Evaluation of Safety and Outcomes of Early Oral Feeding following Total Laryngectomy

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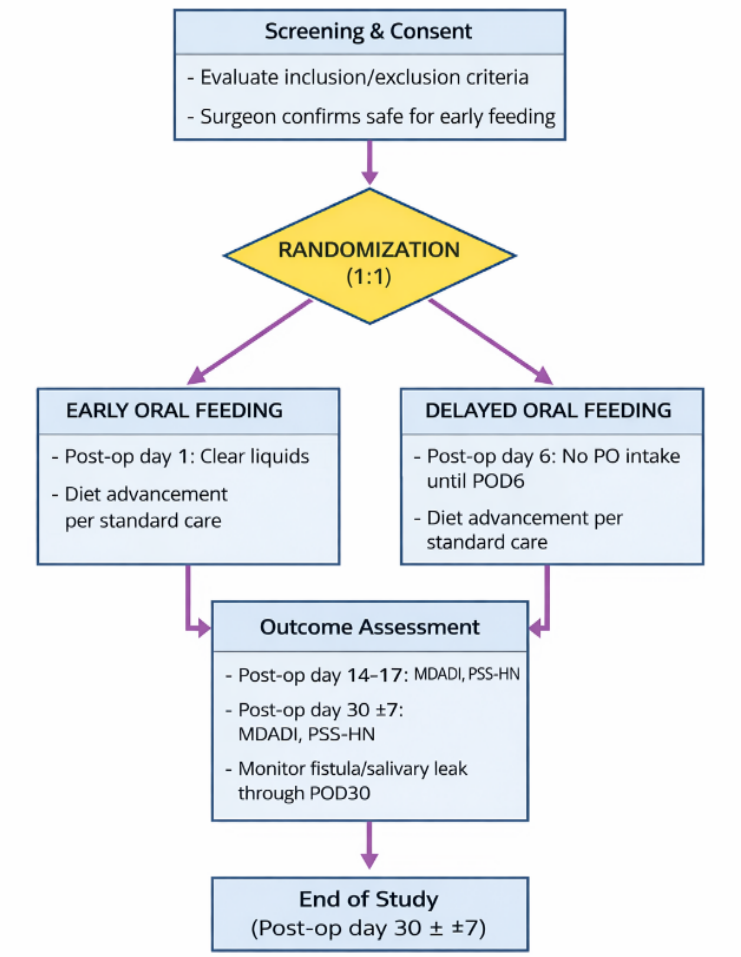
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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	clinical trials management system
DISC	Data Integrity and Safety Committee
ECOG	Eastern Cooperative Oncology Group
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HAART	highly active antiretroviral therapy
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
NCI	National Cancer Institute
NSAE	non-serious adverse event
PCF	pharyngocutaneous fistulas
PI	principal investigator
PS	performance status
SAE	serious adverse event
SOCBP	Subjects of childbearing potential
SRMC	Scientific Review and Monitoring Committee
UF	University of Florida
US	United States
WHO	World Health Organization

STUDY SCHEMA



PROTOCOL SYNOPSIS

Title:	Evaluation of Safety and Outcomes of Early Oral Feeding following Total Laryngectomy
Funding Source(s):	Department of Otolaryngology – Head & Neck Surgery, University of Florida
Rationale:	Traditionally, surgeons have delayed oral feeding in total laryngectomy due to concerns that an early diet may stress suture lines and increase the risk of salivary leaks or fistula formation.[1] However, evidence from small studies evaluating the timing of oral feeding in these patients suggests there is no increased risk associated with early oral feeding.[2–4] Even more, work within the head and neck literature has begun to demonstrate that initiating oral feeding before post-operative day 5 after total laryngectomy is associated with equivalent rates of fistula formation compared with starting oral feeds at post-operative day 6 or beyond.[5–8] Therefore, some have proposed that a shift towards early oral feeding is safe, as patients are able to swallow their own saliva within 24 hours of operation and the intake of clear fluids likely poses no increased risk for complications. In this current study, we hypothesize that, after patients have completed total laryngectomy, dysphagia-related outcomes, collected using the MD Anderson Dysphagia Inventory (**Appendix B**) will be better in patients who received early oral feeding at post-operative day 1 than those who have received delayed oral feeding at post-operative day 6.
Objectives and Endpoints:	Primary Objective: • To evaluate dysphagia-related outcomes in patients who received early versus delayed oral feeding after total laryngectomy. Primary Endpoint: • Comparison of dysphagia-related outcomes using the MD Anderson Dysphagia Inventory (**Appendix B**) in patients who have received early versus delayed oral feeding pre-operatively (if available) and at post-operative days 14 (± 7 days) and 30 (± 7 days).

	Secondary Objective(s): • To evaluate clinical outcomes in patients who received early versus delayed oral feeding after total laryngectomy. • To evaluate patient tolerance and overall oral rehabilitation outcomes in patients who received early versus delayed oral feeding after total laryngectomy. Secondary Endpoint(s): • Comparison of the following clinical outcomes in patients who have received early versus delayed oral feeding within 30 days of surgery: o Proportion of patients who develop pharyngocutaneous fistulas requiring invasive intervention (i.e., surgical or bedside), proportion of surgical site infections, proportion of wound dehiscence. • Comparison of the following patient tolerance and overall oral rehabilitation metrics in patients who received early versus delayed oral feeding within 30 days of surgery: o Rate of oral feeding tolerance, days until nasogastric tube can be removed, hospital length of stay, duration of enteral tube feeding, swallowing function based on the MD Anderson Dysphagia Inventory (**Appendix B**) and the Performance Status Scale for Head and Neck Cancer (**Appendix C**), and patient-reported measures of oral rehabilitation.
Study Design:	This is a randomized, single center phase 2 study.
Accrual Goal:	A total of 120 subjects
Inclusion Criteria:	Individuals eligible for study participation must meet the following criteria: A. Adults ≥ 18 years of age. B. Subjects who have elected to undergo total laryngectomy surgery. C. Subjects receiving free-tissue transfer regardless of indication for total laryngectomy. D. Subjects who are English and/or Spanish speaking. E. Written informed consent obtained from the subject and the subject agrees to comply with all the study-related procedures.

Exclusion Criteria:	Subjects with any of the following will not be eligible for study participation: A. Subjects who have undergone prior major head and neck surgery or radiation therapy involving the larynx (also referred to as surgical salvage patients). B. History of severe dysphagia or with current enteral feeding needs C. Subjects with intraoperative findings of incomplete mucosal closure judged by the operating surgeon to place the patient at risk for breakdown D. Subjects with evidence of flap ischemia or venous congestion on immediate postoperative assessment E. Subjects with uncontrolled post-operative bleeding from reconstruction site. F. Subjects with gross oropharyngeal contamination or infections noted at the time of surgery. G. Subjects with other intraoperative findings, at the surgeon's discretion, that would preclude safe participation in the study. H. History of any other disease, metabolic dysfunction, clinical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of protocol therapy or that might affect the interpretation of the results of the study or that puts the subject at high risk for treatment complications, in the opinion of the treating physician. • Including pre-existing conditions that put them at risk for poor wound healing, including: scleroderma, active AIDS (CD4 count <200 or not on HAART therapy), autoimmune disease, organ transplant patients on immunosuppressive medications. • Including a history of traumatic brain injury, stroke, or dementia. I. Subjects who are confirmed to be pregnant or breastfeeding. J. Prisoners or subjects who are involuntarily incarcerated, or subjects who are compulsorily detained for treatment of either a psychiatric or physical illness.

Efficacy Assessments:	Clinical evaluation of swallow will be performed at baseline (pre-operatively when available), during the post-operative treatment period, and at follow-up visits to assess the efficacy of early oral feeding. This evaluation includes jaw and tongue range of motion, functional swallow assessment using the MD Anderson Dysphagia Inventory (**Appendix B**) and the Performance Status Scale for Head and Neck Cancer (**Appendix C**), and diet assessment. Swallow function and oral intake will be administered by the Head and Neck Speech-Language Pathology team. Information from routine post-operative evaluations during treatment and follow-up visits will be used to measure clinical outcomes and oral rehabilitation metrics. These routine evaluations will involve assessment for post-operative complications, surgical site infections, pharyngocutaneous fistulas development, wound dehiscence.
Statistical Considerations:	The MD Anderson Dysphagia Inventory (**Appendix C**) will be administered and assessed pre-operatively (if available) and at post-operative day 14 (± 7 days) and post-operative day 30 (± 7 days). We will summarize the scores at each assessment time point. The primary analysis, comparing these longitudinally measured outcomes between the two study arms will be conducted using multivariable linear mixed effect models that account for the correlation among the multiple measurements from the same subject. In the model, the time, arm, and interaction term between arm and time will be main fixed effects.
Estimated Enrollment Period:	30 months (2.5 years)
Estimated Study Duration:	42 months (3.5 years)

1. BACKGROUND

The question of when to begin oral feeding following resection and reconstruction following total laryngectomy remains without a definitive answer. There is a growing body of evidence suggesting that early feeding is safe when compared to delayed feeding with regards to the incidence of complications, particularly pharyngocutaneous fistulas (PCF). Based on this growing body of literature, early oral feeding could present several benefits for the patient that make exploring this topic worthwhile in a clinical trial.

1.1 Current Practice: Delayed Oral Feeding

While there is a growing body of evidence showing that early oral feeding is safe and may provide improvements in the ability to start oral intake earlier without an increase in the incidence of PCF, the adoption of this practice among surgeons is still slow. In a recent survey, it was found that the current practice among surgeons at academic centers is to delay oral feeding after head and neck surgery until at least seven days post-operatively.[1]

Fistula formation predisposes patients to infection, increasing the risk of damage to major vessels, delaying wound healing, and delaying the initiation of adjuvant therapy.[2] It is the combination of historical practice and continued clinical concern that likely perpetuates the practice of delayed oral feeding after surgical resection of head and neck cancers.

1.2 Early Oral Feeding Rationale

There has been a shift in the thinking behind when to initiate oral feeding after surgeries of the head and neck. This transition can be attributed to the work done in gastrointestinal surgery by Willcutts et al,[3] who studied the effects of early oral feeding for decades and found reduced hospital length of stay with no increase in the incidence of complications. Small studies have also been performed looking at the effects of early oral feeding after laryngectomy.[4] Even more, work within the head and neck literature have begun to demonstrate that initiating oral feeding before post-operative day 5 after total laryngectomy is associated with equivalent rates of fistula formation compared with starting oral feeds at post-operative day 6 or beyond.[2,4–8] Therefore, some have proposed that a shift towards early oral feeding is safe, as patients are able to swallow their own saliva within 24 hours of operation and the intake of clear fluids likely poses no increased risk for complications.[5,9,10]

A systematic review and meta-analysis conducted by Milinis et al[11] and defined early and late oral feedings by <5 days and >5 days, respectively. They found no significant difference in the rates of PCF between early and late oral feeding arms, showing similar

outcomes across both randomized controlled trials and cohort studies in their review. Similarly, Aires et al[4] reported no significant difference in PCF rates between early and late (5 and 7 days, respectively) oral feeding arms and Timmermans et al[12] founds that initiating oral intake as early as post-operative days 2 to 4 did not increase the incidence of PCF compared to starting feeds on post-operative days 10 to 12. Additionally, Medina and Khafif[2] reported that initiating oral feeding within 48 hours post-surgery was feasible, showing a 5% incidence of PCFs compared to an 11% rate in delayed feeding arms.

Furthermore, there is emerging evidence suggesting that initiating oral feeding shortly after total laryngectomy could provide also provide benefits in terms of shortening the length of hospital stays due to lower post-operative complications. Eustaquio et al[5] showed that early feeding on post-operative day 5 after salvage laryngectomy did not increase PCF incidence (10%). As a result, studies have concluded that early feeding can result in shorter lengths of stay for these patients. Milinis et al[11] reported this trend, which was similarly observed by Serbanescu-Kele et al,[7] who noted that patients receiving nutrition on days 3 to 5 experienced shorter hospital stays compared to those fed on days 7 to 10.

These findings are supported by our current understanding of wound healing. Wound healing occurs through a series of overlapping processes that occur over time.[13,14] It starts with an initial inflammatory phase at the time of injury that peaks at 24-48 hours, along with re-epithelialization that begins within hours of injury and continues for days to weeks.[14] The proliferative phase typically starts 4-5 days after injury and may last for several weeks, and finally maturation and remodeling typically begins around 3 weeks after injury and can last for years.[14] It has been shown that continually renewing surfaces, such as the oral and gastrointestinal mucosa, can undergo early re-epithelialization. In mouse models, it has been shown that complete re-epithelialization of the oral mucosa can occur within 24 hrs of injury.[15] In addition, Le Flem et al[16] found that early oral hydration significantly reduced the risk of PCF.

PCF is a commonly cited complication following total laryngectomy, with an incidence range of 20.8% to 32.7%.[17] These rates can be affected by various factors, including whether the laryngectomy is primary or salvage in nature.[17] Factors that contribute to risk include infections at the surgical site, invasion of the piriform sinus, salvage laryngectomy, total radiation exposure, chronic obstructive pulmonary disease (COPD), low levels of preoperative hemoglobin, previous radiotherapy or chemoradiotherapy, advanced primary tumors, and neck dissection.[18,19] PCF has the potential to extend the duration of hospitalization, postpone adjuvant therapies, and elevate the risk of

morbidity.[20,21] Preventive strategies focus on meticulous surgical techniques, the use of vascularized flaps, and thorough patient optimization before surgery.[21,22]

Though the body of literature for early oral feeding after total laryngectomy is not as robust as other head and neck surgeries, several potential benefits favor the initiation of early oral feedings after total laryngectomy that encourage further research into this topic. Decreased hospital length of stay has been reported by many authors studying gastrointestinal surgery, laryngectomies, and oral cancer resections.[2–9,23] Enteral tube feeds are generally more expensive than oral feeding due to use of specialized equipment, use of feeding solution, and increased nursing care.[24] Enteral tube feeding is also not a risk-free method of feeding, with a number of complications possible like gastroesophageal reflux.[25] A nasogastric tube can also present an ascending path for gastrointestinal flora to the oropharynx leading to infection.[26] Enteral tube feeds can cause local wound trauma, which could contribute to wound breakdown.[27]

Improved feeding outcomes have also been seen with transitioning patients to early oral feeding. This occurs through early return to normal swallowing mechanics.[2,24] Oral feeding also has a potential positive impact on patient quality of life and well-being, with improved psychological outlook and physical comfort.[2,9,23] Ehrsson et al. identified in a survey of head and neck cancer patients that eating is an important factor affecting quality of life.[28] However, additional evidence of the effect of enteral tube feeding on quality of life is currently mixed, with both negative and positive effects of enteral tube feeding reported.[29]

1.3 Study Hypothesis

Overall, current evidence suggests that early oral feeding after total laryngectomy does not increase complications, such as PCFs. It is consistent with wound healing physiology and offers additional benefits, including reduced hospital length of stay, lower care costs, and improved patient comfort and quality of life. For this current study, we will focus on these dysphagia-related outcomes. We hypothesize that, after patients have completed total laryngectomy surgery, dysphagia-related outcomes collected using the MD Anderson Dysphagia Inventory (**Appendix C**) will be better in patients who received early oral feeding at post-operative day 1 than those who have received delayed oral feeding at post-operative day 6.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary

The primary objective is:

- To evaluate dysphagia-related outcomes in patients who received early versus delayed oral feeding after total laryngectomy.

The primary endpoint is:

- Comparison of dysphagia-related outcomes using the MD Anderson Dysphagia Inventory (**Appendix B**) in patients who have received early versus delayed oral feeding pre-operatively (if available) and at post-operative days 14 (± 7 days) and 30 (± 7 days).

2.2 Secondary

The secondary objective(s) is:

- To evaluate clinical outcomes in patients who received early versus delayed oral feeding after total laryngectomy.
- To evaluate patient tolerance and overall oral rehabilitation outcomes in patients who received early versus delayed oral feeding after total laryngectomy.

The secondary endpoint(s) is:

- Comparison of the following clinical outcomes in patients who have received early versus delayed oral feeding within 30 days of surgery:
    - Proportion of patients who develop pharyngocutaneous fistulas requiring invasive intervention (i.e., surgical or bedside), proportion of surgical site infections, proportion of wound dehiscence
- Comparison of the following patient tolerance and overall oral rehabilitation metrics in patients who received early versus delayed oral feeding within 30 days of surgery:
    - Rate of oral feeding tolerance, days until nasogastric tube can be removed, hospital length of stay, duration of enteral tube feeding, swallowing function based on the MD Anderson Dysphagia Inventory (**Appendix B**) and the Performance Status Scale for Head and Neck Cancer (**Appendix C**), and patient-reported measures of oral rehabilitation.

3. STUDY DESIGN

3.1 Study Overview

This is a single center, randomized, phase 2 study. A total of 120 subjects are planned. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study. Total duration of subject participation will be 30 days.

Subjects will be randomized to one of the below listed arms using a 1:1 ratio. For more information on randomization, refer to **Section 10.2 Randomization**.

- **Arm 1 (Experimental: Early Oral Feeding)** - Subjects assigned to Arm 1 will begin oral intake on post-operative day 1 after their standard-of-care total laryngectomy surgery.
- **Arm 2 (Control: Delayed Oral Feeding)** - Subjects assigned to the delayed feeding protocol will begin oral intake on post-operative day 6 after their standard-of-care total laryngectomy surgery.

For more information on oral feeding administration, refer to **Section 7.1 Treatment Schedule/Administration**.

4. SELECTION OF SUBJECTS

Subjects who meet the following inclusion and exclusion criteria will be eligible for participation in this study. **Exceptions to inclusion and exclusion criteria are not permitted**. For questions concerning eligibility, please contact the protocol manager.

4.1 Number of Subjects

A total of 120 subjects are expected to participate in this study.

4.2 Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study participation:

A. Adults ≥ 18 years of age.
B. Subjects who have elected to undergo total laryngectomy surgery.
C. Subjects receiving free-tissue transfer regardless of indication for total laryngectomy.
D. Subjects who are English and/or Spanish speaking.
E. Written informed consent obtained from the subject and the subject agrees to comply with all the study-related procedures.

4.3 Exclusion Criteria

Subjects with any of the following will not be eligible for study participation:

A. Subjects who have undergone prior major head and neck surgery or radiation therapy involving the larynx (also referred to as surgical salvage patients).
B. History of severe dysphagia or with current enteral feeding needs
C. Subjects with intraoperative findings of incomplete mucosal closure judged by the operating surgeon to place the patient at risk for breakdown
D. Subjects with evidence of flap ischemia or venous congestion on immediate postoperative assessment
E. Subjects with uncontrolled post-operative bleeding from reconstruction site.
F. Subjects with gross oropharyngeal contamination or infections noted at the time of surgery.

G. Subjects with other intraoperative findings, at the surgeon's discretion, that would preclude safe participation in the study.
H. History of any other disease, metabolic dysfunction, clinical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of protocol therapy or that might affect the interpretation of the results of the study or that puts the subject at high risk for treatment complications, in the opinion of the treating physician.
    - Including pre-existing conditions that put them at risk for poor wound healing, including: scleroderma, active AIDS (CD4 count <200 or not on HAART therapy), autoimmune disease, organ transplant patients on immunosuppressive medications.
    - Including a history of traumatic brain injury, stroke, or dementia.
I. Subjects who are confirmed to be pregnant or breastfeeding.
J. Prisoners or subjects who are involuntarily incarcerated, or subjects who are compulsorily detained for treatment of either a psychiatric or physical illness.

4.4 Inclusion of Women and Minorities

Any adults that meet criteria are eligible for this trial.

5. REGISTRATION PROCEDURES

All consented subjects must be entered into the University of Florida's Clinical Trial Management System (OnCore) prior to assignment of a subject identification number.

Subjects failing to meet all study eligibility requirements will not be able to participate in the trial.

All eligible and enrolled subjects will receive a unique subject number. This number will be used to identify the subject throughout the study. Subjects withdrawn from the study will retain their subject number.

6. STUDY PROCEDURES

Written informed consent must be obtained prior to performing any study-specific evaluations or tests. Tests or evaluations performed as standard of care within the specified screening period, but prior to informed consent, may be accepted for this study and need not be repeated. Screening measurements will be obtained within 60 days prior to start of surgery (total laryngectomy).
Potential subjects will be provided with a copy of the Informed Consent Form during the preoperative visit and will be provided with the opportunity to take the ICF with them to review and sign at a later date (either during a separate visit or on the day of surgery).

6.1 Schedule of Events

Visit: Procedure:	SCREENING (within 60 days prior to post-op Day 1)	STANDARD-OF-CARE SURGERY (TOTAL LARYNGECTOMY)	RANDOMIZATION[3] (Prior to end of Post-op Day 1)	POST-OP DAY 1[4] AND/OR DAY 6[4]	FOLLOW-UP POST-OP DAY 14 (± 7 DAYS)	FOLLOW-UP POST-OP DAY 30 (± 7 DAYS)
Informed Consent	X					
Demographic Information	X					
Medical History	X					
Physical Exam	X			X	X	X
Pregnancy Test, if CBP	X					
Clinical Evaluation of Swallow[1]	X[1, 2]			X[1]	X[1]	X[1]
Standard-of-care Surgery (Total Laryngectomy)		X				
Randomization[3]			X[3]			
Oral Feeding[4]				X[4]	X	X
Post-operative Evaluation[5]				X[5]	X[5]	X[5]
Adverse Event Review[6]				X[6]	X	X

Abbreviation: CBP = childbearing potential

1 Clinical evaluation of swallow will be done by the Head and Neck Speech-Language Pathology team. This evaluation includes jaw and tongue range of motion, a functional swallowing assessment using the MD Anderson Dysphagia Inventory[30] (**Appendix B**) and the Performance Status Scale for Head and Neck Cancer (**Appendix C**),[31] and diet assessment.

2 If no pre-operative clinical evaluation of swallow was performed, study participation can proceed without it.

3 Study participants will be randomized to either Arm 1 (Experimental: Early Oral Feeding) or Arm 2 (Control: Delayed Oral Feeding). For more details on randomization, refer to **Section 10.2 Randomization**.

4 Early oral feeding will begin on post-operative day 1, while delayed oral feeding will occur on post-operative day 6. For more details on oral feeding, please refer to **Section 7.1 Treatment Schedule/Administration**.

5 Routine post-operative evaluation will involve assessment for post-operative complications, such as surgical site infections, pharyngocutaneous fistulas development, wound dehiscence.

6 Adverse event review will start following the subject's total laryngectomy on postoperative day 1 for subjects on either Arm 1 or 2. AE review will occur again on post-operative day 6 and at the follow-up visits.

6.2 Visit Window Tolerance Table

Visit Name	Window
Screening	**Within 60 days prior to post-op Day 1**
Informed consent, demographic information, medical history, physical exam	
Pregnancy test	If subject is of childbearing potential
Clinical evaluation of swallow	If available at screening. If not, study participation can proceed without it
Surgery	
Total laryngectomy	
Randomization	**Prior to the end of post-op Day 1**
Post-op	**Day 1 or Day 6**
Physical exam, clinical evaluation of swallow, post-operative evaluation	
Oral feeding	If subject is assigned to Arm 1, early oral feeding will begin on post-op day 1. If subject is assigned to Arm 2, delayed oral feeding will begin on post-op day 6. For more details on oral feeding, please refer to **Section 7.1 Treatment Schedule/ Administration**.
Adverse event review	Start on postoperative day 1 for subjects on either Arm 1 or 2. AE review will occur again on post-operative day 6
14-day Follow-up	**Day 14 ± 7 days after surgery**
Physical exam, clinical evaluation of swallow, post-operative evaluation	
Oral feeding	For more details on oral feeding, please refer to **Section 7.1 Treatment Schedule/ Administration**.
Adverse event review	
30-day Follow-up	**Day 30 ± 7 days**
Physical exam, clinical evaluation of swallow, post-operative evaluation	
Oral feeding	For more details on oral feeding, please refer to **Section 7.1 Treatment Schedule/ Administration**.
Adverse event review	

6.3 Follow-up Evaluations

Subjects will have a follow-up visit for clinical evaluation of swallow, post-operative evaluation, and adverse event (AE) review during the 14-day (± 7 days) and 30-day (± 7 days) follow-up visits after surgery.

If the subject is unavailable to travel to the institution, the visit may be made via telephone interview to review for AE resolution or the occurrence of any new AEs. Additionally, external or internal medical records may be consulted with permission of the subject to complete remote visit reporting.

If a subject becomes unreachable during the course of the study, the investigator or study team will make a reasonable effort to contact the subject and document each attempt (in accordance with Section 4.3.4 of the ICH E-6 GCP). If these attempts are not successful, the subject may be declared "lost to follow up." For subjects lost to follow-up, the termination date will be the date the subject was determined to be lost to follow by the study team.

7. STUDY TREATMENT

7.1 Treatment Schedule/Administration for Oral Feeding

Patients in both arms are expected to be hospitalized due to their standard-of-care surgery for a minimum of 7 post-operative days and often longer depending on their clinical status. During hospitalization, participants are monitored frequently (multiple times daily) by the Head and Neck surgical team.

Treatment schedule/administration for oral feeding is as follows per arm:

- **Arm 1 (Experimental: Early Oral Feeding)**
  - **Oral intake will begin on post-operative day 1**, provided that no immediate post-operative complications or safety concerns are identified.
  - Study participants will undergo routine post-operative evaluation by the surgical team to confirm clinical stability.
  - A clinical evaluation of swallow will be performed prior to initiating oral intake.
  - If deemed safe, patients will begin with a clear liquid diet, advancing gradually as tolerated.
    - A clear liquid diet is any nourishment that is a liquid at room temperature and transparent. This diet is easily digested and leaves no residue/undigested material in the gastrointestinal tract.
  - Diet advancement will occur based on patient tolerance and clinical assessment by the surgical and speech-language pathology teams.
- **Arm 2 (Control: Delayed Oral Feeding)**

- **Oral intake will begin on post-operative day 6**. Any concerns for wound complications or swallowing safety will prompt reassessment and modification of the feeding plan at the discretion of the treating surgeon.
- Study participants will undergo routine post-operative evaluation by the surgical team to confirm clinical stability.
- A clinical evaluation of swallow will be performed prior to initiating oral intake.
- If deemed safe, patients will begin with a clear liquid diet, advancing gradually as tolerated.
    - A clear liquid diet is any nourishment that is a liquid at room temperature and transparent. This diet is easily digested and leaves no residue/undigested material in the gastrointestinal tract.
- Continued enteral feeding support until patients demonstrate adequate oral intake.

7.2 Supportive Care

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, antidiarrheals, analgesics, nutritional support, and wound care, when appropriate. Postoperative management, including enteral feeding, oral diet advancement per assigned study arm, and speech-language pathology assessments, will be provided according to institutional standards.

8. TREATMENT DISCONTINUATION

8.1 Screen Failures

Subjects who sign informed consent, but do not meet eligibility criteria, or withdraw prior to eligibility being verified, and undergo at least some of the screening procedures will be considered screening failures. Subjects who sign informed consent and are verified as eligible, but do not proceed to study treatment will be considered "withdrawals." A record of screen failures will be maintained by the study site.

8.2 Criteria for Study Treatment Discontinuation

Subjects who discontinue participation in the clinical study on their own or subjects who are withdrawn by the investigator, for reasons other than completion of treatment, disease progression or toxicity, will be defined as premature withdrawals.

If a subject chooses to withdraw from the study after randomization, including after learning their assigned arm, they will be removed from study participation but will continue to receive standard postoperative care.

A subject will be discontinued from study treatment under the following circumstances:

- Any adverse event (AE) which, in the Investigator's opinion, requires termination of the study medication.
- Disease progression, unless at the discretion of the principal investigator (in collaboration with any co-sponsors or collaborators) continued treatment with study drug is appropriate.
- The development of a second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, affect assessments of clinical status and study endpoints to a significant degree.
- The subject becomes pregnant. Pregnancy will be reported along the same timelines as a serious adverse event (SAE).
- The subject uses illicit drugs or other substances (excluding marijuana), or takes part in activities that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with results.
- The subject is lost to follow-up.

The Investigator will make every reasonable effort to keep each subject in the study unless it is in the subject's best interests to discontinue participation. If a subject is removed from the study or declines further participation, all follow-up evaluations should be performed if the subject is willing and able to be assessed. A description of the reason(s) for withdrawal from the study must be recorded on the case report form (CRF). The Investigator should also ensure that all subjects are followed up for survival status after the Final Visit.

Relevant visit data should be entered on the CRF. Subjects who discontinue following entry will have relevant information completed and recorded on the CRF. All subjects who discontinue because of AEs or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any subject should experience a SAE during the trial or within 30 days of stopping early oral feeding, the Investigator will inform the UF Health Data Integrity and Safety Committee.

8.3 Replacement of Subjects

Subjects will not be replaced if they withdraw from the study or are discontinued after enrollment. The planned sample size includes an allowance for up to 20% attrition, as described in **Section 10. STATISTICAL METHODS**. All randomized subjects will be included in the primary analysis according to their assigned study arm.

Section 8.2 Criteria for Study Treatment Discontinuation.

9. ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event

The term "adverse event" (AE) includes any sign, symptom, syndrome, or illness that appears or worsens in a subject during the period of observation in the clinical study and that may impair the wellbeing of the subject. An AE is therefore any unfavorable and unintended symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. Abnormal lab value or test results constitute AEs if they are considered clinically significant or require therapy.

The AE may be:

- A new illness/condition;
- Worsening of a sign or symptom of the condition under treatment, or of a concomitant illness/condition;
- An effect of the study drug; or
- A combination of 2 or more of these factors.

No causal relationship with the study drug or with the clinical study itself is implied by the use of the term "adverse event."

AEs fall into the categories "serious" and "non-serious."

9.1.2 Serious Adverse Event

A serious adverse event (SAE) is one that at any dose of the study drug or at any time during the period of observation:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to

intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization. "Medically important" should be marked only if no other serious criteria are met.
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)

NOTE: The following hospitalizations are not considered SAEs:
a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event):
- Admissions for a planned, routine, and/or elective medical/surgical procedure. Appropriate documentation is required in these cases.
- Admission or prolonged hospitalization for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

An "unexpected SAE" is any SAE for which the nature, specificity or severity is not consistent with the currently known adverse event profile of the disease under study or the investigational agent(s).

9.1.3 Non-serious Adverse Event

A non-serious adverse event (NSAE) is any AE not meeting any of the SAE criteria in the above **Section 11.1.2 Serious Adverse Event**.

9.2 Period of Observation

Following the subject's total laryngectomy on postoperative day 1, all adverse events (AEs) and serious adverse events (SAEs) must be recorded in the subject's case report form until the end of the observation period provided below.

Recording of AEs and SAEs will continue through 30 days after surgery. The investigator should notify the Data and Safety Monitoring Committee (DISC) and any other required regulatory bodies of any SAE occurring after this time period that is believed to be related to the study intervention or protocol-specified procedures.

9.3 Documenting and Reporting of Adverse Events by Investigator

All AEs and SAEs must be fully recorded in the subject's case record form, but only those AEs and SAEs related to the study intervention will be reported in the electronic data capture system.

The Investigator or their designee will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. AEs will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause (if known/available).

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs.

When a clear diagnosis is available that explains the abnormal objective findings, this diagnosis will be recorded as an AE and not the abnormal objective findings (e.g., viral hepatitis will be recorded as the AE and not the transaminase elevation). If a definitive diagnosis is not available, then the sign(s) (e.g., clinically significant elevation of transaminase levels) or symptom(s) (e.g., abdominal pain) will be recorded as the AE.

Every attempt should be made to describe the AE in terms of a diagnosis that encompasses the component signs and symptoms. If only nonspecific signs or symptoms are present, then these should be recorded as separate diagnoses on the pages of the case report form.

All subjects who have AEs, whether considered associated with the use of study drug or not, must be monitored to determine the outcome. The clinical course of the AE will be followed according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the Principal Investigator considers it medically justifiable to terminate follow-up. Should the AE result in death, a full pathologist's report should be supplied, if possible.

9.3.1 Assessment of Causal Relationship of Study Drug

The Investigator will provide an assessment of the potential causal relationship between AEs and study medication by determining whether or not there is a reasonable possibility that the event was caused by the study medication. The relationship or association of the AE to the study medication will be characterized as not related, the relationship is "cannot be ruled out" or related:

Related: Associated or having a timely relationship with the study intervention; or the event has a reasonable causal relationship to study interventions as judged by the reporting investigator.

The relationship is "cannot be ruled out": based on study interventions, the reporting investigator determines that a possibility exists that an outcome may have been caused or influenced by the study event in question (e.g., administration of a study drug); no definite alternative cause/influence was present.

Unrelated: Unassociated or without a timely relationship; evidence exists that an outcome is most likely related to a cause other than the event in question (e.g., disease progression).

9.3.2 Intensity of Adverse Events

The intensity of adverse changes in physical signs or symptoms will be graded according to the most up-to-date CTCAE version. For all other AEs not described in the CTCAE, the intensity will be assessed by the Investigator using the following categories:

Mild (Grade 1) – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.

Moderate (Grade 2) – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.

Severe (Grade 3) – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible.

Life-threatening (Grade 4) – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

Death (Grade 5) – the event resulted in death.

9.3.3 Action Taken with Study Intervention

The action the Investigator took with study intervention (oral feeding) as a result of the event should be recorded as one of the following:

None – No action was taken with regard to the study intervention as a result of the AE.

Interrupted – Study intervention was stopped due to the AE, but was later resumed at the same dose.

Permanently discontinued – The subject was withdrawn from the study due to the AE.

Only one item should be chosen. If multiple actions apply, the following "worst case" scenario hierarchy should be used to determine the preferred entry: permanently discontinued > dose decreased > interrupted.

9.3.4 Definition of Outcome

The outcome of the AE should be recorded as one of the following:

Resolved without sequelae – The subject fully recovered from the AE with no observable residual effects.

Resolved with sequelae – The subject recovered from the AE with observable residual effects.

Not resolved – The AE was present at the time of last observation.

Unresolved at end of reporting period

Death – The subject died as a result of the AE.

9.4 Immediately Reportable Events

9.4.1 Serious Adverse Events

SAEs must be reported to the project manager, and entered into OnCore, within **24 hours** of discovery of the event. If only limited details are known, these should be reported within that time frame and follow-up reports can be submitted for elaboration, clarifications, or corrections. Any email correspondence must be kept in the trial file at the study site. The site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Follow-up information will be submitted to the project manager, stating that this is a follow-up to a previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the participant continued or withdrew from study participation. The project manager will confirm that the event and any necessary follow-ups are reported to the UFHCI Data and Safety Integrity Committee (DISC), the sponsor, and any other regulatory authorities as required (FDA, etc.)

9.4.2 Other Events Requiring Immediate Reporting

Pregnancies should be documented and reported per the reporting guidelines below.

Institution Immediate Reporting Information
SAEs and pregnancies must be reported to the project manager, or assigned designee at: euribesanchez@ufl.edu As well as entered in OnCore, the study CTMS.

9.4.2.1 Pregnancies

All pregnancies, regardless of outcome, must be reported to the project manager, including pregnancies that occur in the partner of a study subject. Pregnancies will be submitted by the project manager to DISC and any other regulatory authorities as required.

10. STATISTICAL METHODS

The sections below provide an overview of the statistical considerations and analyses.

10.1 Data Collection and Management Plan

Data will be collected via paper source documents and the medical record, and will subsequently be entered into a validated electronic data capture system which will be monitored and audited on a regular basis to ensure accuracy.

Data entry will be performed by trained study personnel, including the study coordinator and designated research staff, under the supervision of the Principal Investigator.

All study data will be stored on secure, password-protected institutional servers, with access restricted to authorized members of the research team. Each subject will be assigned a unique study identification number, and identifiable information will be stored separately from study data to maintain confidentiality.

Data quality will be ensured through routine data monitoring and periodic audits conducted by the study team.

10.2 Randomization

Participants will be allocated using a 1:1 ratio to early oral feeding or delayed feeding with the National Institute of Health "Clinical Trial Randomization Tool." A single 1:1 allocation list (Experimental versus Control) for 100 positions will be exported to an Excel workbook. The file is password-protected and placed on a secure drive accessible only to the study coordinator, who is not involved in patient care. The enrolling

investigator will contact the study coordinator, who will disclose the next unopened row in sequence and record the subject's study ID in the adjacent column. Therefore, the list remains concealed until the moment of assignment, ensuring that future allocations cannot be predicted, even though the trial is open label.

Stratified-block permute randomization with a block size of 4 will be used to minimize the chance of baseline imbalance. Specifically, we plan to stratify randomization by operating surgeon.

10.3 Sample Size Justification

We are planning a randomized controlled trial to evaluate the impact of early feeding on dysphagia-related outcomes using the validated measure: the MD Anderson Dysphagia Inventory (MDADI, **Appendix B**) composite score. Participants will be randomly assigned in a 1:1 ratio to either the early feeding arm or the delayed feeding arm.

In a prior study, MDADI composite scores were approximately normally distributed, with a baseline mean of 83, a post-treatment mean of 72, and a standard deviation (SD) of 16.9.[32] We assume that the true minimal clinically important difference (MCID) between the early and delayed feeding arms corresponds to a 50% improvement in the mean decline observed previously that is, 5.5 points for MDADI (50% of 11).

The primary analysis will compare mean change scores (baseline to post-treatment) between arms using a two-sided, two-sample t-test assuming equal variances and a Type I error rate (α) of 0.05. Based on varying the assumed common SD between 5 and 15, a sample size of 50 participants per arm (100 total) provides >80% power to detect a mean difference of 6 points, except when the SD approaches 15 (**Figure 1**). The power estimated based on a single post-treatment using a simple approach is expected to be conservative. The primary analysis, based on a mixed effects model incorporating both post-treatments at days 14 and 30 with an appropriate correlation structure, is expected to provide greater efficiency and, consequently, increased power under reasonable assumptions. Power calculations were conducted in PASS 2025 (version 25.0.3).

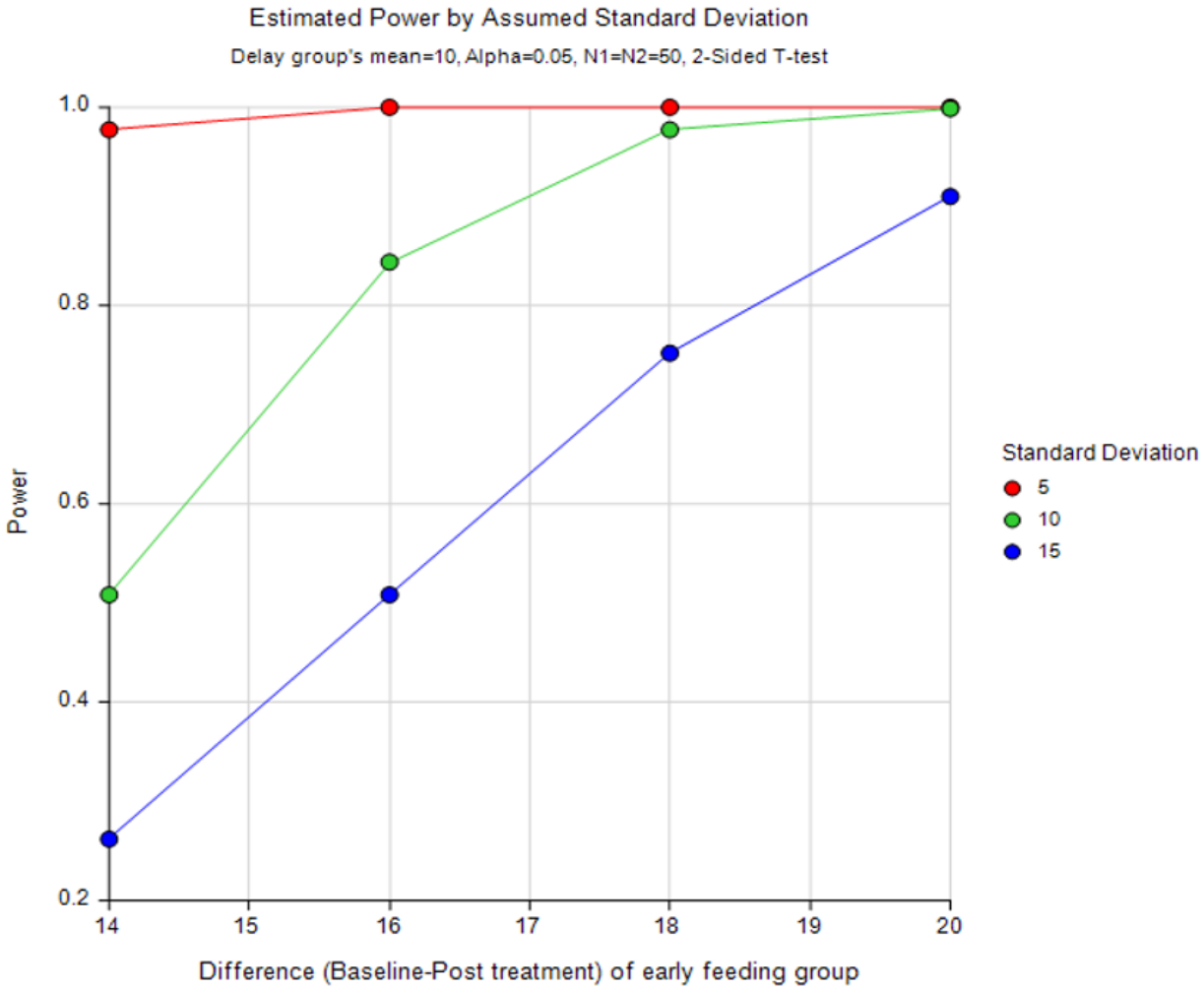


Figure 1. Estimated power by assumed standard deviation at 5, 10, or 15.

Based on accrual rates at the UF clinical site, we expect to enroll approximately 50 eligible patients per year. Allowing for a 20% dropout rate, a total sample size of 120 patients (60 per arm will be recruited over an anticipated 2.5-year accrual period. Clinically, we anticipate that the true dropout rate will likely be close to 0%, as post-operative assessments occur as part of routine standard-of-care; however, a 20% dropout rate will be assumed for statistical planning purposes to ensure adequate study power.

10.4 Analysis Populations and Estimand

1) Intent-to-treat (ITT) population: all enrolled/assigned patients will be included in the primary analysis according to their assigned feeding group.
2) Per-protocol population: patients who adhered to the study protocol will be included in secondary analyses.

3) Safety population: all patients who adhered the protocol will be included in safety analyses.

The primary estimand targets the effect of early versus delayed oral feeding on dysphagia-related outcomes following total laryngectomy.

- Population: patients undergoing total laryngectomy are eligible for oral feeding per protocol.
- Intervention: early oral feeding versus delayed oral feeding.
- Variable: MDADI (**Appendix B**) total score measured at pre-operative baseline, post-operative day 14 (+/- 7 days), and day 30 (+/- 7 days).
- Summary measure: difference in mean MDADI scores between groups over time, with primary focus on post-operative assessments, adjusted for baseline and correlation structure.

10.5 Analysis of Primary Endpoint

The primary endpoint will be analyzed in the ITT population. We will summarize the scores at each assessment time point. The primary analysis, comparing these longitudinally measured outcomes between the two study arms, will be conducted using multivariable linear mixed-effect models that account for the correlation among the multiple measurements from the same subject. In the model, the time, arm, and interaction term between arm and time will be the main fixed effects. Variable and model selections will be conducted using appropriate statistical approaches.

10.6 Analysis of Secondary Endpoints

Secondary endpoints include proportion of patients who develop pharyngocutaneous fistulas requiring invasive intervention (surgical or bedside) within 30 days post-surgery, proportion of surgical site infections, proportion of wound dehiscence, rate of oral tolerance, days until the nasogastric tube can be removed, hospital length of stay, swallow function based on the MDADI (**Appendix B**) and the Performance Status Scale for Head and Neck Cancer (**Appendix C**), and patient-reported measures of oral rehabilitation. All these endpoints will be summarized using descriptive statistics and compared between arms using appropriate statistical tests, including Fisher's exact test for discrete data and Wilcoxon rank test for continuous data as well as logistic and linear regression modeling approaches.

Handling missing items in the quality-of-life questionnaires:

Because of the nature of the study, missing data are expected to be minimal. This is justified by the fact that the primary and secondary outcome assessments occur within a short follow-up period (30 days postoperatively), during which patients are closely monitored as part of routine clinical care. Many outcome measures, including

postoperative complications (e.g., pharyngocutaneous fistula, salivary leak, wound complications) and hospital-based metrics (e.g., length of stay, enteral feeding duration), are routinely documented in the electronic medical record. Additionally, a substantial portion of assessments are performed during the inpatient hospitalization period or at scheduled postoperative visits that are part of standard care, reducing the likelihood of loss to follow-up.

However, any missing data will be handled using multiple imputation under the missing-at-random assumptions. The extend and pattern of missing outcome data will be evaluated, and appropriate statistical methods will be applied depending on the endpoint type and missing data pattern. Sensitivity analysis will be conducted, as appropriate, to assess the robustness of the results to the assumptions regarding missing data.

10.7 Analysis of Safety Data

Safety analyses will be performed in the per-protocol population, defined as patients who adhered to the study protocol. The safety and tolerability of the intervention is determined by reported AEs, physical examinations, laboratory findings, post-operative evaluations, and clinical evaluations of swallow. All patients will be assessed regularly for potential occurrence of AEs from the time of subject's postoperative day 1 until 30 days after total laryngectomy surgery. AEs and SAEs will be summarized with the incidence and percentage of patients with at least one occurrence of a preferred term (according to the most severe NCI-CTCAE Version 6.0 grade) will be included. The relationship to the intervention will be summarized separately. Duration of AE will be determined and included in listings along with action taken and outcome. Laboratory results will be classified according to NCI-CTCAE, Version 6.0. Incidence of laboratory abnormalities will be summarized; laboratory results not corresponding to an NCI-CTCAE Version 6.0 term will not be graded. Laboratory toxicity shifts from baseline to worst grade will also be provided. The results from physical examination and vital sign measurement will be tabulated. Descriptive statistics will be provided as appropriate.

10.8 Interim Analysis

No interim analysis is planned. All primary and secondary endpoints will be evaluated at post-operative days 14 and 30 days, and the final analysis will be performed after all data have been collected and finalized. An independent DISC will periodically review safety data, and the study team will follow its recommendations as appropriate.

10.9 Data Integrity and Safety Committee

This protocol will be reviewed and monitored by the University of Florida Health Cancer Institute Data Integrity and Safety Committee (UFHCI DISC) in accordance with their

policies and procedures. They will review and monitor study progress, toxicity, safety and other data from this trial. Questions about subject safety or protocol performance will be addressed with the sponsor-investigator, statistician and study team members. Should any major concerns arise, the DISC will offer recommendations regarding whether or not to suspend the trial.

UFHCI DISC data and safety monitoring activities include:

- Review of clinical trial conducted for progress and safety
- Review of all adverse events (AEs) requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the sponsor-investigator of recommended action
- Notification of sites coordinated by the UFHCI of AEs requiring expedited reporting and subsequent committee recommendations for study modifications

In compliance with the UFHCI data and safety monitoring plan, the PI or designee will provide a Data Integrity and Safety Committee Report to DISC at the predetermined timelines for the level of risk category assigned during the initial SRMC (Scientific Review and Monitoring Committee) review, which occurs prior to initial IRB approval.
UFHCI investigator-initiated protocols will be classified into one of the following categories of risk by the SRMC (see *SRMC manual* for further details):

- Level 1 – **Low risk** Investigator Initiated interventional trials.
- Level 2 – **Moderate risk** Investigator Initiated or externally sponsored interventional (such as drug, biologic or device) trials using FDA approved or commercially available compounds or interventions.
- Level 3 – **High risk** Investigator Initiated or externally sponsored interventional trials (such as investigator-sponsored INDs, Phase I trials, studies requiring biosafety approval, or other areas that may be designated by NIH as high risk).
- Level 4 – Complex trials involving **very high risk** to subjects and a high level of complexity such as first in human or gene transfer studies.

The risk level assigned by SRMC will determine the appropriate level of DISC monitoring required, with increased monitoring required for higher-risk trials.

10.10 Data Monitoring

UFHCI (University of Florida Health Cancer Institute) Quality Assurance team will perform remote monitoring and may make monitoring visits to the trial sites periodically during the trial to confirm that all sites are complying with the protocol. Source documents will be reviewed for completion and validated against data submitted electronically via

Electronic Data Capture. The site investigator/institution guarantee access to source documents by UFHCI or its designee and appropriate regulatory agencies. As part of the responsibilities assumed by conducting this study, the Principal Investigator (PI) agrees to maintain and have available for monitoring adequate case records (accurate source documents and case report forms) for the subjects treated under this protocol.

The trial site may also be subject to quality assurance audit by any collaborating sponsors or their designee as well as inspection by appropriate regulatory agencies.

It is important for the site investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

10.11 Principal Investigator Responsibilities

Per UF IRB requirements, the PI is personally responsible for conducting and supervising the conduct of human subjects research by "protecting the rights, safety, and welfare of subjects under the investigator's care." The PI also must ensure that all the research conducted is done so in an ethical manner and in accordance with all federal, state, and local laws and regulations, institutional policies, and the requirements of the IRB.

Oversight is defined as "management by overseeing the performance or operation of a person or group; watchful care, superintendence, general supervision". Any person serving as a PI has voluntarily accepted these responsibilities and is expected to fully comply with these requirements.

The PI will be primarily responsible for continuous monitoring of AEs, protocol violations, and other immediate protocol issues. The study coordinator will collect information on subjects enrolled through the use of electronic or paper AE forms, case report forms, and informed consent forms.

11. EMERGENCY PROCEDURES

11.1 Emergency Contact

In emergency situations, the treating physician should contact the Principal Investigator by telephone at the number listed on the title page of the protocol.

11.2 Emergency Treatment

During and following a subject's participation in the study, the treating physician and/or institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the study.

12. ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

12.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Principal Investigator and Co-Investigators abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki.

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board (IRB) approval before initiation of the study.

The Principal Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.
All potential serious breaches must be reported immediately to the protocol manager and the IRB of record, if applicable. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

12.2 Institutional Review Board

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling, information to be provided to subjects, and any updates. The investigator should provide the IRB with reports, updates, and other information (e.g., amendments, and administrative letters) according to regulatory requirements or institution procedures.

12.3 Compliance with Laws and Regulations

It is intended that the proposed study be conducted according to the International Conference on Harmonization E6 Guideline for Good Clinical Practice (GCP) and the Declaration of Helsinki. Please refer to the International Conference on Harmonization and GCP:
https://www.fda.gov/media/93884/download;
Declaration of Helsinki:
https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/;
Code of Federal Regulations, Title 21:

https://www.ecfr.gov/cgi-bin/text-idx?gp=&SID=2fa30a11d9a46ebee8122c33aefd684c&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl

All UF investigator-initiated trials, meeting the criteria of the FDAAA's applicable clinical trials, will be registered with ClinicalTrials.gov by the protocol manager or assigned designee. All studies must be registered prior to enrollment of the first participant. The protocol manager or assigned designee will maintain the responsibility of updating trials registered with ClinicalTrials.gov. Per FDA requirement, information must be updated at least every twelve months and the registry must be updated within thirty days of any changes in recruitment status or completion of the study. The protocol manager will determine if registration and updates to the NCI CTRP are required.

12.4 Delegation of Investigator Responsibilities

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions. The Principal Investigator will maintain a list of Co-Investigators and other appropriately qualified persons to whom they have delegated significant study-related duties.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment). Systems with procedures that ensure the quality of every aspect of the study will be implemented.

12.5 Subject Information and Informed Consent

Before being enrolled in this clinical trial, the subject must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her. An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all ICH, GCP, and locally required regulatory elements. The document must be in a language understandable to the subject and must specify the person who obtained informed consent.

After reading the informed consent document, the subject must give consent in writing. The written informed consent will be obtained prior to conducting any study-related procedures or tests. The subject's consent must be confirmed at the time of consent by the personally dated signature of the person conducting the informed consent discussions and a copy of the consent form (preferably signed) must be given to the

subject for their records.

The PI will retain the original signed consent document. The PI will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

12.6 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

Subjects will be told that the IRB, UF Health DISC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection law.

12.7 Protocol Amendments

Once the study has started, amendments should be made only in exceptional cases. Protocol amendments will not be implemented without prior written IRB approval. All amendments will be submitted to the IRB and SRMC (as applicable), and written verification that the amendment was submitted and subsequently approved is to be obtained, and notification will be sent out to the applicable study teams, prior to implementing the amendment.

On an emergency-basis, to eliminate an immediate safety hazard to a subject, a protocol deviation may be implemented immediately, provided the IRB and project manager are notified within **5** business days with a full justification and description of the event.

12.8 Case Report Forms

The Principal Investigator and/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 protocol-required outcomes for safety monitoring and data analysis. All study data will be entered electronically in an Electronic Data Capture system in accordance with the protocol schedule of events and guidelines developed in the Data Management Plan for the study, using a secure access account.

All protocol data is the sole property of the Department of Otolaryngology – Head & Neck Surgery, University of Florida, and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the Department of Otolaryngology – Head & Neck Surgery, University of Florida.

12.9 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

UF Health Cancer Institute requires that all study documentation be maintained for at least 6 years from the date of final study publication. No study records may be destroyed without prior authorization from UF.

13. REFERENCES

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14. APPENDICES

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Appendix A: PROTOCOL VERSION HISTORY / SUMMARY OF CHANGES

Protocol Version Number	Protocol Version Date	Affected Section(s)	Summary of Revisions Made
1.0	2026-APR-22	N/A- Initial protocol	

Appendix B: MD ANDERSON DYSPHAGIA INVENTORY

Patient Name: _____ **Date**: _____

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 the statements may apply to you.

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

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

Thank you for completing this questionnaire!

Reference: This is the MD Anderson Dysphagia Inventory as published in Chen AY, Frankowski R, Bishop-Leone J, et al. The Development and Validation of a Dysphagia-Specific Quality-of-Life Questionnaire for Patients With Head and Neck Cancer: The M. D. Anderson Dysphagia Inventory. Arch Otolaryngol Head Neck Surg. 2001;127(7):870–876. doi:10.1001/archotol.127.7.870.

Appendix C: PERFORMANCE STATUS SCALE FOR HEAD AND NECK CANCER

Patient Name: _____ **Date**: _____

NORMALCY OF DIET

100	Full diet (no restrictions)
90	Full diet (liquid assist)
80	All meat
70	Raw carrots, celery
60	Dry bread and crackers
50	Soft chewable foods (e.g., e.g., macaroni, persons in selected places canned/soft fruits, cooked vegetables, fish, hamburger, small pieces of meat)
40	Soft foods requiring no chewing (e.g., mashed potatoes, apple sauce, pudding)
30	Pureed foods (in blender)
20	Warm liquids
10	Cold liquids
0	Non-oral feeding (tube fed)

PUBLIC EATING

100	No restriction of place, food or companion (eats out at any opportunity)
75	No restriction of place, but restricts diet when in public (eats anywhere but may limit intake to less "messy" foods (e.g., liquids)
50	Eats only in presence of selected persons in selected places
25	Eats only at home in presence of selected persons
0	Always eats alone
999	Inpatient

Continued on next page

UNDERSTANDABILITY OF SPEECH

100	Always understandable
75	Understandable most of the time; occasional repetition necessary
50	Usually understandable; face-to-face contact necessary
25	Difficult to understand
0	Never understandable; may use written communication

Reference: This is the Performance Status Scale for Head and Neck Cancer as published in List MA, D'Antonio LL, Cella DF, et al. The Performance Status Scale for Head and Neck Cancer Patients and the Functional Assessment of Cancer Therapy-Head and Neck Scale. A study of utility and validity. Cancer. 1996;77(11):2294-2301.