1) Protocol Title

"Safety and Efficacy of the Swallow Expansion Device (SED) for Improvement of Swallowing in Patients with Life-Threatening Aspiration Secondary to Feeding Tube Dependent Oropharyngeal Dysphagia: A Single-Site, Open-Label, Phase I Human Trial"

2) Author of Protocol

UC Davis Research Investigator: Dr. Peter Belafsky, MD, MPH, PhD

3) IRB Review History

This application has been reviewed as IRB ID 390418-1. However, due to the time lapse, we are resubmitting it as for an initial review.

4) Objectives

DESIGN: A single-center, open label, Phase I human trial

DURATION: The initial feasibility study will be 2 years with 5 patients. The FDA has indicated that based on the safety results of this initial study, we may request an expansion of the study to 20 patients.

POPULATION**:** The first 5 subjects of the initial feasibility study will be limited to adult patients with profound feeding tube dependent oropharyngeal dysphagia (OPD) of at least 12 months duration. All patients will be at risk for life threatening aspiration and pneumonia due to the inability to tolerate any food safely by mouth and recruited from the clinical practices of the investigators at the Center for Voice and Swallowing, Department of Otolaryngology, University of California, Davis. If the FDA approves expanding the study, then 15 more subjects will be added.

HYPOTHESIS: The swallow expansion device (SED) will be safe and efficacious for individuals with aspiration and profound oropharyngeal dysphagia (OPD).

PRIMARY OBJECTIVE: Characterize the safety of the SED. Any implant infection, cricoid cartilage damage, implant rejection necessitating removal or other signs of irritation or injury will be noted.

SECONDARY OBJECTIVES: Characterize the efficacy of the SED by evaluating upper esophageal sphincter (UES) opening, swallowing safety, and dysphagia-specific quality of life following implantation of SED.

5) Background

High Prevalence of Oropharyngeal Dysphagia (OPD)

The three primary functions of the larynx are airway protection, respiration, and phonation (Tucker, 1987). If the larynx is unable to provide adequate airway protection during deglutition or the pharynx is unable to provide adequate bolus transit through the upper esophageal sphincter, oropharyngeal dysphagia (OPD)

ensues. Causes of OPD include stroke, head and neck cancer, head injury, advancing age, cricopharyngeus muscle dysfunction, amyotrophic lateral sclerosis, pseudobulbar palsy, Alzheimer's disease, Parkinson's disease, multiple sclerosis, muscular dystrophy and myasthenia gravis. OPD adversely affects approximately 30% of all hospitalized patients (Altman, 2010), 75% of individuals in nursing homes (Spieker, 2000) and 78-81% of patients post-stroke (Martino, 2005). Epidemiological studies suggest that dysphagia also impacts 22% of all adults 50 years or older and most individuals by 80 years of age (Howden, 2004). Concurrent chemoradiation for head and neck cancer is associated with a 45% incidence of prolonged feeding tube dependent OPD and an incidence rate for aspiration of 59% (Nguyen, 2004; Nguyen, 2006). The incidence of swallowing difficulties in persons with Parkinson's disease is nearly 100% (Rosenbek, 2009). Despite the high prevalence of dysphagia, current treatment options are limited and millions of people remain disabled.

Impact of OPD

The impact of OPD on quality of life, morbidity, mortality, and health care expenditure is significant. In a survey of nasopharyngeal cancer survivors, dysphagia was the most important predictor of diminished quality of life (Lovell, 2005). Elevated anxiety and depression are associated with dysphagia in head and neck cancer patients (Nguyen, 2006). Dysphagia in persons after total laryngectomy is associated with markedly increased social isolation, significantly impaired global functioning, depression, and anxiety, and in the general population, dysphagia is associated with depression and reduced general health (Eslick, 2008; Maclean, 2009). Dysphagia is also associated with the feeling of helplessness, and the majority of persons with OPD believe that their condition is untreatable (Ekberg, 2002). Complications of dysphagia include aspiration, dehydration, pneumonia, malnutrition, depression, and death. The dysphagia-specific mortality rate in persons treated with chemoradiation for head and neck cancer is 9% (Nguyen, 2006). Aspiration pneumonia is one of the most common causes of death after stroke and is the most common cause of death in persons with Parkinson's disease (Schmidt, 1994; Rosenbek, 2009). Of the 77 million hospitalizations in the U.S. in 2004-2005, the adjusted mortality rate associated with OPD was 13.7, and hospital stays associated with dysphagia were twice as long as those for nondysphagic patients, representing a cost per year in the U.S. of $547 billion (Altman, 2010). Because of the high economic cost of OPD, the significant impact of OPD on quality of life, and the associated morbidity and mortality, improved recognition and treatment of this disorder are warranted.

Treatment Options for Profound OPD are Severely Limited

For persons with OPD, current treatment options include diet modification, swallowing therapy, intraoral prosthetics, non-oral feeding and invasive surgery. If a comprehensive dysphagia assessment with videofluoroscopy or nasoendoscopy reveals difficulty with certain food consistencies, dietary restrictions may be recommended or food rheology may be manipulated. Depending on the individual needs and the cognitive ability of the patient, swallowing therapy may include

exercise, sensory enhancement, postural changes, transcutaneous electrical stimulation, and swallowing maneuvers (Blumenfeld, 2006; Logemann, 2008; Mepani, 2009). Dental prosthetics may be employed to restore function to defects of the palate and tongue. If conservative management is unsuccessful in mitigating OPD, surgery may be considered. Surgical procedures shown to improve swallowing function in certain individuals with OPD include esophageal and upper esophageal sphincter dilation, cricopharyngeus muscle botulinum toxin injection, cricopharyngeus muscle myotomy, medialization laryngoplasty, arytenoid adduction, laryngohyoid suspension, pharyngoplasty, epiglottopexy, lateral thyrolaminectomy, great auricular to superior laryngeal neurorrhaphy, diverticulectomy and diverticulotomy in patients with a hypopharyngeal diverticulum, vocal fold closure, laryngotracheal separation, and total laryngectomy. The aim of these operations is to improve laryngopharyngeal sensation, airway protection, and upper esophageal sphincter opening. Regardless of our best efforts, these treatments fail in a significant percentage of individuals.

Rationale for Study

Biomedical devices, such as artificial joints and pacemakers, are accepted and commonly used in medicine. While great progress in biomedical devices has been made for many other disorders, there is currently no device available to assist with the act of deglutition. We have developed a biomedical device (Swallow Expansion Device, SED) that assists with swallowing by mechanically opening the upper esophageal sphincter and allowing food and liquid to safely enter the esophagus. The SED has proven safe in cadaver and live animal studies (Belafsky, 2010). A Phase I, feasibility human trial is indicated to move the SED forward and improve the care of patients with OPD.

6) Inclusion and Exclusion Criteria

Screening

All individuals will be provided with a patient brochure describing the study and will have signed the consent form before enrollment screening. After signing the consent form, the potential candidate will be asked about their demographics (age, date-of-birth). Physical characteristics will be collected, such as weight, height, pain scale, and breathing scale. Information on the individual's present and past medical history as well as medication history will be collected. A general physical examination will be performed. A serum or urine β-HCG (urine test must have a sensitivity of 25-50 mIU/mL) pregnancy test will be given to those women within childbearing age to confirm that they are not pregnant.

The potential subject will receive a fluoroscopic swallow study to ensure profound OPD, diminished UES opening (< .55 cm for individuals under 65 years of age, < .40 cm for individuals over 65 years of age), and an inability to tolerate any food safely by mouth. Potential subjects will also an endoscopy to determine laryngeal sensory threshold (< 6 mmHg air pulse pressure or a complete absence of the laryngeal adductor reflex on palpation

of the arytenoid with a flexible laryngoscope). Swallowing safety will be assessed with the Penetration Aspiration Scale (PAS: score of 5-8 indicates severe swallowing disability).

The potential subject will complete the following assessments: 1) Abbreviated Mental Test Score (AMTS) to assess cognition, 2) Block and Box Test (BBT) to assess manual dexterity (ability to grasp the SED post), and 3) dysphagia specific quality of life instrument, the 10-item Eating Assessment Tool (EAT-10). The potential subject must demonstrate that they have the physical strength to pull the SED post forward, as evidenced by the ability to lift a 5-pound weight off of a table and keep it elevated for 10 seconds. The 5 lb weight criteria is based on previous patient experience in which patients were able to control swallowing on their own with a suture by opening the upper esophageal sphincter with a mean pound-force of 4.18 (± 0.68) (Belafsky, 2010).

Inclusion Criteria

1) Profound oropharyngeal feeding tube dependent dysphagia of greater than 12 months duration, as documented by the prevalence of aspiration on fluoroscopic swallow study.
2) Must be receiving 100% of nutritional requirements by enterogastric tube.
3) 18 years of age and older, acceptable forms of documentation for verification of age include birth certificate, passport, and/or driver's license.
4) Diminished UES opening defined as less than .55 cm for individuals under 65 years of age and less than .40 cm for individuals over 65 years of age on fluoroscopic swallow study.
5) Failure of > 3 months of dysphagia therapy within 3 months of study enrollment.
6) No documented history of noncompliance with feeding recommendations.
7) Cognition that is within normal limits, as evidenced by an Abbreviated Mental Test Score (AMTS) score greater than 6.
8) Manual dexterity that is within normal limits for age, sex, and hand, as evaluated by a Block and Box Test (BBT).
9) Physical strength to pull the SED forward, as evidenced by the ability to lift a 5 lb weight off of a table and keep it elevated for 10 seconds.
10) Ability to understand the informed consent and comply with follow-up, as evidenced by appropriate questions, responses, and comments during the initial evaluations and a normal Abbreviated Mental Test Score.
11) Bilateral vocal fold mobility or unilateral vocal fold immobility in which the individual is able to attain complete glottic closure as evidenced on endoscopy.

Exclusion Criteria

1) Profound oropharyngeal feeding tube dependent dysphagia < 12 months duration.
2) Esophageal phase dysphagia as defined as personal history and/or documented diagnosis of esophageal dysmotility, hiatal hernia, stricture, eosinophilic esophagitis, erosive peptic esophagitis, and/or systemic disease affecting the esophagus.
3) Able to safely consume any food or liquid by mouth, as documented by fluoroscopic swallow study.
4) Normal UES opening, as evidenced by UES opening greater than .55 cm for individuals under 65 years of age and greater than .40 cm for individuals over 65 years of age on fluoroscopic swallow study.
5) Currently pregnant, as evidenced by a positive result on a pregnancy test if the patient is within child bearing age (younger than 60 years of age).
6) 17 years of age and younger, acceptable forms of documentation for verification of age include birth certificate, passport, and/or license.
7) Success full receipt of dysphagia therapy or < 3 months of dysphagia therapy within 3 months of study enrollment.
8) Lack of manual dexterity to operate swallowing expansion device as determined by a Block and Box Test (BBT) score below the normal limits per age, sex, and hand.
9) Inability to lift a 5 lb weight off of a table and keep it elevated for 10 seconds.
10) Lack of cognitive ability to operate swallowing expansion device or provide informed consent as evidenced by an Abbreviated Mental Test Score (AMTS) score less than 6.
11) Active tumor involving the cricoid or laryngeal cartilage.
12) Known allergic reaction to titanium as evidenced by personal history of allergic or adverse reaction to titanium.
13) Infection of cartilage, head, and/or neck at time of evaluation and/or implantation as documented by recent imaging study or abnormal physical examination.
14) Presence of a tracheotomy tube or airway obstruction necessitating a tracheotomy tube.
15) A documented history of noncompliance with recommendations to take nothing by mouth.
16) Patients with an insensate larynx. Laryngeal sensation will be assessed with laryngopharyngeal sensory testing. An insensate larynx is defined as a laryngopharyngeal sensory threshold < 6 mmHg air pulse pressure or a

complete absence of the laryngeal adductor reflex on palpation of the arytenoid with a flexible laryngoscope.

17) Patients with a current, at the time of evaluation, and/or history of Zenker's diverticulum.
18) Patients with sialorrhea at the time of evaluation with or without oral commissure incompetence.
19) Patients with profound xerostomia at the time of evaluation.
20) Patients with orocutaneous or pharyngocutaneous fistualae at the time of evaluation.
21) Patients with a current, at the time of evaluation, and/or history of immunosuppression, as defined by the patient having a diagnosed immunodeficiency disorder or on immunosuppressive medication.
22) Patients with a current, at the time of evaluation, and/or history of coagulopathy, as defined by the patient having a diagnosed coagulation disorder or on anticoagulation medication (e.g., baby aspirin, OTC non-steroidal anti-inflammatories, herbal agents, and warfarin, etc.) that cannot be temporarily stopped for the procedure.
23) Patients taking sedatives, narcotics, muscle-relaxants, anxiolytics, medical marijuana, alcohol, nicotine, medicinal nicotine, or other mind-altering medications that may affect safe patient use of the swallowing device.
24) Patients taking antifibrotic medications.
25) Patients with bilateral vocal fold immobility in any position, as evidenced on endoscopy.
26) Patients with unilateral vocal fold immobility and unable to attain complete glottic closure, as evidenced on endoscopy.
27) Patients with current, at the time of evaluation, and/or documented history of subglottic stenosis, as evidenced on endoscopy.
28) Patients with current, at the time of evaluation, and/or documented history of airway obstruction, as evidenced on endoscopy.
29) Patients with a life expectancy < 2 years.

Adults unable to consent, individuals who are not yet adults (infants, children, teenagers), pregnant women, and prisoners are excluded.

If all inclusion criteria and screening assessments are satisfied (and exclusion criteria are negative), the potential subject will be asked to enroll in the study.

Table 1: Patient assessments, frequency, and criteria

Tests and evaluations	Frequency	Scale / assessment criteria
EAT-10 survey	Prior to SED	Dysphagia specific quality of life

	implantation Month 6 2 years (end of study)	will be assessed with the Eating Assessment tool (EAT-10). The EAT-10 is a validated self-administered disease specific quality of life instrument for dysphagia. EAT-10 survey results over the course of the study are a secondary endpoint.
Abbreviated Mental Test Score (AMTS)	Prior to SED implantation	A score of > 6 is required for study inclusion.
Block and Box Test (BBT)	Prior to SED implantation	A score within the normal limits per age, sex, and hand is required for study inclusion.
5 pound weight lift	Prior to SED implantation	The ability to hold the weight off the table for 10 seconds is required for study inclusion.
Laryngopharyngeal sensory threshold	Prior to SED implantation	A threshold of < 6mmHg air pulse pressure is required for study inclusion.
Fluoroscopic swallow evaluation	Month 2 2 years (end of study)	Results over the course of the study will be evaluated as primary and secondary endpoints.
Determination of 8 point Penetration Aspiration Scale (PAS)	Month 2	0 = indicates a safe swallowing 1-2 = indicates mild swallowing disability 3 – 5 = moderate swallowing disability 5 – 8 = severe swallowing disability [results over the course of the study are a primary safety endpoint].

7) Number of Subjects

The total number of subjects to be enrolled locally for the initial feasibility study, N=5. Expanded study, N=20 (add 15 more subjects to study).

8) Recruitment Methods

a) Local:

Initially, 5 subjects will be recruited from the clinical practice of the Investigator (UC Davis Department of Otolaryngology, 2521 Stockton Blvd., Sacramento, CA). The patient population will include all individuals with chronic (>12 months) tube-dependent OPD who have failed traditional therapy and available surgical options. They will all be at risk for life threatening aspiration and pneumonia as determined by previous fluoroscopic swallow

assessment. All patients must possess the cognitive ability and manual dexterity to pull the device forward during swallowing. Although the majority of persons with profound tube-dependent OPD are > 50 yrs of age, there is no contraindication based on age, gender, race, or socioeconomic status. The study will be limited to adults 18 years of age and older.

Once a candidate for study entry has been identified, the Investigator or Co-Investigator will carefully explain the details of the study, and the candidate will be given a brochure describing the SED. If subjects are interested in the study, they will go through the informed consent process at the Department of Otolaryngology Voice and Swallowing Center (6th floor of Glassrock Building). During this process, they will be given a copy of the UC Davis Permission to Take Part in a Human Research Study form, which describes the study, and the Experimental Subject's Bill of Rights to review with research study personnel. Subjects are encouraged to ask any questions/voice concerns. If and when the subject consents, they will be asked to sign and date the informed consent form, Bill of Rights form, and HIPAA Authorization form, of which they will then receive signed and dated copies. Subjects will next undergo screening.

b) HIPAA:

A waiver of HIPAA will be submitted for screening and/or recruitment procedures. The screening procedures pose no more than minimal risk to the participants. The participant's rights and welfare will not be adversely affected by waiving consent. The waiver is needed to conduct records research to find potential patients that fit the inclusion / exclusion criteria, which fits the HIPAA Privacy Rule "preparatory to research provision."

This study involves the collection of PHI for recruitment purposes. Identifiers collected are name, date of birth, and medical record. The data will be stored electronically on an established database that is secure, password protected, and currently IRB-approved for the Department of Otolaryngology. Only investigators listed on the protocol will have access to the database.

Data sheets used in the collection of PHI and generation of the recruitment database will be destroyed upon completion of the recruitment process. No data will be disclosed from the study.

We assure that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information for which an authorization or opportunity to agree or object is not required by 45 CFR 164.512.

9) Compensation to the Subjects

Subjects will not be compensated.

10) Study Timelines

The initial feasibility study will be 24 months with 5 patients. The study will be expanded to 20 patients pending FDA approval of the safety results of the initial feasibility study. The estimated date of study completion is 2 years after the final subject is implanted with the SED. We estimate 1-3 months for data analysis, depending upon whether the study population is 5 or 20 patients.

Table 2: Schedule of Events by Time

Time	Prior to SED Implantation	Day 0	Day 1	Week 1	Weeks 3, 5, & 7	Week 8 (Month 2)	Months 3 - 5	Month 6	Months 6 -23	Months 24 (2 yrs)
Event	Fluoroscopic swallow evaluation (UES opening)	SED surgery in out-patient clinic	Follow-up phone call	Follow-up clinic visit	Follow-up clinic visit	Follow-up clinic visit	Monthly follow-up clinic visits	Follow-up clinic visit	Monthly follow-up clinic visits .	Follow-up clinic visit
	Penetration Aspiration Scale (PAS)									
	Laryngo-pharyngeal sensory threshold					Fluoroscopic swallow evaluation (UES opening)		EAT-10 survey		EAT-10 survey
	Abbreviated Mental Test Score (AMTS)									Fluoroscopic swallow evaluation (UES opening)
	Block and Box Test (BBT)			Skin suture removal		Penetration Aspiration Scale (PAS)				
	EAT-10 survey									Penetration Aspiration Scale (PAS)
	Lift a 5 lb weight off a table and hold for 10 seconds					Dietary changes				Surgical removal of SED

11) Study Endpoints

The primary objective of the experiment is to characterize the safety of the SED. Any implant infection, cricoid cartilage damage, implant rejection necessitating removal or other signs of irritation or injury will be noted at each monthly clinical visit and over the course of the study and recorded on the case report form.

The secondary objective of the study is to characterize SED efficacy as defined by UES opening, swallowing safety (Penetration Aspiration Scale: PAS), and dysphagia-specific quality of life (EAT-10).

For evaluation of both UES opening and swallowing safety (PAS), all measurements will be made from a de-identified pre-recorded digital video presented in random order at the end of the last time point to two investigators fully masked to SED use and time of recording (before SED implantation, and 2 months and 2 years post-SED implantation). Fluoroscopy trials will be digitally recorded using a Sony MD-1000 DVD recorder (Sony Corp. of America, New York, NY) and imported into ImageJ 1.41 for the Macintosh (National Institute of Health, Bethesda, MD).

UES opening will be measured via fluoroscopy. Our quantitative assessment has been previously reported but will be briefly described (Leonard, 2006; Leonard, 2008a; Leonard, 2008b). A digital still image will be captured at the point of maximum UES opening with and without anterior traction of the SED. The software will be calibrated to the known length of the SED that is visible in the fluoroscopic image. The distance between the anterior and posterior pharyngo-esophageal segment at the point of maximum UES opening will be calculated using analysis software with ImageJ.

Swallowing safety, a measure of swallowing efficacy, will be assessed with the Penetration Aspiration Scale (PAS), a validated measure of swallowing safety determined on videofluoroscopy (Ludlow, 2007). A score of 1 indicates a safe swallow (material does not enter the airway). A score of 2-3 indicates mild, 4-5 moderate, and >5-8 severe swallowing disability (material enters the airway, it passes below the vocal folds, and no effort is made to expel it). The patient is initially fed a 1 cc bolus of thin barium. If no aspiration is detected, the patient is then administered a 3 cc and then 20 cc bolus, or largest bolus possible, of barium. If any aspiration is detected at any stage of the study, the procedure is terminated immediately. The PAS will be calculated for the largest swallowed bolus size on fluoroscopy.

Dysphagia specific quality of life will be assessed with the Eating Assessment tool (EAT-10). The EAT-10 is a validated self-administered disease specific quality of life instrument for dysphagia (Belafsky, 2008). The EAT-10 will be administered prior to device implantation, 4 months after use of the device (6 months after implantation), and at 2 years after device implantation.

12) Procedures Involved

Device Implantation:

Once enrolled in the study, the patient will be scheduled for surgical implantation of the SED, which will be performed at the UC Davis Swallowing Center outpatient operating room. Before the surgery, the patient will receive pre-operative clearance from the anesthesia service as well as appropriate pre-operative prophylactic antibiotics with 1g Cefazolin delivered intravenously. Immediately before the procedure, the patient will be given intravenous sedation, which is achieved with a combination of appropriate doses of Versed and Fentanyl, per continuous anesthesia monitoring.

Once under sedation, the patient will be placed in the supine position with a shoulder roll. The neck will be prepped and draped in the usual sterile fashion. A combination of anesthetic and vasoconstrictor agent (2% lidocaine, two 1:100,000 units of epinephrine) will be injected into the incision site and underlying soft tissue and strap muscles. A 4 cm incision will be made in a cosmetically appealing skin crease 3 cm below the level of the cricoid cartilage. The subplatysmal skin flaps will be elevated, and the strap muscles divided in the midline. The cricoid will be identified, and the SED will be secured to the anterior rim of the cricoid with five 2-0 prolene sutures. The wound will be irrigated with antibiotic impregnated irrigation and the strap muscles closed over the SED. The SED post will be brought out through the skin at the level of the cricoid cartilage 3 cm above the incision. The skin will be closed in two layers with suture and/or surgical staples. Antibiotic ointment will be applied to the incision. Before discharge, the patient will be instructed in local wound care. They will also be kept on 500 mg Cefazolin administered per their existing PEG tube 4X daily for 10 days.

Immediately Post-Implantation:

Immediately following surgery, each patient will be given post-surgery care instructions, "Patient Instructions For Use", and a medical wallet card with emergency contact information. Each patient will be called on the first postoperative day to ensure that the patient is doing well and to monitor for any adverse events. If there is any indication of an adverse event, the patient will be seen immediately in the clinic. The patient will otherwise return to the clinic one week after device implantation. The skin sutures will be removed, and the incision will be evaluated for any signs of infection or implant rejection. The patient will be instructed on how to daily care for and clean the device and will return to clinic for an evaluation three, five, and seven weeks post-surgery. The patient will be told to not use the device or eat or drink anything by mouth until two months (week 8) after device implantation and only after physician evaluation and approval because the device could become loose or infected and need to be removed.

Two Month Post-Implantation Evaluation for Use:

Two months post-implantation, the patient will return to the clinic for a fluoroscopic swallowing evaluation with and without anterior traction on the SED. If swallowing is

improved and there is no aspiration, the patient will be taught how to coordinate pulling the SED with the correct amount of force at the appropriate time during swallow. Initial experience with a suture in humans suggests that patients readily adapt to manual control of the UES (Belafsky, 2010). There will be an initial training period in which a patient is instructed to do a limited number of pulls (1st week: 10 pulls / meal; 2nd week: 20 pulls / meal; 3rd week: 30 pulls / meal; 4th week: 40 – 50 pulls / meal). Patients will then be able to use the SED *ad lib*. If the SED is not approved for use in the patient, it will be removed.

The rationale for limiting the number of pulls initially is to slowly and safely build up proficiency with the device. Under mechanical testing, the SED post-to-plate weld withstood up to 1,096,00 cycles of 6.3 pounds of pull force. This calculates to a life expectancy of 5 years when used 600 times per day, the normal number of swallows per day (John Hopkins, 2013). We feel that this is an adequate safety factor considering that it is more than double the length of the 2-year study, which at the end, the SED will be removed and the fact that the SED is designed to use while eating, not while spontaneous swallowing. It expected that subjects will use a pull force less than that used in the mechanical testing; in a 6-patient study where sutures were placed around the cricoid cartilage and the patients manually pulled on the sutures, the patients were able to control swallowing on their own by opening the upper esophageal sphincter with a mean pound-force of 4.18 (± 0.68) (Belafsky, 2010). This is approximately 2 lbs less than the mechanical testing.

In order to monitor the number of pulls, the physician will give the patient a monthly calendar form and hand clicker to record the number of pulls per meal. The total number of pulls / day will be recorded. Besides ensuring safety monitoring of the number of pulls, the forms will allow a record of progress with time. Calendar forms will be reviewed and provided at each monthly clinic visit.

Patients will receive instruction on steps to take if the SED post breaks or the device malfunctions. These include the following: 1) Immediately stop using the device, 2) Keep the area clean and dry, 3) Call the emergency physician telephone number listed on the patient wallet card; 4) If there is any bleeding, pain, fever or symptoms of breathing difficulty, go immediately to the nearest emergency room or call 911, and 5) If a piece of the device breaks off, place it in a bag and bring it to your doctor. In addition, the IRB and FDA will be notified of any adverse event, and it will be recorded on the case report form and on a separate Adverse Event Form.

Monthly Follow-Up Visits:

At each monthly follow-up visit, subjects will be evaluated for and questioned about overall health, secretion management, current diet, dysphagia symptoms, pulmonary status, pain, safety concerns, and changes in medical status. The physical appearance of the implant site will be evaluated for infection, cartilage damage, injury/irritation, infection, and implant rejection to determine SED safety. Subjects will be weighed to ensure proper

nutrition and asked to bring in their monthly record of SED pulls per day. Any concerns or necessary dietary adjustments will be addressed at this time. It is hoped that a patient will use the SED to such an extent that they can eventually enjoy most of their food via deglutination. However, even if a patient has limited use of the SED and must rely on the majority of nutrition/hydration delivered via feeding tube, the very act of swallowing is beneficial as it improves oral hygiene (flushing out bacteria, saliva) and stimulates oropharyngeal muscles and nerves.

If there are signs of irritation or injury to the implant site or if the patient complains about discomfort due to SED use, the patient will be instructed on how to modify the number of SED pulls per day and care for the implant site. Follow-up calls to the patient will be made to determine if there is improvement. If there is no change, the patient will be told to return to the clinic. If there is improvement, the patient will be instructed on how to continue their course of SED use and will be re-evaluated at the next follow-up clinic visit. They will be told to contact the Voice and Swallowing Center at any time if they have problems or questions. If there are any signs of skin infection or implant rejection, the patient will receive appropriate antibiotics and wound care. If there is any sign of abscess or implant rejection, or any infection does not resolve with appropriate antibiotics, the device will be removed. This can be performed in the clinic or minor procedure room under local anesthesia. Patients will undergo routine PEG maintenance and replacement as per routine care.

If due to extenuating-circumstances the larynx and SED implant are to be removed together then both will be retained to further study how the device integrated into the laryngeal tissue. Also during SED implant removal, photographs may be taken of the implant site in vivo and ex vivo. Implant removal at the 24 month study period will be considered as part of the study, if the Implant is removed after the 24 month study period then any surgical procedure to remove it will be considered as part of standard of care.

Patients will undergo a dynamic fluoroscopic swallow study and penetration aspiration scale (PAS) two months after the SED has been placed. They will be administered the EAT-10 four months after use of the device (6 months post-SED implantation). These procedures are done to evaluate SED efficacy.

Pending FDA review of the data at the 6-month post-implantation time point and FDA approval, the study will continue to 2 years post-implantation. During this time, the monthly follow-up visits will continue to evaluate device safety. At month 24, patients will undergo final dynamic fluoroscopic swallow and PAS exams and EAT-10 survey. The patient will be scheduled to have the device removed at the completion of the study.

All clinical and laboratory information required by this protocol will be present in the source documents. Sites will refer to the Source Document Guidelines. All stated evaluations are to be recorded on the CRF and keyed into the database unless otherwise specified.

13) Data Management and Confidentiality

Power Analysis:

Per FDA request, the initial feasibility study will be limited to 5 patients. This number of patients will give limited power but provide essential data to evaluate SED safety. If the study is expanded to a sample size of 20 patients following FDA review, we will have at least 85% power to detect a 0.6 standard deviation improvement in safety and efficacy (approximately the equivalent of a shift from the median level to the 73rd percentile). We would have an 88% chance of seeing at least one example of any adverse effect such as infection that occurred in 10% or more of individuals with an SED implant.

Data Analysis:

Per FDA's request, the initial feasibility study will include 5 patients. The cumulative incidence of SED implant infection or other complications, such as cricoid damage and/or implant rejection, related to the SED implant will be shown graphically by a Kaplan-Meier curve, and a six-month cumulative incidence of infection and complication will be estimated with 95% confidence intervals by a life-table approach. The same evaluation approaches will be used pending FDA approval of the study and expansion to 20 subjects for two-years.

Mean UES opening, swallowing safety (PAS), and EAT-10 scores will be compared before and after placement of the implant by analysis of variance, treating examiner as a fixed effect and patient as a random effect to account for repeated measures. UES opening and PAS scores will be compared before and after anterior traction using analysis of variance as described above. All tests will be one-sided, as this study is designed for screening with interest only in detecting improvements in swallowing; tests will be at level 0.05, with Bonferroni correction for multiple comparison. Quality of life with the EAT-10 will be assessed at baseline, 6 months and at 24 months after device implantation. Baseline and 24 month data will be available for FDA review of the initial feasibility study.

Data collected will be stored in a locked file cabinet in the PI's office and on a secure database accessible only by password in the Department of Otolaryngology, so that confidentiality is maintained. Each participant will be given a de-identified alphanumeric code so that the data is not identifiable to the participant. Any adverse reactions will be recorded, notified to the Investigator, IRB and FDA as appropriate.

Dr. Belafsky will maintain the following records, which will be only available to the study team or upon request of the IRB or FDA:

a) All study subject records including signed informed consent forms, case report forms, and any supporting documentation,

b) All correspondence including required reports,

c) Records of shipment of the devices,

d) Records of sterilization and receipt of devices,

e) Records of disposition of a device,

f) Signed investigator agreements including financial disclosure information,

g) Records concerning complaints and adverse device effects whether anticipated or not,

h) Any other records that the FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.

The researchers will keep all necessary data in the Department of Otolaryngology for no more than 10 years, at which time it will be destroyed. The data will be kept for this length of time so that it will be available for the FDA to review for future clinical studies and marketing approval of the SED. If information from the study is published or presented at scientific / educational meetings, names and other personal information will not be used.

14) Provisions to Monitor the Data to Ensure the Safety of Subjects

Study Monitors

Drs. Peter Belafsky and Maggie Kuhn
2521 Stockton Blvd, Ste. 7200, Sacramento, CA 95817

The UC Davis Health System Clinical Trials Resource Group will also assist with monitoring and quality assurance through review of the clinical documents and data. The Group is housed on campus as part of the Clinical and Translational Science Center and ensures compliance with FDA, GCP, and IRB regulations, and UC Davis Health System SOPs and P&Ps as related to clinical research.

Principal Investigator Responsibilities

As PI, Dr. Belafsky, will be responsible that the following are carried out:

- Ensure that the protocol is being followed
- Ensure that changes to the protocol are approved by the UC Davis IRB
- Ensure that accurate and complete records are being maintained by the site
- Ensure that accurate and complete reports are being made to the sponsor and the UC Davis IRB
- Ensure that the information in the investigator's report is complete, accurate, and legible

- Ensure that there are no omissions in the reports of data that may be directly or indirectly relevant to the study
- Ensure that missing examinations are noted in the reports
- Ensure that subjects failing to complete the study are noted along with the reason for such failure
- Ensure that informed consent is documented

The study monitors will be responsible for ensuring that the investigative site is performing their duties as set forth above, and that the investigator understands the following:

- Investigational status
- Device accountability
- Protocol
- Obligation of regulatory requirements
- IRB review and approval
- Obtaining informed consent
- Access to adequate number of subjects
- Access to adequate facilities
- Sufficient time to participate in the study and
- How to use the device

Dr. Belafsky will also provide the following reports in a timely manner to the UC Davis IRB and FDA to ensure the safety of the subjects:

- Unanticipated Adverse Device Effects
- Withdrawal of IRB Approval
- Withdrawal of FDA Approval
- Progress Reports
- Recalls and Device Disposition
- Final Report
- Informed consent
- Significant Risk Device Determination

Reviewing Data, Auditing and Inspecting

The initial feasibility study will be 24 months with 5 patients. The study will be expanded to 20 patients pending FDA review and approval of the safety results of the initial feasibility study.

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and compliance and quality assurance groups

of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance and quality assurance offices.

15) Withdrawal of Subjects

Subjects will be withdrawn from the study without their consent for the following reasons:

Permanent Treatment Discontinuation

- Abscess.
- Implant rejection.
- Infection does not resolve with antibiotics.
- Requirement for prohibited concomitant medications (see exclusion criteria).
- Pregnancy.
- Completion of treatment as defined in the protocol.
- Request by subject to terminate treatment.
- Clinical reasons believed life threatening by the physician.
- MRI imaging (SED removed if MRI is needed).

Premature Study Discontinuation

- Failure by the subject to attend 3 consecutive clinic visits.
- Subject repeatedly noncompliant with study procedures, as prescribed.
- Pregnancy or breast-feeding.
- Request by the subject to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the subject.
- Any evidence of infection or injury not capable of being treated by local care and antibiotics.
- Subject judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the IRB, Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), or investigator.

Subjects will be scheduled for explantation of the SED. They will be provided with post-surgery instructions of care. The event will be recorded on the two

following case report forms: Off-Study Form and Early Off-Study SED Removal Form.

16) Risks to Subjects

Adverse Event Reporting

An adverse event (AE) is any unwanted medical occurrence in a subject that does not necessarily have a causal relationship with the study intervention. An AE can be any unfavorable or unintended sign, symptom, or disease temporarily associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. An adverse device effect (ADE) is a device-related AE.

All AE's will be classified as anticipated, unanticipated, or serious. All potential hazards listed in the Risk Evaluation and Mitigation Strategies (Table 3) are considered "anticipated." All events not listed in the Risk Evaluation and Mitigation Strategies are considered "unanticipated." Expected events that occur with a greater frequency than expected are also considered "unanticipated." A "serious" AE is defined as any untoward medical occurrence that meets any one of the following criteria:

1. Results in death or is life-threatening at the time of the event
2. Requires inpatient hospitalization, or prolongs hospitalization
3. Results in a persistent or significant disability / incapacity
4. Is a congenital anomaly / birth defect (in a participants offspring)
5. Requires medical or surgical intervention to preclude permanent impairment of body function or damage to body structure based on suspected use of a medical device
6. Is medically judged to be an important event that jeopardized the subject, and, for example, required significant measures to avoid one of the above outcomes

AEs that occur during the study, whether considered device / procedure-related or not, will be recorded on the CRF Adverse Event Form and, ultimately, reported in the IDE study. The CRF AE form asks for AE description, start/stop date, outcome, severity, plausible relationship to the study device, action taken (including withdrawal), and AE classification. AE severity will be defined as mild (event that causes mild discomfort or inconvenience and resolves without treatment), moderate (event that requires medical intervention or medication to treat), or severe (event that requires intervention to prevent permanent impairment or damage, an event that requires or prolongs hospitalization, or an event that is disabling, causing permanent damage, life threatening, or causing death). Any necessary treatment or intervention required and the resolution status of the AE will also be documented. Each AE will be followed to resolution. If the AE presents an unreasonable risk to the to the subjects, the SED will be removed and the study terminated for the subject.

Study personnel must notify the Investigator of any unanticipated or serious AE within 24 hours of learning about the event. The investigator

will notify the IRB and FDA within 5 days of becoming aware of the AE.

Table 3: Risk Evaluation (According to 21 CFR 812.25(c)) and Mitigation Strategies

No.	Potential Hazard	Resultant Harm	Risk Evaluation Discussion	Mitigation Strategy
1.	Surgical Procedure	Pain	The device is placed through a small, minimally invasive skin incision under intravenous sedation with anesthesia monitoring. The patient will be brought into the UC Davis Swallowing Center outpatient operating room and placed supine. The neck will be prepped and draped in the usual sterile fashion. The implant is secured to the anterior rim of the cricoid cartilage five 2-0 prolene sutures. The suture is placed through the implant and then around the anterior rim of the cartilage to anchor the device. This technique has shown to be effective in securing the device safely in human cadavers and sheep.	Pre-operative clearance from the anesthesia service; routine surgical sedation; crico-thyroid notch will be infiltrated with 2% lidocaine.
2.	Surgical Procedure	Bleeding		Minimally invasive 4 cm skin incision
3.	Surgical Procedure	Infection		Pre-operative prophylactic antibiotics with 1G Cefazolin. Prophylactic antibiotics administered per patients existing PEG tube for 10 days.
4.	Surgical Procedure – suturing technique	Effects on cricoid cartilage	The implant is secured to the anterior rim of the cricoid cartilage with five 2-0 prolene sutures. Each suture is placed through the implant and then around the anterior rim of the cartilage to anchor the device. Sutures are not placed through the cartilage, and no fixation with surrounding tissue is made. The surgical technique and placement of the device has shown to be effective in securing the device safely in human cadavers and sheep.	Patient evaluation throughout the study per protocol and documented on Case Report Form (CRF).

No.	Potential Hazard	Resultant Harm	Risk Evaluation Discussion	Mitigation Strategy
5.	Device dropped or deemed unsterile in some manner	Delay or abort procedure	There is no increased risk with this surgical procedure as with any other surgical procedure.	(Flash sterilization will not be allowed) Additional sterile devices will be available to prevent procedure cancellation with minimal delay.
6.	Device Plate	Damage to vascular or neural structures	Profound dysphagia is severely disabling. Patients are constantly coughing and choking on their own saliva and are at an enduring risk of aspiration and pneumonia and death. Tube feeds are expensive and dehumanizing. Patients become depressed and socially isolated. The risks associated with implantation of the SED are outweighed by the potential gain in swallowing safety and quality of life improvement to the patient.	This risk has been included on the patient consent form.
7.	Device Plate	Damage to the cricoid cartilage causing dyspnea		This risk has been included on the patient consent form.
8.	Device Post	Infection at entry site Skin irritation	Titanium is highly biocompatible, and titanium implants have precedent in head and neck surgery and are commonly used in traumatic and oncologic reconstruction. The post protrusion through the skin in a manner similar to a common body piercing.	Pre-operative prophylactic antibiotics with 1G Cefazolin Prophylactic antibiotics administered per patients existing PEG tube for 10 days Healing per normal/usual body piercing ASTM F67-00, grade 2 - unalloyed titanium for surgical implant applications Endotoxin testing per ANSI/AAMI ST72, USP <161>, USP <85>, EP 2.6.14, JP 4.01 Steam sterilized per ISO 17665-1:2006

No.	Potential Hazard	Resultant Harm	Risk Evaluation Discussion	Mitigation Strategy
9.	Mechanical trauma – e.g., rolling over while sleeping	Tearing of skin/cartilage Dislodging from cartilage Damage to esophagus	The post protrusion through the skin in a manner similar to a common body piercing.	Precaution included in the IFU. Patient wallet card has emergency Otolaryngology contact information.
10.	Lateral torque; anterior pull (unexpected) Mechanical trauma – e.g., getting clothes caught while dressing/undressing, caught on towel while drying	Tearing of skin/cartilage Dislodging from cartilage Damage to esophagus	The loop design provides a soft, blunt, fingertip sized surface to tactilely locate between the finger and thumb surfaces for the patient to hold onto. The loop is thought to be less likely to catch onto clothing or blankets, with its smooth round design vs. a perpendicular bar that could allow looped threads to slip over either end of the bar. The loop design has not shown any problems of this nature in testing conducted to date.	Precaution included in the IFU. Mechanical integrity testing. Patient wallet card has emergency Otolaryngology contact information.
11.	Severe mechanical trauma separating post from plate	Device inoperable by patient Damage to esophagus	The post protrudes through the skin in a manner similar to a common body piercing. The small size of the plate and post length lends to it being highly improbable that sheer force can be applied at the right angle to separate the post from the plate.	Weld inspection. Mechanical integrity testing. Precaution and instructions included in IFU. Patient wallet card has emergency Otolaryngology contact information.
12.	Severe mechanical trauma pushes post end back through skin - e.g., car airbag deployment; severe coughing	Device inoperable by patient Skin injury, bleeding, pain Requires surgical intervention to relocate through appropriate exit	The post protrudes through the skin in a manner similar to a common body piercing.	Precaution included in the IFU. Patient wallet card has emergency Otolaryngology contact information.

No.	Potential Hazard	Resultant Harm	Risk Evaluation Discussion	Mitigation Strategy
13.	Intended use of device – engaging post to open UES	Weld fails, separating post from plate	Swallowing dysfunction (oropharyngeal dysphagia: OPD) is common and costly. The impact of OPD on quality of life, morbidity, mortality, and health care expenditure is significant. The SED is intended to reduce the aspiration of saliva, allow for the oral consumption of food, and improve (transform) an individual's quality of life.	Weld inspection. Mechanical integrity testing. Precaution and instructions included in IFU. Patient wallet card has emergency Otolaryngology contact information.
14.	Unintended use of the device - too much tension on post	Dislodges plate from cartilage; tissue tears	Healing occurs in eight weeks. During this time, the Swallow Expansion Device (SED) plate becomes incorporated by a thick fibrous capsule, which ensures a strong integration with the cricoid cartilage.	Mechanical integrity testing Precaution included in the IFU. Patient wallet card has emergency Otolaryngology contact information.
15.	Unintended use of device - too little tension on post	Upper esophageal sphincter (UES) under expanded, swallowing does not occur; aspiration		Mechanical integrity testing Precaution included in the IFU and patient wallet card has emergency Otolaryngology contact information.

No.	Potential Hazard	Resultant Harm	Risk Evaluation Discussion	Mitigation Strategy
16.	Implanted device design – anatomy concerning: 1. Mobility of cricoid cartilage during speech and swallowing; and 2. Percutaneous placement of device	Local wound infection	Cartilaginous infections are difficult to manage, particularly those of the cricoid cartilage. In addition, cricoid cartilage infections (chondritis) can lead to devastating complications of loss of cartilage and breathing difficulties from loss of cricoid cartilage stability.	To minimize patient harm associated with infection, patients will be closely monitored every two weeks for the first two months after implantation. They will then be monitored monthly until two years after device implantation. Monitoring, besides visual examination by a physician, includes a pain scale and ease of breathing scale, both of which could be indications of adverse effects on the cricoid cartilage. Any sign of infection will be immediately treated with appropriate antibiotics. The implant will be removed if there is any sign of infection that does not resolve with antibiotics or any sign of abscess formation, tissue or cartilage damage, or implant rejection.
17.	Implanted device – corners or edges of plate	Stress concentrations, tissue damage over time	The Swallow Expansion Device (SED) plate becomes incorporated by a thick fibrous capsule, which ensures a strong integration with the cricoid cartilage.	All edges of the plate have a rounded radius vs. square. Electro-polishing of finished device removes burrs that may be present; visual inspection. Mechanical integrity testing.
18.	Implanted device	Remodeling, deformation, chondritis	The implant is secured to the anterior rim of the cricoid cartilage with five 2-0 prolene sutures. The suture is placed through the implant and then around the anterior rim of the cartilage to anchor the device. This technique has shown to be safe and effective in securing the device in human cadavers and sheep. There was no histological evidence of chondritis or cartilage damage in our animal experiments.	Patient evaluation throughout the study per protocol and documented on Case Report Form (CRF). Two years after implantation the study will be terminated and the implant will be removed. The patients are under routine medical care for their condition, and the implant will be part of their history and on-going routine medical care.

No.	Potential Hazard	Resultant Harm	Risk Evaluation Discussion	Mitigation Strategy
19.	Implanted device	Device rejection	As with any implant, there is a risk of implant infection and rejection. Titanium is highly biocompatible. Titanium implants have precedent in head and neck surgery and are commonly used in traumatic and oncologic reconstruction.	This risk is included on the patient consent form. Device constructed from ASTM F67-00, grade 2 - unalloyed titanium for surgical implant application. To minimize patient harm associated with rejection, patients will be closely monitored every two weeks for the first two months after implantation. They will then be monitored monthly until two years after device implantation. The implant will be removed if there is any sign of infection that does not resolve with antibiotics or any sign of abscess formation, tissue or cartilage damage, or implant rejection.
20.	Implanted device	Inability to perform emergency tracheotomy or standard airway intubation	Because the location of the implant is in close proximity to the location of a tracheotomy tube, this implant may be at an increased risk of becoming infected	This risk has been included on the patient consent form. Precaution included in the IFU and patient wallet card. Removal of the device is recommended should a tracheotomy be required. Removal of the device can be performed at the time of tracheotomy tube placement or at anytime before the procedure.

No.	Potential Hazard	Resultant Harm	Risk Evaluation Discussion	Mitigation Strategy
21.	Implanted device	Radiation exposure from fluoroscopic swallow study Impact from radiation therapy	Subjects will be exposed to radiation when undergoing fluoroscopy. Because fluoroscopy is a standard procedure in the Department of Otolaryngology to assess swallowing, it is already approved by the UC Davis Health System Radiation Use Committee and monitored by Radiation Safety Program at UC Davis. The potential risks from the Modified Barium Swallow (MBS) studies (evaluation) are negligible. MBS does involve some radiation to the neck. The exact amount of radiation varies with the time of exposure, settings and equipment used. One study in the literature reported a 5 minute MBS study delivers an effective dose of 0.4 mSv (40 mrem), which they stated was equivalent to 10 chest x-rays (Wright et al., Dysphagia, 1998. 13:113-115). Other sources have reported different levels of radiation. One of the Boston University co--investigators had a physicist measure radiation exposure for 2 ½ minutes of MBS; the results were a whole body effective dose of 9 mrem. This would convert to only 18 mrem for a 5 minute study. Moreover, the University of South Carolina Radiation Safety Office web site (http://www.musc.edu/fanda/risk/radiation) states that a chest x-ray yields 8 mrem, with a range of 3 to 20 mrem. Thus, it appears that the two examinations (the MBS and chest x-ray) are very similar in the level of radiation exposure. Thus, the risk of radiation exposure from a MBS is negligible. The effect of the device on radiation therapy to the neck is uncertain.	This risk has been included on the patient consent forms. Should radiation therapy to the neck be required, we recommend removal of the device prior to the initiation of therapy. Precaution added to IFU for healthcare provider.

No.	Potential Hazard	Resultant Harm	Risk Evaluation Discussion	Mitigation Strategy
22.	Implanted device	Seroma	Titanium is highly biocompatible and magnetic resonance imaging (MRI) compatible. Titanium implants have precedent in head and neck surgery and are commonly used in traumatic and oncologic reconstruction.	This risk has been included on the patient consent forms.
23.	Implanted device	Erosion		This risk has been included on the patient consent forms.
24.	Implanted device	Allergic response		This risk has been included on the patient consent forms. Device constructed from ASTM F67-00, grade 2 - unalloyed titanium for surgical implant application.
25.	Implanted device	Migration or loosening	Based upon animal experiments, a 2-month waiting period prior to use of the device allows for a mature fibrous capsule to form. This allows the device to become integrated onto the cricoid cartilage before patient use.	This risk has been included on the patient consent forms and IFU.
26.	Implanted device	Pain – at implant site or while swallowing	Profound dysphagia is severely disabling. Patients are constantly coughing and choking on their own saliva and are at an enduring risk of aspiration and pneumonia and death. Tube feeds are expensive and dehumanizing. Patients become depressed and socially isolated. The risks associated with implantation of the SED are outweighed by the potential gain in swallowing safety and quality of life improvement to the patient.	This risk has been included on the patient consent forms. Patient evaluation of pain scale (1-5) throughout the study documented on Case Report Form (CRF) Two months after implantation and prior to patient use, a fluoroscopic swallow evaluation will be performed with and without anterior traction on the device.

No.	Potential Hazard	Resultant Harm	Risk Evaluation Discussion	Mitigation Strategy
27.	Implanted device	Impaired swallowing	The Penetration Aspiration Scale (PAS) is a validated measure of swallowing safety determined on video-fluoroscopy. A score of 0 indicates a safe swallow. A score of 1-2 indicates mild, 3-5 moderate, and >5 indicates severe swallowing disability.	This risk has been included on the patient consent forms. Two months after implantation and prior to physician approval of patient SED use, a fluoroscopic swallow evaluation will be performed with and without anterior traction on the SED. Swallowing safety will be assessed with the Penetration Aspiration Scale (PAS). The PAS will be calculated from de-identified pre-recorded digital video for the largest swallowed bolus size on fluoroscopy before placement and two months after placement of the SED by an investigator without knowledge of the presence or absence of SED use.
28.	Implanted device	Security system activation – e.g. retail stores, airports	Titanium is highly biocompatible. Titanium implants have precedent in head and neck surgery and are commonly used in traumatic and oncologic reconstruction.	This risk has been included on the patient consent forms. Patient will have a wallet card.

No.	Potential Hazard	Resultant Harm	Risk Evaluation Discussion	Mitigation Strategy
29.	MRI and/or CT incompatibility	Misdiagnosis with imaging procedure; dislodging of device	Titanium is highly biocompatible and magnetic resonance imaging (MRI) compatible. Titanium implants have precedent in head and neck surgery and are commonly used in traumatic and oncologic reconstruction.	We recommend that device be removed before MRI. Precaution added to IFU and patient wallet card. Plate and post constructed of ASTM F67-00, grade 2 - unalloyed titanium for surgical implant application. Report *Evaluation of Magentic Field Interactions, Heating, and Artifacts at 3-Tesla for the Swallow Expansion Device (SED)* ▪ Magnetically induced forces and torques ▪ Heating of the device produced by the magnetic and RF fields during imaging ▪ Image artifacts produced from presence of device FDA Guidance – Establishing Safety and Compatibility of Passive Implants in the MR Environment ASTM F2052 *Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Device in the Magnetic Resonance Environment* ASTM F2119 -07 *Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants* ASTM F2182-11 *Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging* ASTM F2503 *Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment* IFU includes: ▪ MR field conditions (1.5T and/or 3T; open and/or cylindrical MR systems) ▪ Spatial gradient ▪ Displacement force ▪ MR heating

No.	Potential Hazard	Resultant Harm	Risk Evaluation Discussion	Mitigation Strategy
30.	Image artifact or lack of artifact with CT (contrast and non-contrast), PET, nuclear medicine, ultrasound images of the thyroid.	Misdiagnosis with imaging procedure	Titanium is highly biocompatible and magnetic resonance imaging (MRI) compatible. Titanium implants have precedent in head and neck surgery and are commonly used in traumatic and oncologic reconstruction.	Should imaging of the neck be required, inform the healthcare providers about the implant prior to the procedure. Should the patient's physician determine the imaging procedure absolutely necessary, removal of the device prior to the initiation of the imaging procedure is recommended. Precaution included in the IFU and patient wallet card.
31.	Endotoxins	Adverse reaction	Titanium is highly biocompatible. Titanium implants have precedent in head and neck surgery and are commonly used in traumatic and oncologic reconstruction.	Device labelled sterile Endotoxin testing per ANSI/AAMI ST72, USP <161>, USP <85>, EP 2.6.14, JP 4.01

17) Potential Benefits to Subjects

Subjects may directly benefit from having improved swallowing. The improvement may be mild or significant. They may be able to better swallow their saliva. There is a possibility that they will be able to eat or drink some food or liquid once the device is implanted, which may benefit them psychologically, socially and nutritionally. Use of the SED may decrease the risk of aspiration and pneumonia. Even if a subject has limited use of the SED and must rely on the majority of nutrition/hydration delivered via feeding tube, the very act of swallowing is beneficial as it improves oral hygiene (flushing out bacteria, saliva) and stimulates oropharyngeal muscles and nerves.

18) Sharing of Results with Subjects

At the conclusion of the study, all results will be made available to the subjects.

19) Setting

All recruiting and procedures will be conducted at 2521 Stockton Blvd, Sacramento, CA 95817, where the Department of Otolaryngology is housed. Recruitment will occur in the Voice and Swallowing Center, and the surgery will occur in the Swallowing Center outpatient operating room.

20) Resources Available

Personnel

Investigator, Dr. Peter Belafsky, MD, MPH, PhD: Dr. Belafsky's primary clinical interests are the comprehensive diagnosis and management of voice, swallowing, and airway disorders. As Medical Director of the Voice and Swallowing Center at UC Davis, Dr. Belafsky treats a wide array of laryngeal and esophageal disorders. These disorders include but are not limited to vocal fold paralysis and paresis, vocal fold dysfunction (VCD), laryngopharyngeal reflux (LPR), chronic cough, and dysphagia caused by stroke, ALS, Zenker's diverticulum, esophageal motility disorders, Parkinson's disease, and swallowing problems suffered as a consequence of the treatment of head and neck cancer. Dr. Belafsky has pioneered minimally invasive treatments of voice and swallowing disorders. As the primary investigator, Dr. Belafsky will be responsible for personally enrolling and consenting all subjects. He will also be the primary surgeon an all implant placements and will be responsible for patient follow-up, adverse event, and device monitoring. He will oversee data collection and will be responsible for data analysis.

Co-Investigator, Dr. Maggie Kuhn, MD: Dr. Kuhn's primary clinical interests are the evaluation and treatment of routine and complex disorders of voice, airway and swallowing. As a fellowship-trained laryngologist, she has experience in caring for a broad spectrum of patient conditions.

These include hoarseness due to injury, neurogenic disease, malignancy, aging or misuse/overuse, dysphagia resulting from chronic disease, surgery, cancer treatment or cerebrovascular accident and dyspnea secondary to airway stenosis, vocal fold dysfunction or benign neoplastic disease. As the co-investigator, Dr. Kuhn will be responsible for assisting with device implantations, data analysis, and patient follow-up.

Laryngology Fellow: Dr. Naren Venkatesan is a laryngology clinical fellow working under the direction of Drs. Belafsky and Kuhn. He will be responsible for assisting Drs. Belafsky and Kuhn during the surgical implantations and will contribute to the data analysis and patient follow-up.

Clinical Research Coordinator: The clinical research coordinator will be responsible for organizing, oversight, and storage of all IRB consent and protocol forms. S/he will also assist with patient follow-up, device and adverse event monitoring, and will be responsible for data collection and storage. The CRC will need to well-versed in the conduct of clinical investigations involving humans, Good Clinical Practice, IRB and FDA regulations.

Feasibility of recruiting subjects

The FDA has approved the implantation of only 5 patients. The Division of Laryngology has a pool of suffering patients who have been waiting years for device implantation. The study participants will be chosen from this pool of existing patients.

Study effort

Dr. Belafsky will devote 5% effort to this project. Dr. Kuhn will similarly devote 5% effort to this project. The clinical trials coordinator will devote 25% effort to this project. This will ensure more than adequate time to manage the enrolled subjects.

Facilities

The Otolaryngology Department is housed in the Glassrock Building on the main School of Medicine campus. The department owns and operates fluoroscopy systems, which in many hospital settings would be housed separately in Radiology. Clinic staff and investigators are thoroughly familiar with reading and interpreting fluoroscopic studies as the Center for Voice, Speech and Swallowing Center sees a high volume of patients yearly (400-500). The Center maintains a large database of fluoroscopy studies from dysphagic patients. In addition, the Swallowing Center outpatient operating room is also located in the Glassrock Building.

Medical / Psychological resources

A member of the research team (Dr. Belafsky or Dr. Kuhn) will be available by cellphone or pager 24 hours a day throughout the time of the entire study. The clinical trials coordinator will also be available daily throughout the study period.

Study personnel communication

A study kick-off meeting will be conducted before the initiation of the trial. Weekly meeting and communication between study personnel will occur every Wednesday afternoon at 4pm before the initiation of dysphagia conference. Daily communication will occur as needed to address adverse events or other study-related problems that arise.

21) Prior Approvals

The FDA has approved this IDE study providing that we obtain IRB approval. The FDA has indicated that based on the safety results of an initial feasibility study of 5 patients for at least 6 months, we may request an expansion of the study to 20 patients.

22) Provisions to Protect the Privacy Interests of Subjects

Efforts will be made to limit use or disclosure of subject personal information, including research study and medical records, to people who have a need to review this information as per UCDMC policy on protecting patient information. We cannot promise complete confidentiality. Organizations that may inspect and copy subject information include the IRB, the U.S. Food and Drug Administration, and other University of California representatives responsible for the management or oversight of this study.

Personal information about the subject will be coded so that their name will not be associated with any information pertaining to the results, publications, or presentations regarding this study. All data and information will be maintained and stored securely (i.e., locked file cabinets, password protected computers, coded video and audio files) in the Department of Otolaryngology, University of California, Davis, so that confidentiality is maintained. This consent form will be filed in an official area. People who will have access to the subject's information will include the Investigator and research study personnel. The Investigator and study personnel will only access the data for research purposes.

Subjects will be informed of the provisions to protect their privacy during the consent process, including all forms of written, spoken, and electronic personal and health information. Subjects will told that they are free to ask any question about their privacy at any time. All study procedures will take place in the privacy of medical offices / rooms.

23) Compensation for Research-Related Injury

If a subject is injured, UC Davis Medical Center will always provide medical care. The sponsor (the Regents of the University of California) will pay for injuries / complications directly attributable to the study material. Insurance will pay for medically necessarily services for injuries / complications attributable to the disease or procedure.

24) Economic Burden to Subjects

Parts of this study are considered standard care to be covered by subjects or their insurance. Standard care procedures include the pre-surgery fluoroscopy swallowing examination, endoscopy examination, and pregnancy test. After the surgery, standard care includes follow-up clinic visits.

25) Consent Process

The informed consent process will occur at 2521 Stockton Blvd, Sacramento, CA 95817, in the Voice and Swallowing Center of the Department of Otolaryngology as per SOP: Informed Consent Process for Research (HRP-090). The potential subject is free to take as much time as they would like between the time that they are informed about the study and consenting. During the consent process, the potential subject will be asked at certain periods of time to reiterate what is described in the consent document to ensure that they understand the study. Patients will be asked to sign a HIPAA Authorization for Research form at the time of consent.

Non-English speaking subjects will not be asked to participate.

Due to the inclusion / exclusion criteria of this study, adults unable to consent will not be included in this study.

26) Process to Document Consent in Writing

We will follow the standard operating procedures for the written document of consent as all participating subjects will be asked to sign the informed consent.

27) Drugs or Devices

The SED is manufactured by Kluge Design, Inc. (Rogers, MN), an FDA GMP Compliant, ISO:13485:2003 and ISO:9001:2008, company. Life Science Outsourcing, Inc., an FDA registered and ISO 13485:2003 certified full service Medical Device Contract Manufacturer located in Brea, California, will clean, package and sterilize the SEDs and ship them via FedEx to the UC Davis Swallowing Center outpatient clinic operating room (OR) in the Glassrock Building. The administrative nurse responsible for the OR will record the shipment on the study's Inventory Sheet for SED Implant. The nurse will verify that the shipment arrived intact, the contents match the shipping invoice, and the packaged implants do not have any breach of packaging or damage. Implants are to be discarded if any breach or damage is found.

SED implants will be stored and locked in closed cabinets of the UC Davis Swallowing Center outpatient operating room where all sterilized surgical equipment is located. The temperature range in the OR is monitored to be 68-72°F, and the humidity range is monitored to be 20-60%. Hand hygiene facilities are adjacent to the storage area. The ventilation system is designed so that the air flows out of the sterile storage area. Packaging has been validated for 36 months per ISO 11607-1:2006.

Before surgery, the serial number of the SED that is checked-out for surgery, date, and device condition will be recorded on the Inventory Sheet for SED Implants. The serial number will also be written on the CRF and the bar code sticker from the sterilized packaging will be attached to the CRF. The SED package will be opened 5 minutes before surgery. If there is any breach in packaging or damage to the device at this time, the SED will be discarded. Similarly, the SED will be discarded and replaced if it is dropped prior or during surgery, as explained in the Healthcare Providers Instructions For Use. Before surgery, staff will conduct standard UC Davis Health System patient identification procedure.

Dr. Peter Belafsky has obtained an IDE (G100100-02) for the SED. On November 22, 2013, the FDA approved the IDE. Dr. Belafsky will undertake the responsibilities of IDE sponsors and investigators as listed in 21 CFR 812 and obtain IRB approval before beginning the study.

The UC Davis Health System Electronic Medical Records was certified as compliant with 21 CFR Part 11 by Teresa Porter, Chief Compliance Officer, UC Davis Health System, on January 18, 2011.

All investigators of this clinical trial will comply with the regulations governing financial disclosure by clinical investigators as described in 21 CFR Part 54. Investigators with no disclosable financial interests in or arrangements with the sponsor of the covered clinical study will submit Form FDA 3454. Those who have disclosable financial interests in and/or arrangements with the sponsor will submit Form FDA 3455.

In regards to Quality System Regulation (QS)/Good Manufacturing Practices (GMP) - 21 CFR Part 820, the SED medical device is manufactured by Kluge Design, Inc. (Rogers, MN), an FDA GMP Compliant, ISO:13485:2003 and ISO:9001:2008, company. Life Science Outsourcing, Inc., an FDA registered and ISO 13485:2003 certified full service Medical Device Contract Manufacturer located in Brea, California, will clean, package and sterilize the SEDs and ship them via FedEx to the UC Davis Swallowing Center outpatient clinic operating room (OR) in the Glassrock Building. Validations of mechanical testing and cleaning, packaging, and sterilizing were included in the approved IDE amendment. The implants will be stored and locked in closed cabinets of the UC Davis Swallowing Center outpatient operating room where all sterilized surgical equipment is located. The temperature range in the OR is monitored to be 68-72°F, and the humidity range is monitored to be 20-60%. Hand hygiene facilities are adjacent to the storage area. The ventilation system is designed so that the air flows

out of the sterile storage area. Packaging has been validated for 36 months per ISO 11607-1:2006. These conditions are in conformance to AAMI ST79.

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