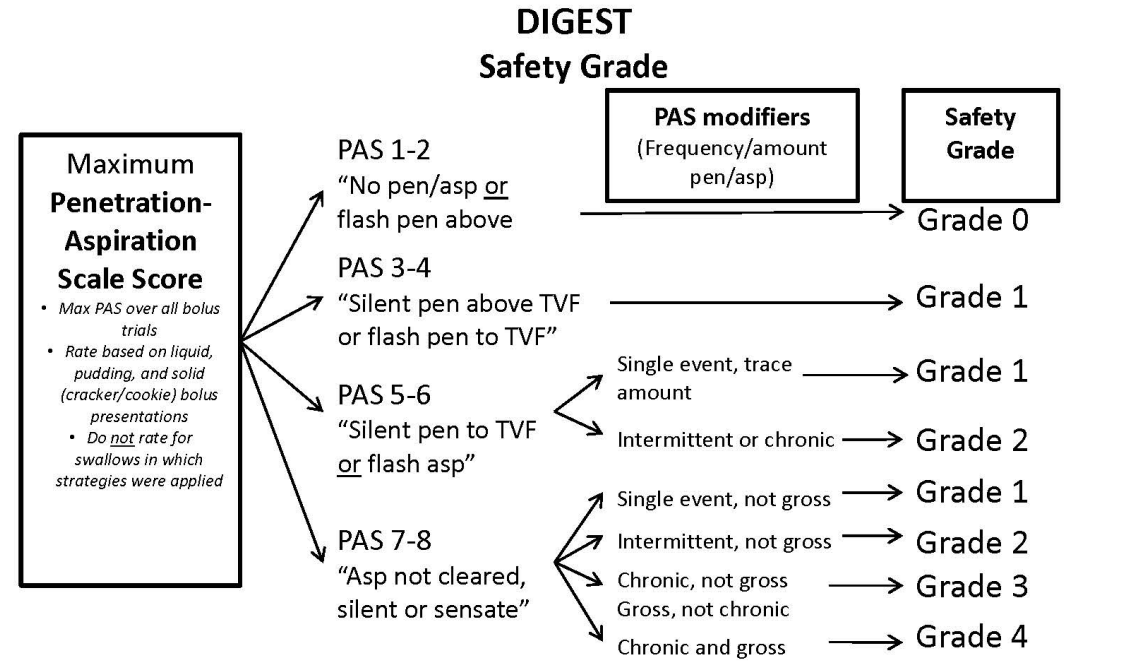
MBSImP™© Bolus Specific Scoring Grid (for optimal use in scoring practice & training) Clinician:_____

Patient Name:_____

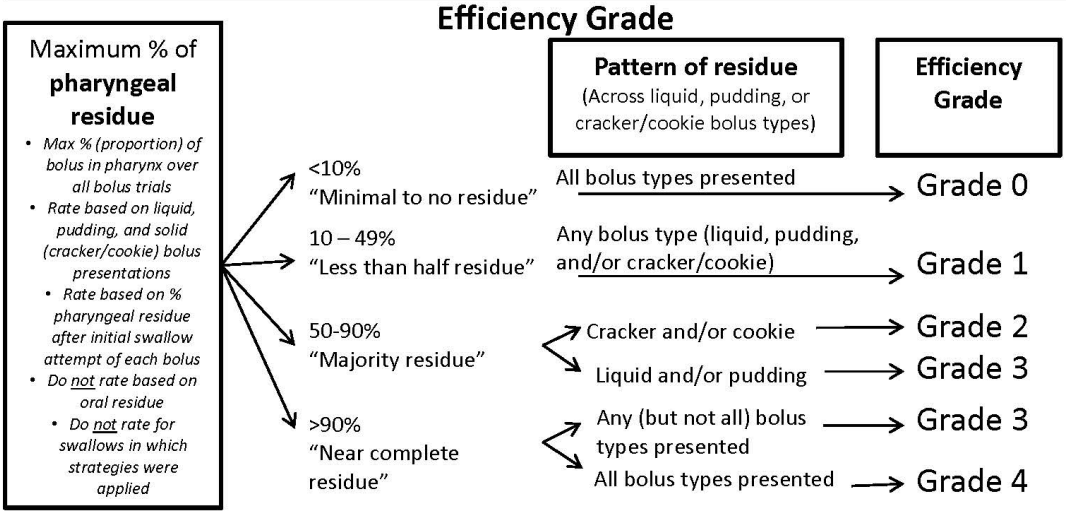
Date:_____

	LATERAL VIEW										AP VIEW		
COMPONENT	Thin				Nectar			Honey	Pudding	Solid	Nectar	Pudding	OI SCORES
	5 ml Tsp.	5 ml Tsp.	Controlled Single Sip	Sequential Swallow	5 ml Tsp.	Controlled Single Sip	Sequential Swallow	5 ml Tsp.	5 ml Tsp.	½ cookie & 5ml Pudding	5 ml Tsp.	5 ml Tsp.	
1. Lip Closure (0 - 4)													
2. Tongue Control during Bolus Hold (0 - 3)													
3. Bolus Prep/Mastication (0 - 3)													
4. Bolus Transport/Lingual Motion (0 - 4)													
5. Oral Residue (0 - 4)													
6. Initiation of Pharyngeal Swallow (0 - 4)													
7. Soft Palate Elevation (0 - 4)													
8. Laryngeal Elevation (0-2)													
9. Anterior Hyoid Movement (0 - 2)													
10. Epiglottic Movement (0-2)													
11. Laryngeal Vestibular Closure (0 - 3)													
12. Pharyngeal Stripping Wave (0-2)													
13. Pharyngeal Contraction (0 - 3)													
14. PES Opening (0 - 3)													
15. Tongue Base Retraction (0 - 4)													
16. Pharyngeal Residue (0 - 4)													
17. Esophageal Clearance Upright Position (0 - 4)													

Appendix J: Dynamic Imaging Grade of Swallowing Toxicity



Frequency/pattern of pen/asp:	Amount of pen/asp
If **max PAS≥5**, PAS 5-6 or PAS 7-8 occurred:	If **max PAS≥5**, amount of barium on or below TVF based on worst performance on any single bolus:
☐ Single event	☐ Trace (resembles faint coating, droplets or trickle of barium on/below TVF)
☐ Intermittent (on multiple but <50% of trials on a single consistency)	☐ Neither trace nor gross
☐ Chronic (majority [≥50%] of thin liquid trials and/or on >1 consistency)	☐ Gross (>25% bolus volume)



	S0	S1	S2	S3	S4
E0	0	1	2	3	3
E1	1	1	2	3	3
E2	1	2	2	3	3
E3	2	2	3	3	4
E4	3	3	3	4	4

Appendix K: INFO 25 Survey

Confidential

INFO25

Please complete the survey below.

Thank you!

We are interested in the information you have received about aspects of your disease and its treatment, in order to improve your health care. There are no right or wrong answers. The information that you provide will remain strictly confidential.

	During your current disease or treatment, how much information have you received on:	Not/none at all	A little	Quite a bit	Very much
1)	The diagnosis of your disease?	○	○	○	○
2)	The extent (spread) of your disease?	○	○	○	○
3)	The possible cause of your disease?	○	○	○	○
4)	Whether the disease is under control?	○	○	○	○
5)	The purpose of any medical test you have had or may undergo?	○	○	○	○
6)	The procedures of the medical test?	○	○	○	○
7)	The results of the medical tests you have already received?	○	○	○	○
8)	The medical treatment (chemotherapy, radiation therapy, surgery or other)?	○	○	○	○
9)	The expected benefit of the treatment?	○	○	○	○
10)	The possible side effects of your treatment!	○	○	○	○
11)	The expected effects of the treatment on disease symptoms?	○	○	○	○
12)	The effects of the treatment on social and family life?	○	○	○	○
13)	The effects of treatment on sexual activity?	○	○	○	○
14)	Additional help outside the hospital (e.g. help with daily activities, self help groups, district nurses)?	○	○	○	○
15)					

	Rehabilitation services (e.g. physiotherapy, occupational therapy)?	○	○	○	○
16)	Aspects of managing your illness at home?	○	○	○	○
17)	Possible professional psychological support?	○	○	○	○
18)	Different places of care (hospitals/outpatient services/home)?	○	○	○	○
19)	Things that you can do to help yourself get well (rest, contact with others)?	○	○	○	○

20)	Have you received written information?	○ Yes ○ No
21)	Have you received information on video?	○ Yes ○ No
22)	Were you satisfied with the amount of information you received?	○ Not at all ○ A little ○ Quite a bit ○ Very much
23)	Do you wish to receive MORE information?	○ Yes ○ No
24)	Do you wish you had received LESS information?	○ Yes ○ No
25)	Overall has the information you have received been helpful?	○ Not at all ○ A little ○ Quite a bit ○ Very much

Appendix L: Demographic Survey

Confidential

Demographic Survey

Please complete the survey below.

Thank you!

1)	Ethnicity	◯ Caucasian ◯ African American ◯ Hispanic ◯ Asian ◯ Other ◯ Prefer not to answer
2)	Sex	◯ Male ◯ Female ◯ Other ◯ Prefer not to answer
3)	Marital status	◯ Married ◯ Single ◯ Divorced ◯ Widowed ◯ Other ◯ Prefer not to answer
4)	Insurance	◯ Private insurance ◯ Government (Medicare/medicaid) ◯ Other ◯ Prefer not to answer
5)	Highest degree attained	◯ < high school ◯ High school diploma ◯ Some college ◯ Associate's degree ◯ Bachelor's degree ◯ Post-graduate degree ◯ Prefer not to answer
6)	Smoking history	◯ None ◯ < 10 pack year (prior) ◯ >10 pack year (prior) ◯ < 10 pack year (current) ◯ >10 pack year (current)
7)	Alcohol use	◯ None ◯ Previous ◯ Current
8)	Address	_____
9)	Zipcode	_____

Appendix M: Pre-screening Questionnaire

1. Do you own either an Android or Apple-iOS based smartphone or tablet?

☐Yes ☐No

2. Do you have access to an internet connection or a sufficient monthly data plan (~200MB/month) or greater?

☐Yes ☐No