Pharyngeal Electrical Stimulation Evaluation for Dysphagia after Stroke (PhEED)

Investigational Device	Phagenesis Phagenyx System
Sponsor	Phagenesis Ltd Enterprise House, Pencroft Way Manchester Science Park M15 6SE, UK
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ClinicalTrials.gov Number: NCT03358810

Investigator Signature Page

My signature below indicates my agreement to conduct this study in accordance with this study protocol, Good Clinical Practices, and applicable requirements of the governing IRB/EC and applicable laws and regulations. I agree to supervise the study staff and the utilization of investigational study devices including ensuring their usage is only in connection with this study and protocol.

Richard L. Harvey MD

Investigator Name (print)

Investigator Signature

3-20-18

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ABBREVIATIONSAND ACRONYMS

ABS	Acrylobutdiene Styrene
ANCOVA	Analysis of Covariance
ASHA	American Speech Language Hearing Association
BI	Barthel Index
CI	Confidence Interval
CMP	Clinical Monitoring Plan
COPD	Chronic Obstructive Pulmonary Disease
cPAS	Cumulative Penetration Aspiration Score
CFR	Code of Federal Regulations
CRF	Case Report Form
CXR	Chest X-ray
CT	Computed Tomography
DC	Discharge from the hospital
DMC	Data Monitoring Committee
DOSS	Dysphagia Outcome and Severity Score
DSRS	Dysphagia Severity Rating Scale
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Score
EMG	Electromyography
EQ-5D	EuroQoL 5 Dimension Questionnaire
EQ-VAS	EuroQoL Visual Analogue Scale
eTMF	Electronic Trial Master File
FDA	Food and Drug Administration
FEES	Flexible Endoscopic Evaluation of Swallowing
FOIS	Functional Oral Intake Scale
GCPs	Good Clinical Practices
GMP	Good Manufacturing Practices
HCP	Health Care Professional
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazards Ratio
Hz	Hertz

ICD	Implantable Cardiovascular Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ISC	Independent Statistical Center
ISO	International Organization for Standardization
ITT	Intent-To-Treat
LED	Light Emitting Diode
LOS	Length of Stay
mA	milli-Amp
MAUDE	Manufacturer and User Facility Device Experience
MBS	Modified Barium Swallow
MBSimP	Modified Barium Swallow Impairment Profile
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
MM	Medical Monitor
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
MS	Multiple Sclerosis
mSv	milli-Sievert
NCT	National Clinical Trial
NET	Nasoenteric (or nasoenteral) Tube
NG	Nasogastric
NGT	Nasogastric Tube
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
NSR	Non-significant Risk
OD	Outer Diameter
OR	Odds Ratio
PAS	Penetration Aspiration Scale
PEG	Percutaneous Endoscopic Gastrostomy
PES	Pharyngeal Electrical Stimulation
PI	Principal Investigator
PP	Per Protocol
PPS	Pulse Per Second
QoL	Quality of Life
RCT	Randomized Controlled Trial
RI	Roll-in
RR	Relative Risk
SAE	Serious Adverse Event
SLP	Speech Language Pathologist

SLT	Speech Language Therapist
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SSR	Sample Size Re-assessment
TMS	Transcranial Magnetic Stimulation
tsp	teaspoon
UK	United Kingdom
US	United States
USB	Universal Serial Bus
VFSS	Video Fluoroscopic Swallowing Study

STATEMENT OF COMPLIANCE

This study will be conducted in accordance with the relevant parts of the Code of Federal Regulations (21 CFR 50, 54, 56, 812), ISO 14155:2011, the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practices (GCPs,) and the ethical principles that have their origin in the Declaration of Helsinki and its subsequent amendments. Additional state and local regulations will be followed, when applicable.

Investigators and sites must have protocols, informed consent forms and any other patient materials related to the study plan approved by the Institutional Review Board (IRB) or Ethics Committee (EC) in writing. Prior to enrollment, the sponsor or designee will review the written approvals for completeness, including the required elements of the consent form, and the sponsor will provide device, protocol and study administration training. The continued eligibility for participation by an investigator and the institution requires maintenance of all approvals (e.g. annual reviews, amendment reviews).

Each patient will provide written informed consent, indicated by a signature and date, according to the regulatory and legal requirements of the participating site and applicable regulations. The process must allow for ample time, opportunity to ask questions and an understanding that informed consent in research is voluntary. A copy of the informed consent and any additional patient information must be given to each patient. The process and consent execution are also to be documented in the medical record.

Patient confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. The study protocol, documentation, data, and all other information generated will be held in strict confidence to the extent allowed by law, including Protected Health Information (PHI). No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title	**P**haryngeal **E**lectrical Stimulation **E**valuation for **D**ysphagia after Stroke (PhEED)
Study Description	This is a randomized, sham-controlled, patient masked, outcome assessor-blinded study to assess a Pharyngeal Electrical Stimulation (PES) Catheter for treatment of oropharyngeal dysphagia following a stroke. The main clinical outcomes will be measured by videofluoroscopic swallowing study (VFSS) and bedside swallowing assessments at 48 hours. Randomization will use stratification based on site and baseline PAS. Minimization may also be included to ensure

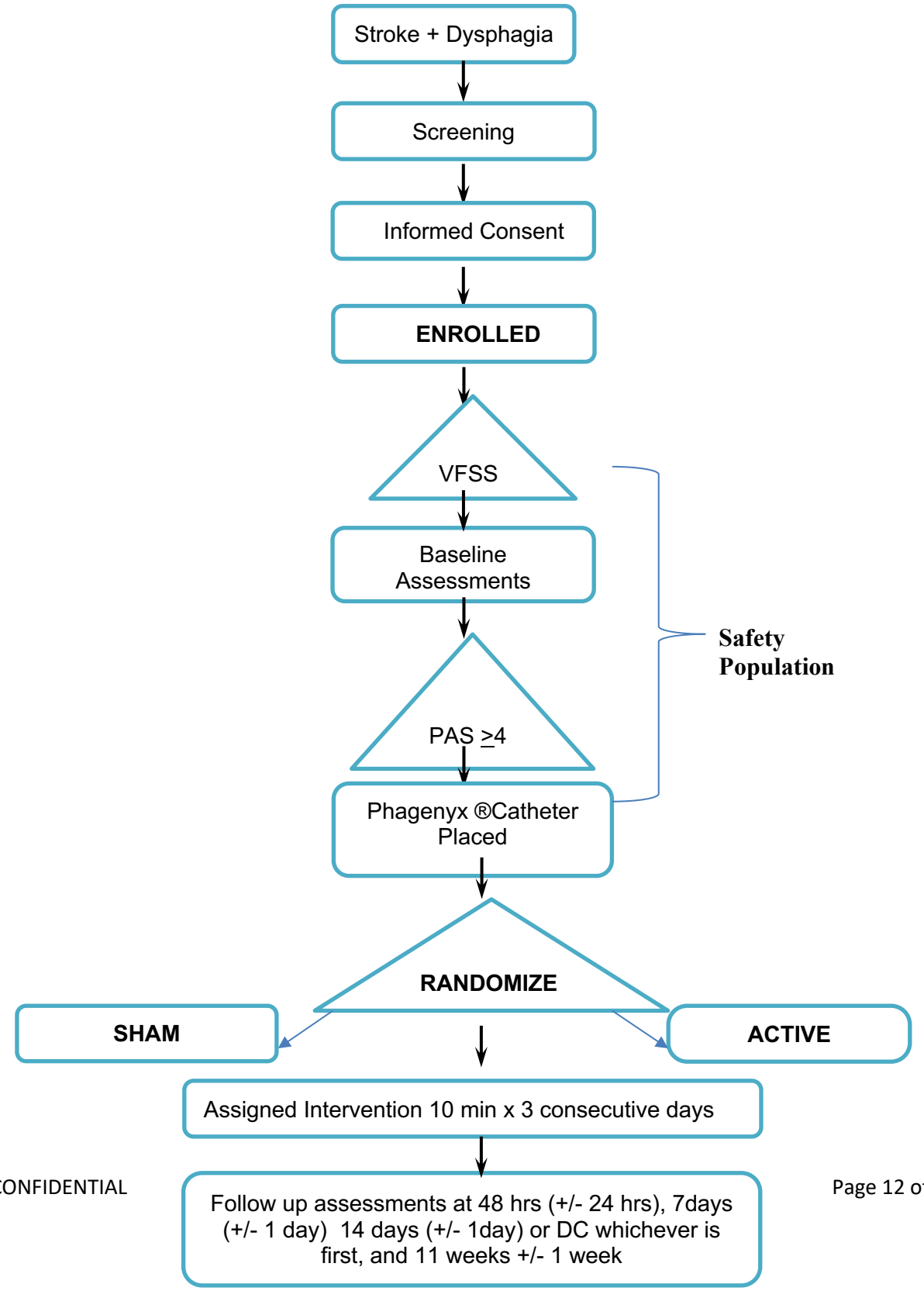
	group balance for study site and additional baseline covariates. All patients will have the Phagenyx® Catheter placed prior to randomization, and will receive either an active treatment of Pharyngeal Electrical Stimulation (PES) or a sham treatment performed by a healthcare professional (HCP) that is un-blinded to treatment assignment. All other speech pathology standard dysphagia care will be provided by a speech language pathologist (SLP) that is blinded to treatment assignment. Administration of all protocol-specific assessments will be conducted by personnel blinded to treatment assignment. The study will follow an adaptive group sequential design with unblinded sample size re-assessment. To ensure 180 evaluable patients with 7-day data and assuming a 20% dropout rate, 225 patients will be enrolled initially. An interim analysis for futility will occur after the first 60 patients complete their 7-day visits and another interim analysis will be performed for efficacy and futility after 120 patients complete their 7-day visits. The total sample size may be increased up to 338 patients after the second interim analysis to ensure up to 270 evaluable patients. Up to 15 investigational centers across the US and Europe will participate in this study. The enrollment period is expected to be approximately 24 months and patient participation will last for approximately 11 weeks. Patients will be assessed at the following intervals: baseline, 48 hours, 7 days, 14 days or at discharge, whichever is first, and 11 weeks after completion of the study treatments.
Study Objectives	Primary Objective: To evaluate the efficacy of Phagenyx® treatment in reducing the severity of unsafe swallows. Secondary Objective: To evaluate the efficacy of Phagenyx® treatment in improving nutritional management. Exploratory Objectives: • To further characterize the efficacy of Phagenyx® treatment in reducing the severity of unsafe swallows. • To further characterize the efficacy of Phagenyx® treatment on nutritional management changes. • To evaluate the efficacy of Phagenyx® treatment on improving quality of life. • To evaluate the efficacy of Phagenyx® treatment on general stroke health outcomes.
Study Endpoints	Primary Endpoint: Swallowing safety of a bolus based on PAS of each swallow, determined by a videofluoroscopic swallowing study (VFSS) 48 hours after completion of investigational

	treatment, converted to a trichotomized ordinal response of safe (PAS 1-3), penetration (PAS 4-5), or aspiration (PAS 6-8). Each patient contributes up to 12 post-treatment repeated measurements using Penetration Aspiration Scale (PAS) including 6 swallows of thin and 6 swallows of nectar <u>Secondary Endpoints:</u> - Functional Oral Intake Scale (FOIS) at 7 days following the last investigational treatment - Dysphagia Severity Rating Scale (DSRS) at 7 days following the last investigational treatment <u>Exploratory Endpoints</u>: • The severity of unsafe swallows will be further evaluated via: o PAS outcome by each consistency (thin and nectar) o Physiologic measurement obtained using the Modified Barium Swallow Impairment Profile (MBSImP) metrics will be extracted from the thin and nectar thick swallows by the core lab by using the baseline and follow up VFSS data. These validated and reliable metrics of critical swallowing movements will be explored for their relationship to the primary study endpoint (PAS). o PAS dichotomized as safe (PAS 1-3) or unsafe (PAS 4-8) • Nutritional management changes will be further evaluated via: o Dysphagia Severity Rating Scale (DSRS) at 14 days or discharge, whichever is first, and 11 weeks following the last investigational treatment. o Time from baseline to removal of enteral feeding (i.e., removal of NG tube or PEG or transition to oral feeding, or first diet upgrade) o Functional Oral Intake Scale (FOIS) at 14 days or discharge, whichever is first, and 11 weeks following the last investigational treatment • Quality of life (QOL) will be assessed at baseline and 11 weeks following the last investigational treatment via the following instruments: o EuroQoL-5 Dimension Questionnaire (EQ-5D) and EuroQoL-Visual Analogue Scale (EQ-VAS) • General stroke health outcomes will be assessed by: o Time to discharge from site in which treatment is received

	○ Discharge destination from the site in which treatment is received ○ Patient location (home, institution) at 11 weeks ○ Days on antibiotics during hospital stay ○ NIH Stroke Scale (NIHSS) at baseline, 14 days or discharge, and 11 weeks ○ Modified Rankin Scale (mRS) at baseline, 14 days or discharge, and 11 weeks ○ Barthel Index (BI) at baseline, 14 days or discharge, and 11 weeks ○ New onset pneumonia, using a standardized definition adapted from the STROKE-INF study[26] at baseline, 48 hours, 7 days, and 14 days or discharge, whichever is first. ○ Hospital readmission rate ○ Number of CXR (related to suspect pneumonia)
Study Population	Up to 338 patients who have been diagnosed with dysphagia caused by stroke will be enrolled at approximately 15 centers across the US and Europe.
Regulatory Classification	This study is designed to support a *de novo* submission for a non-significant risk (NSR) device in the United States. The study device received CE mark in 2012.
Number of Sites	There will be approximately 15 centers across the US and Europe. The majority of the centers and patients enrolled will be from the US.
Description of Study Intervention	The Phagenesis Phagenyx® System is indicated for the treatment of neurogenic oropharyngeal dysphagia. The Phagenyx® system is a two-part neurostimulation system. It is composed of a durable component called the Base Station and the single-use sterile disposable Phagenyx® Catheter. The Base Station acts as the user interface and provides the means to generate, optimize and monitor the delivery of electrical stimulation. The Base Station has the following functions: • Stimulation - Generation, optimization and output of controlled electrical stimulation • User Interface - Receives, stores and outputs data regarding the patient, user, product and treatment The Phagenyx® Catheter design is based on that of a nasogastric tube (NGT), but incorporates electrodes with appropriate wiring and insulation for delivery of electrical stimulation to the pharyngeal mucosa. The Phagenyx® Catheter has been designed to also deliver enteral nutrition to the patient as needed.
Study Duration	The study is expected to take approximately 24 months from

	the time of first patient enrollment to the final study visit.
Patient Duration	The duration for each patient will be approximately 11 weeks.

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

	Screening	**Baseline**	**Phagenyx Treatment** (10 minutes per day, 3 consecutive days)	**48±24 Hour Follow-up**	**7±1 Days Follow-up**	**14-±1 days or discharge, whichever is first**	**11±1 Weeks Follow-up**
				Follow-up timing is based on last Phagenyx treatment.			
Medical History and Demographics	X						
Exam of nasopharynx		X[1]			X[1]	X	
Informed Consent	X						
ECG monitoring (for the first 20 patients randomized to active treatment)			X[2]				
Heart Rate and Blood Pressure Monitoring(for the first 20 patients randomized to active treatment)			X[2]				
NIHSS		X				X	X
Modified Rankin Score (mRS)		X				X	X
Barthel Index		X				X	X
FOIS		X			X	X	X
DSRS		X			X	X	X
EQ-5D, EQ-VAS		X					X
Pregnancy Test		X[3]					

VFSS		X[4]		X			
Pneumonia Assessment		X		X	X	X	
Adverse Event (AE) Assessment		X	X	X	X	X	X
Blinding Assessment						X	

[1] Assessment of nasopharynx at baseline, 1 week after catheter is in place and at catheter removal using flashlight or pen light. In the event of patient complaint or obvious symotoms, a fiberoptic exam is required and any adverse events are to be reported.
[2] Rhythm strip (30 seconds) printed at immediately prior to commencing PES treatment, 5 minutes into each of the three treatment sessions, and immediately post treatment. Continual ECG monitoring during PES to observe for any arrhythmias. Heart rate and Blood Pressure to be documented immediately prior to and after PES.
[3] Required only for females of child-bearing potential
[4] Baseline VFSS must meet the threshold criteria of demonstrating a PAS of ≥ 4, in three of the six boli (5 mL/1 tsp/bolus), during swallowing “thin liquid” barium media as assessed by the clinical staff administering the VFSS, unless its considered to be too high risk, then 2 swallows will qualify.

2 INTRODUCTION

2.1 STUDY BACKGROUND AND RATIONALE

Dysphagia is common in the post-stroke setting. It is associated with increased incidence of in-hospital pneumonia, worse outcome and greater resource utilization.

The actual incidence of dysphagia is very difficult to estimate since there is no standardization across dysphagia screening protocols with respect to administration or interpretation. Martino et. al.,[1] attempted to define the incidence of dysphagia in the post-stroke setting by performing an extensive review of the stroke literature spanning from 1966 through May 2005. Of 104 articles initially identified, 24 articles included relevant information. Due to the heterogeneous nature of dysphagia assessment, it was not possible to pool any results across multiple studies. Only swallow screening tests were performed to diagnose dysphagia in nine of the studies. Incidence based only on swallowing screening demonstrated a 37-45% incidence among patients in both acute and rehabilitation settings. More extensive clinical or instrumental testing was performed in the remaining 16 studies. In depth testing was not always performed in the acute care setting; however, the highest incidence rates of dysphagia were observed among the acute studies that used videofluoroscopy (64-78%). In 4 acute studies using very similar clinician testing, incidence rates varied between 51-55%. There was a reported incidence range from 40-81% among 3 studies performed in the rehabilitation setting, but all three studies limited enrollment to brainstem strokes and relied only on clinician testing.

The timing in the resolution of post-stroke dysphagia is also very difficult to estimate. There is a general belief that spontaneous resolution will occur within the first week to month, with only a few patients demonstrating persistent dysfunction beyond 6 months. Mann et. al.[2] set out to systematically define the true persistence at a single referral center in Australia. Sixty-five of 128 patients (51%; 95% CI, 42-60%) had a clinical presentation of dysphagia in the acute stroke setting. This incidence increased to 82 patients (64%; 95% CI, 55-72%) when videofluoroscopy was used to diagnose dysphagia. Follow up assessments were made at six months. Ninety-seven (97) of the 112 patients assessed at six months had returned to their pre-stroke diet (87%; 95% CI, 79-92%), but clinical evidence of swallowing abnormality remained in 56 patients (50%; 95% CI, 40-60%) and VFSS confirmed abnormalities in 51 (46%) with full aspiration in 17 (11%).

A number of researchers have similarly attempted to quantify the incidence of pneumonia, or “chest infection” in the post-stroke setting. Similar to studies of dysphagia incidence, published reports also lack standardization with respect to inclusion criteria, diagnostic methods and timeframes for reporting. Katzan et. al.,[3] performed a large retrospective review of a 29-hospital-wide population cohort in the US to determine the incidence of pneumonia and its impact on 30-day mortality from 1991-

1997. They report a 6.9% pneumonia incidence among 14,293 patients. Upon excluding patients that were dying or had Do Not Resuscitate orders within the first 3 days, the incidence became 5.6% out of 11,286 patients. Bivariate analysis between pneumonia and admission factors indicated that stroke severity (NIHSS score) and general indictors of frailty were predictors for pneumonia. No analysis for dysphagia was included.

Mann et al's study reported chest infections in 26 of 112 patients at 6-months (20%; 95% CI, 14-28%) with 12% of these occurring within the first month of stroke admission. Multivariate analysis demonstrated that the only independent predictor of chest infection was dysphagia[2].

Smithard et. al.,[4] prospectively studied 121 consecutive stroke patients admitted to their center in the UK. Twenty five percent of patients developed a chest infection. Incidence was stratified based on dysphagia diagnosis. Patients considered to have an unsafe swallow via bedside swallow assessment demonstrated a 33% rate of chest infection compared to 16% for patients with a safe swallow.

Dziewas et al.,[5] Masiero et al.,[6] and Arnold et al.,[7] all report their single-center experiences with pneumonia in patients that are dysphagic in the acute post-stroke setting. Dziewas et. al., prospectively followed 100 patients considered to have severe dysphagia among 527 assessed via swallow assessment (19%) at their center in Germany[5]. Nasogastric tube (NGT) placement was indicated for those with severe dysphagia. Pneumonia developed in 44% of patients in whom an NGT was placed, primarily within the first 2-3 days. There was no difference in the stroke lesions characteristics between patients that developed pneumonia and those that did not. Multivariate analysis demonstrated that stroke severity (via NIHSS) and severe facial palsy were risk factors for developing pneumonia.

Maseiro et al., prospectively studied 67 consecutive patients with oropharyngeal dysphagia diagnosed by flexible endoscopic evaluation of swallowing (FEES) within 7 days of first acute stroke in their hospital in Italy[6]. There were an initial 9 incidents of pneumonia, but two patients had a recurrence requiring hospital readmission. Hence, the overall incidence was 11 cases for the 67 admissions, or 16.4%, overall. Among dysphagic patients, they found that a history of chronic obstructive pulmonary disease (COPD), silent aspiration, and level of consciousness were independent risk factors for the development of pneumonia.

Arnold et al., reported on a retrospective review of 507 ischemic stroke patients treated at a tertiary care center in Switzerland from Jan 2012 through Nov 2014[7]. Dysphagia was present in 118 patients (20.7%) assessed by extensive clinical testing. In-hospital pneumonia occurred more frequently in dysphagic patients (22.9% vs. 1.1%), and multivariate analysis demonstrated the presence of dysphagia was independently associated with pneumonia (OR, 27.4; 95% CI, 10.2-73.7; P <0.001).

Martino et al., found that, similar to dysphagia reporting, the reporting of pneumonia is also highly variable with respect to timeframe of analysis and means of diagnoses[1].

Pooling the few studies with sufficient data to allow this, the presence of dysphagia conferred a relative risk (RR) of 3.17 (95% CI, 2.07-4.87) for developing pneumonia, and the RR increased more than three-fold among patients with confirmed aspiration (RR, 11.56; 95% CI; 3.36-39.77).

Katzan et al.'s, retrospective analysis indicated that pneumonia conferred a relative risk for 30-day mortality that was six time greater for patients with pneumonia than without (26.9% vs. 4.4%, $p<0.001$)[3]. After adjusting for independent factors, the RR for 30-day mortality was still almost 3 times greater for patients with pneumonia (2.99; 95% CI, 2.44 to 3.66). The authors estimate that 10% of all deaths following stroke are attributable to pneumonia.

The studies that specifically assessed post-stroke dysphagia demonstrate that the presence of dysphagia also confers a greater relative risk of poor outcome. Specifically, Dziewas et al., found that dysphagic patients who developed pneumonia needed the NGT to remain in place for a longer period of time, with a median of 15 vs. 2 days or an average of 16.3±7.2 vs. 4.9±4.8 days ($p<0.001$) for patients with pneumonia vs. those without. Dziewas et al., found among those having a poor 3-month outcome (modified Rankin Score (mRS) ≥ 4), had a higher incidence of pneumonia during their hospital stay than did those that had a good (mRS ≤ 1) or moderate (mRS = 2 or 3) outcome, at 70% vs. 23% and 24%, respectively. Duration of enteral feeding was also longer in patients with a poor outcome at 3 months[5].

Smithard et al., and Arnold et al., also report that the presence of dysphagia is associated with longer hospital stays and higher mortality. Mortality was 37% for patients with dysphagia vs. 6% for those without dysphagia among patients reported on by Smithard et al., and the presence of dysphagia was a significant predictor for mortality after adjusting for confounding variables[4]. In the 2016 report by Arnold et al., mortality was 27% among patients with dysphagia vs. 7.4% for those without. The risk of death was higher for the subgroup of dysphagic patients requiring tube feeding. The occurrence of pneumonia was only weakly associated with mortality risk[7].

Mann et al's study cited only five deaths within the first six months among 117 patients for whom six-month data was available; however, all of the deaths occurred in patients with dysphagia, and was associated with chest infection in four of the five cases[2].

Several studies have indicated that dysphagia increases hospital length of stay. However, additional resources associated with the care for these patients may be found in antibiotic requirements and chest radiographs[7]. Dysphagic patients are also more likely to require in-patient care during post-stroke rehabilitation[4,7,8]. Arnold's study found that the presence of dysphagia was a strong independent predictor (OR 3.1, 95% CI, 1.7-5.5, $p<0.001$) of institutionalization at 3 months[7].

Bonilha et. al., analyzed the 1-year cost of dysphagia in 3200 patients experiencing a first stroke across the state of South Carolina for 2004[8]. They found that each case of dysphagia added a cost of $4510, and additional cost burden was associated with hospital and durable medical expenses as well as the need for a skilled nursing facility. The 2012 overall cost associated with stroke in the US was 33 billion dollars. Costs associated with stroke are expected to triple by 2030, as the general population ages[9].

Hence, effective treatments focused on facilitating the recovery of swallowing could provide an overall economic benefit to society.

Despite dysphagia imparting both patient-specific and social-economic burden, there is very little standardization with respect to dysphagia treatments or even evidence-based recommendations for treatment. Foley et. al.,[10] intended to update Martino et al.,'s earlier work[1] with a follow-on report including data up to Aug 2007, and specifically considering targeted treatments and their associated outcomes for post-stroke dysphagia. The published findings demonstrate very heterogeneous results, and pooled analyses were not possible. Descriptive findings anecdotally suggest that dysphagia treatment is associated with reduced pneumonia risk in the acute post-stroke setting.

2.2 CURRENT STANDARD OF CARE

The American Speech-Language and Hearing Association (ASHA) provides a "Scope of Practice in Speech-Language Pathology" that outlines what a speech-language pathologist is trained to evaluate and treat in general terms but does not identify or recommend use of specific techniques or modalities. General approaches in treating dysphagia include both direct and indirect therapies. Direct therapies are those that include swallow retraining, training of compensatory mechanisms to improve airway protection during swallowing and diet modification to reduce the risk of aspiration. Indirect therapies target the underlying pathology associated with the dysphagia through medication, surgery, or by muscle strengthening, sensory stimulation (e.g., ice probes, air puffs), neuromuscular electrical stimulation or cortical stimulation.

In a recent review of 53 published dysphagia rehabilitation studies spanning an 18-month period, Druila et. al.,[11] found that direct swallowing therapy was used in only one of 27 studies, indirect therapies were used in 10 studies, and a combined approach was used in the remaining 16. The size of the effect associated with each therapy was calculated and compared across studies. Their findings indicate that treatment effects in dysphagia are small to moderate. Some studies demonstrated no benefit in objective measures but small to moderate effects in patient reported outcome which, they conclude, likely reflect placebo effects. The only studies that demonstrated a large effect size were those performed in dysphagic patients in the acute stroke setting, but it appeared that spontaneous recovery may have provided a greater effect size than the therapy alone based on improvements in sham groups, as well.

AmpcareESP and VitalStim are two neuromuscular electrical stimulation devices currently marketed in the US for therapeutic use after dysphagia. Both administer external stimulation to the neck. Critical review of the literature for neuromuscular stimulation found that results are generally promising, but that no high-quality controlled studies have been performed that provide definitive evidence of efficacy[12]. In a special interest website publication, ASHA posted the following opinion regarding the use of products such as the VitalStim: "*There is scant evidence to support the use of electrical stimulation as a treatment strategy for dysphagia in either the adult or pediatric*

population. ASHA is strongly committed to evidence-based practice and urges members to consider the best available evidence before utilizing any product or technique. ASHA does not endorse any products, procedures, or programs."[13]
Cortical stimulation to treat dysphagia is being explored by administering pharyngeal electrical stimulation, transcranial magnetic stimulation and transcranial direct current stimulation. None of these methods are commercially available in the US.

2.3 PHAGENESIS PHAGENYX® SYSTEM

2.3.1 DEVICE DEVELOPMENT

The design of the Phagenesis Phagenyx® System evolved from basic research into the way the motor cortex coordinates and controls swallowing. Studies were initially conducted in healthy volunteers to generate a cortical topographical representation of the oral, pharyngeal and esophageal swallowing musculature. Topographical maps were created by measuring the evoked motor responses measured via electromyography (EMG) in the oropharynx and mylohyoid muscles created by stimulating the cortex via transcranial magnetic stimulation at intensities 110% of the threshold that evoked a minimal EMG response. Topographical maps display the areas that produce graded magnitudes of the motor responses. It was discovered that cortical control of swallowing is discretely located in the motor and pre-motor cortex of both hemispheres of the brain, and the arrangement exhibits an asymmetric bias towards one or other of the hemispheres, so that there is a dominant hemisphere[14].

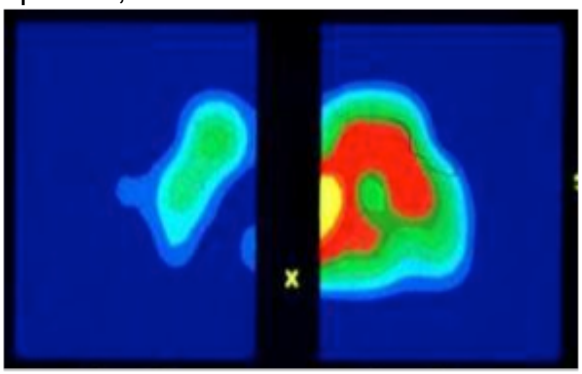


Figure 1: Cortical swallowing representation. This healthy individual shows a dominance of swallowing control activity in the right hemisphere *(yellow represents the greatest magnitude of motor response and dark blue a lack of response; "X" indicates centerline)*

This discovery led to the hypothesis that a unilateral stroke affecting the dominant swallowing hemisphere was likley to give rise to dysphagia, while a stroke affecting the non-dominant hemisphere was not. This hypothesis was confirmed in a study of 20 patients experiencing a unilateral hemispheric first-time stroke[15]. Eight (8) of the 20 patients presented with swallowing difficulties during the instrumental videofluoroscopic swallow study. All 20 patients underwent transcranial magnetic stimulation with recording of evoked potentials in the oropharynx. Dysphagic patients demonstrated weak EMG signals associated with stimulation of either hemisphere, whereas patients

without dysphagia demonstrated strong EMG signals when the unaffected side was stimulated.

Twenty-eight (28) patients with unilateral hemispheric stroke were subsequently studied over their initial 3-month post-stroke course. Dysphagia was present in 71% of patients upon initial assessment and in 46% and 41% at one and three months, respectively. Cortical mapping of the motor pathways to the pharynx was performed at baseline and at one and three months using the methodology previously described. Non-dysphagic and persistently dysphagic patients showed little change in pharyngeal representation in either hemisphere at one and three months compared with baseline, but patients that recovered their swallowing function had an increased pharyngeal representation in the unaffected hemisphere at one and three months without change in the affected hemisphere. A functional reorganization of the brain by which swallowing control was transferred from the damaged hemisphere to the undamaged one was proposed as the mechanism of swallowing recovery.

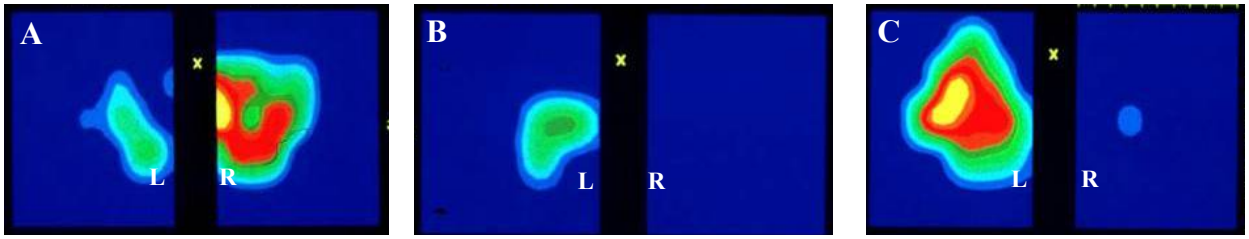


Figure 2: Cortical reorganization associated with swallowing recovery. A) Typical cortical representation of swallowing motor cortex in a healthy individual; B) Typical cortical representation of swallowing function in a dysphagic patient who was thought to exhibit dominance in the right hemisphere; C) Typical cortical representation of patient who has recovered swallowing function: the dominance of control has moved to the left hemisphere.

Following the observation of this natural functional reorganization, Hamdy and colleagues began investigating the use of various sensory stimuli to drive this functional reorganization. Sensory inputs were tested (e.g., tactile, temperature, aversive taste) as well as experimental modes including transcranial direct current, magnetic field and electrical stimulation in the oropharynx (unpublished data). Transcranial magnetic stimulation was used to produce cortical maps based on evoked oropharyngeal motor responses to assess the cortical excitability in the motor centers associated with swallowing before and after each study intervention to assess the extent to which an intervention increased cortical activity. Pharyngeal electrical stimulation demonstrated promise. The rapid increase in cortical excitation after just ten minutes of stimulation is illustrated in **Figure 3**. Moreover, these changes persisted for 30 minutes after stimulation was discontinued thus suggesting that continuous stimulation was not necessary to facilitate reorganization[16].

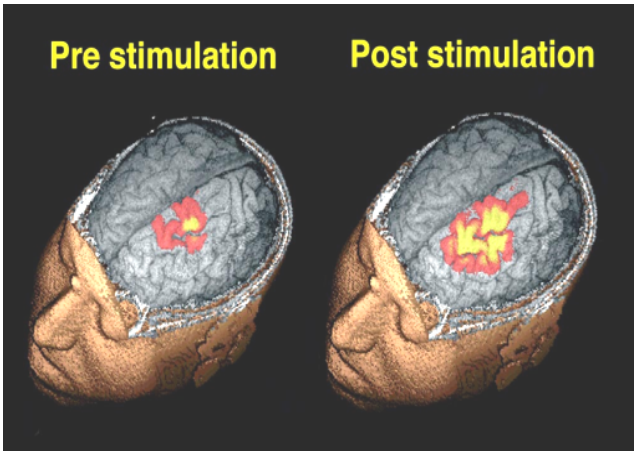


Figure 3: Cortical excitation associated with pharyngeal electrical stimulation

The Phagenesis Phagenyx® System was designed to harness the fact that pharyngeal stimulation led to increased and prolonged cortical excitation to expressly facilitate the cortical reorganization associated with improved swallow function. Phagenyx administers electrical stimulation optimized to drive cortical excitation and facilitate the cortical reorganization responsible for swallowing control and coordination. Electrical stimulation is delivered directly to the pharyngeal mucosa which is innervated by nerves involved in triggering pharyngeal swallowing and airway protection.

2.3.2 DEVICE DESCRIPTION

The Phagenesis Phagenyx® System is indicated for the treatment of post-stroke neurogenic oropharyngeal dysphagia. Phagenyx® is a two-part neurostimulation system. It is composed of a durable component, the Base Station, and the single-use sterile disposable Phagenyx® Catheter. The Base Station acts as the user interface and provides the means to generate, optimize and monitor the delivery of electrical stimulation. The Phagenyx® Catheter design is based on that of an NGT, but incorporates electrodes with appropriate wiring and insulation for delivery of electrical stimulation to the pharyngeal mucosa. The Phagenyx® Catheter has been designed to also deliver enteral nutrition to the patient as needed. Phagenyx® received CE Mark in 2012.

The Base Station has the following functions:

- Stimulation - Generation, optimization and output of controlled electrical stimulation
- User Interface - Receives, stores and outputs data regarding the patient, user, product and treatment

Figure 4 provides the front and back appearances of the Base Station with key features labeled.

The design of the Base Station and associated software complies with medical device electrical and software standards. Moreover, appropriate hardware risk control measures have been taken so that a software failure is not associated with risk of serious injury. Hence, the overall safety of the Phagenyx® System is Class A.

Figure 4: Phagenyx® Base Station with labeled components:

a) Touchscreen – Touch sensitive glass screen
b) Casework – High density Acrylobutdiene Styrene (ABS.) Easy clean surface
c) On/Off switch – Push button switch with integrated LED indicator to show when unit is turned on
d) USB port cover – Easy lift material to provide protection and convenient access to USB port
e) Current and battery indicators – Lights to show when system is actively delivering current or being charged
f) Connector to Phagenyx® Catheter – For connection to the Smart Connector on the Phagenyx® Catheter prior to treatment
g) Cable clip – Securing point for the treatment cable
h) Cable tidy – Convenient storage position for the treatment cable
i) Treatment cable – Cable and connector through which data and the treatment current is delivered to the patient
j) Cable groove – Retaining feature on the cable tidy to ensure the correct tension is applied to the Treatment cable
k) Mains Supply socket - Recessed socket to receive standard mains supply cable

The Phagenyx® Catheter is a two-part construction. The inner core is in the form of a nasogastric (NG) feeding tube with a guidewire. The outer part is in the form of a thin walled Sleeve that incorporates two ring electrodes, insulated wires located in the walls of the Sleeve to deliver the current, and a connector (the S-connector) (**Figure 5**). The Sleeve is designed to be positioned over the NG tube and to be capable of freely moving up and down along its length. The Phagenyx® Catheter is available in one size only. The NG tube has an outer diameter (OD) of

8F (2.75 mm), and is 123 cm long to provide sufficient length to access the stomach for feeding purposes and pH sampling. The outer Phagenyx® Catheter sleeve has an OD of 11.5F (3.85 mm) and is approximately 70 cm long.

The Phagenyx® Catheter is supplied as a single-use sterile product. The Phagenyx® Catheter and accessories are supplied in a formed tray (**Figure 6**). The tray and contents are terminally sterilized using ethylene oxide.

There are two accessories parts supplied with the Phagenyx® Catheter:
1. A Garment Clip to secure the external parts of the Phagenyx® Catheter to alleviate weight
2. A Transition Adaptor to enable standard connections for feeding delivery

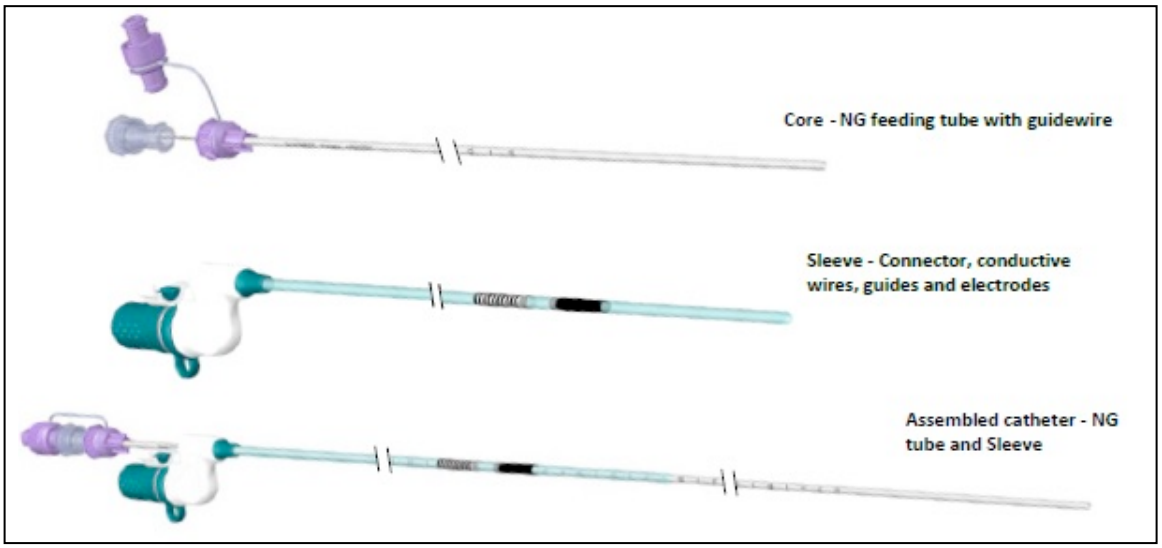


Figure 5: Phagenyx Catheter

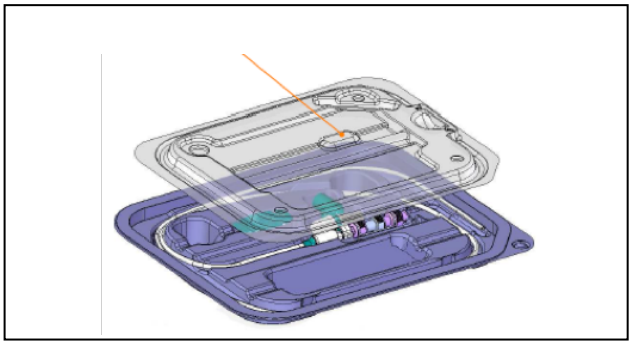


Figure 6: Phagenyx® Catheter packaging with accessories

2.3.3 DEVICE USE

The Phagenyx® Catheter is placed so that the electrodes are positioned at the junction between the oropharynx and the laryngopharynx at a position that is equivalent to the junction between the C3 and C4 cervical vertebrae. Electrical stimulation is applied to

the oropharyngeal mucosa via a pair of bipolar ring electrodes as depicted in **Figure 7**. The electrical stimulation is composed of pulse trains at an intensity of 5-50mA with a pulse width of 200 μs at a frequency of 5 Hz. Hence, a ten-minute treatment period is composed of 3000 swallowing stimuli with 600 ms of "on" time in which electrical current is being applied. Less than 1 kcal of heat is produced over the treatment period with minimal local temperature increase.

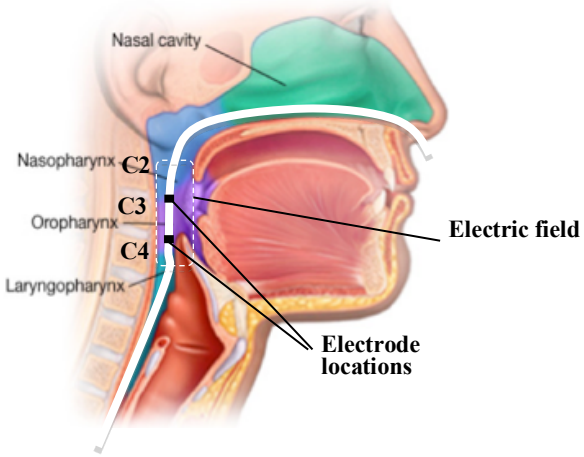


Figure 7: Transnasal placement of the Phagenyx® Catheter and area of electrical stimulation

2.4 RISK/BENEFIT ASSESSMENT

2.4.1 POTENTIAL AND KNOWN RISKS

Design and Manufacturing

Residual risks associated with the design and manufacturing of the Phagenyx® System have been reduced to acceptable levels. The electrodes are formed from 304 steel polished tubing that is cut, de-burred and rounded to remove any sharp edges. These 3 mm wide cylinders are then crimped onto the polyurethane tubing and the tubing is subsequently reflowed to seal the edges of the electrodes and bring the surface of the tubing to the same level as the surface of the electrodes. The effect of this processing ensures a seamless transition from tubing to electrodes without exposed edges or sharp features. The outer diameter of the electrodes is less than that of a 12 Fr nasogastric feeding tube falling within the range of dimensions that represent standard practice for enteral feeding devices. The finish at the tube-electrode interface undergoes a 100% inspection at the point of manufacture. The Phagenyx® Catheter is placed so the electrodes are positioned at the junction between the oropharynx and the

laryngopharynx at a position that is equivalent to the junction between the C3 and C4 cervical vertebrae. The electrodes are thus in an anatomical area that is much larger than the 11.5F Phagenyx® Catheter, and thus mucosa is not expected to be compressed against the metal. Relative movement between the electrodes and mucosa will certainly occur; however, there is no source of pressure locally to apply force between electrodes and tissue. Moreover, the electrode and tubing surfaces are contiguous, hence any pressure is evenly spread and analogous to that encountered with a standard fine bore feeding tube.

Phagenyx® Catheter Placement

Complications associated with injuring or perforating the nasogastric tract upon misplacement of an NGT are a seemingly sparse occurrence with a literature search resulting in only rare case reports. Arguably, the two metal electrodes on the surface of the Phagenyx® Catheter may increase the risk of local effect upon the pharyngeal mucosa by creating inflammation, erosion, or even ulceration. As described in the paragraph above, the design and anatomical placement of the electrodes minimizes risk severity and likelihood.

Patients will be exposed to the inherent risks associated with placement of any NGT, and patients who receive nutrition orally or via PEG will be exposed to additional risks of requiring the nasogastric Phagenyx® Catheter remain in place for the time required to complete the three consecutive daily stimulation sessions. Patients who participate at sites that utilize NGTs for feeding may have the Phagenyx® Catheter indwelling for longer than the time required to administer study treatment and therefore may be exposed to incremental risks associated with the design of the Phagenyx® Catheter incorporating embedded electrodes.

Nasogastric tube feeding is common practice and thousands of tubes are inserted daily without incident. However, there is a risk that the tube may become misplaced into the lungs [17] during insertion, or move out of the stomach at a later stage. The actual incidence of complications related to NGT placement is very low. Sparks et al., performed a meta-analysis which demonstrated the potential severity of pulmonary complications as well as the rare incidence in which they occur: pneumothorax and subsequent death occurred in 0.35% and 0.05% cases of nasoenteral tube (NET) placement, respectively[18].

The risk of accidental enteral feeding into the airway following misplacing a nasogastric tube is rarely mentioned in published literature. However, the United Kingdom National Patient Safety Agency issued a National Safety Alert in 2011 in attempts to raise awareness of this risk and provide guidelines to reduce the risk[18] of feeding into the airway. The alert emphasizes that while “thousands of tubes are inserted daily without incident,” grave harm may result in unrecognized misplacement of a nasogastric tube. To mitigate this risk, verification of proper NG tube placement is standard clinical practice and is also part of the instructions for use for placing the Phagenyx® Catheter.

Sinusitis has been linked to the presence of NG tubes used for enteral feeding in studies of patients developing nosocomial infections while in intensive care. The presence of the nasal tube causes obstruction in the normal flow of sinus fluids and can therefore lead to increased risk of bacterial colonization and development of hospital-acquired sinusitis[19]. Current practice methods in Europe and the US provide for replacing nasoenteric feeding tubes with a PEG if an extensive enteral feeding duration is required (e.g., 2-3 weeks in Europe[20] and typically even sooner in the US), so lengthy nasogastric intubation times are not expected in this study.

Nasoenteric feeding tubes may easily become dislodged due to patient mental status, transfers, or positional changes. While this phenomenon is most frequent in acute stroke patients, it may also occur in the sub-acute period. Attachment of the Phagenyx® Catheter to the patient's nose will be performed via the standard practice used at each investigational site. The Phagenyx® Catheter is packaged with a garment clip so that it may be fastened to the patient's garment in a manner that will relieve the weight of the connectors and attached cables thereby minimizing the risk of any injury to the nasal wing tissue.

Placement of an NGT would seemingly place patients at an increased risk of epistaxis; however, review of the literature produced only two publications that referenced epistaxis in relationship to use of an NGT, and both citations were associated with endoscopic NET placement[40, 41] rather than NGT placement.

A list of the risks associated with the Phagenyx® System and stroke can be found in Section 8.2

Radiation Exposure

The VFSS is considered the "gold standard" in the US for diagnosing the nature and severity of dysphagia as well as providing feedback on the effects of dysphagia therapy[21]. Hence, it would not be unusual for a dysphagic patient to undergo at least two VFSS studies over the course of being treated for dysphagia after stroke. The investigational protocol specifies two VFSS assessments be performed within a 1-week period to standardize baseline measures and to provide feedback on the dysphagia treatment under investigation shortly after the intervention. Patients typically undergo a non-instrumented dysphagia assessment before referral for an instrumented VFSS. Participating sites will be instructed to use the study-specific VFSS protocol for patients referred to an instrumented dysphagia assessment if they also appear to meet the rest of the study inclusion/exclusion criteria. Patients meeting the study criteria will require one subsequent VFSS performed according to the study-specific VFSS protocol. Hence, patients will be exposed to one, and possibly two, more VFSS than they would if they were not enrolled in this study.

The VFSS imparts a small dose of ionizing radiation. Zammit-Maempel et. al., reported a median exposure time of 171 seconds and an associated dose of 0.20 milliSieverts or mSv[43], while Moro and Cazzani reported a median exposure time of 149 seconds and

an associated dose of 0.35 mSv[44]. The standardized VFSS protocol proposed for this study is associated with an average duration of 2.9 minutes radiation exposure (95% confidence interval 2.8-3.0 minutes). Extrapolating from the relationship Moro and Cazzani published, the VFSS time of 2.9 min (174 sec), relates to an effective dose of ~0.44mSv[45].

Table 1 provides background information on relative average absorbed doses of ionizing radiation that a person would experience when exposed to various sources. On average, a U.S. resident receives an annual radiation exposure from natural sources of about 3.1 mSv. In addition, man-made sources of radiation from medical, commercial and industrial activities contribute roughly 3.1 mSv more to our annual exposure[46]. Computed tomography (CT) scans, are among the largest of these sources, with a head CT contributing 2mSv[47].

The average amount of radiation to which a patient is exposed over the duration of the VFSS is expected to be 2.9 minutes with an average absorbed dose of 0.44mSv ionizing radiation, with some variation dependent on site-specific imaging equipment. Hence patients participating in this study will experience radiation exposures that are less than 25% of the radiation associated with a head CT exposure and about 0.9% of the annual maximum permitted by the FDA radiation dose for radioactive drug research[48]. Comparing to background radiation, VFSS radiation exposure is equivalent to 1.7 months of natural exposure.

Table 1: Average absorbed radiation doses from various sources

Radiation Source	**Absorbed Cellular Dose** (mSv)
Background naturally occurring radiation, yearly	• 3.1
VFSS	• 0.44
Head CT	• 2

FDA Regulations on Radioactive Drug Research:	
Maximum radiation dose to whole body, active blood-forming organs, lens of eye, gonads	• Single dose = 35 • Annual and total dose = 50
Other organs	• Single dose = 50 • Annual and total dose = 150

A strategy that is popularly used to decrease radiation exposure is reducing the pulse rate of the radiation beam emitted during VFSS. The emitted radiation beam can be either continuous or pulsed. When pulsed, the pulse rate is defined as the number of pulses per second (pps) of the x-ray beam. Pulse rates for fluoroscopy commonly

include 30, 15, 7.5, and 4pps. Radiation exposure is reduced as pulse rate is reduced. Specifically, Aufrichtig et al., demonstrated average dose reductions of 22% at 15 pps and 49% at 7.5 pps when compared to doses at 30 pps[49]. Decreasing pulse rate also has a direct and proportional effect on the number of unique images in which a swallow is captured. Since the oropharyngeal swallow only lasts approximately one second, when pulse rate is decreased from 30 to 15, the number of unique images available to judge swallowing impairment also decreases from 30 to 15. Bonilha and colleagues reported differences in both judgment of swallowing impairment and treatment recommendations when pulse rates are reduced from 30 pps to 15 pps to minimize radiation exposure[50]. Differences between penetration aspiration score for the four pulse rates tested indicate that pulse rate may have a high impact on attributes of the interpretation of the VFSS.

The standardized VFSS protocol proposed for use in this study specifies a continuous pulse rate of 30 pps. The patient population exposed to ionizing radiation in this study will be of advanced age, with similar studies enrolling patients with an average age over 70 years. Thus the relative incremental risk associated with study-specific exposure to ionizing radiation is considered minimal based on the stochastic nature of risk associated with ionizing radiation exposure.

Finally, the objective of the VFSS is to assess the degree to which boli of incrementally thicker media penetrate or aspirate into the airway. Hence, the method by which risk of aspiration is studied also imparts an incremental risk of patients developing aspiration pneumonia after performing the VFSS. Jo et. al., recently published a retrospective review of the occurrence of pneumonia developing after aspiration during VFSS at their teaching hospital in Chuncheon, South Korea[51]. The authors reviewed 696 VFSS for cases in which blood cultures were performed within 3 days following the VFSS due to newly developed infectious signs. Pneumonia was suspected when there was some evidence of respiratory infectious signs in clinical, radiological, and laboratory findings. Fifteen cases of pneumonia were identified in this manner. Review of the VFSS procedure records indicated that only seven of these cases (1%) could be attributed to the VFSS.

2.4.2 POTENTIAL BENEFITS

Potential benefits resulting from this study:

- Information gained from the conduct of this study may be of benefit to other people with oropharyngeal dysphagia following stroke in the future.

The ideal patient population and treatment regimen for optimizing the use of pharyngeal electrical stimulation are still not completely understood now. However, most studies have demonstrated that patients with post-stroke dysphagia benefit to some degree from pharyngeal electrical stimulation when assessed using standardized measures of swallowing function and performance.

Alternative treatments include other types of stimulation approaches (e.g., neuromuscular, direct neural, transcranial) for which there is little evidence for adoption into general practice. Patients will receive the standard interventions for dysphagia that are practiced at the participating institution and generally accepted by ASHA.

2.4.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Post-stroke dysphagia in the hospital setting is associated with poor outcomes. It is known to increase the risk of life threatening and difficult to treat infections as well as increase mortality. If unresolved, dysphagia represents a major long-term disability burden, impacting patient survival, cost of care and quality of life. There are no clinically proven evidence-based treatments for dysphagia.

The Phagenyx® System is a NSR device. The safety profile associated with the use of the Phagenyx® System is well characterized by evidence accumulated from multiple clinical studies and ongoing post-market surveillance involving over 30 institutions in five countries over a period of 15 years. There are no characteristic device or treatment specific effects that are considered to be serious adverse events. The additional risks associated with the clinical study design are all well understood and can be easily mitigated. None of the protocol-specific assessments are expected to add significant risk over those risks inherent in the care of patients suffering dysphagia in the subacute stroke setting.

Patients participating in this study are expected to be exposed to only marginal incremental risk over standard of care, and some patients may experience more expedient and more successful outcomes associated with their dysphagia treatment. Hence, the benefits associated with study participation are expected to outweigh any incidental incremental risk.

3 STUDY OBJECTIVES AND ENDPOINTS

STUDY OBJECTIVES	STUDY ENDPOINTS
Primary	
To evaluate the efficacy of Phagenyx® treatment in reducing the severity of unsafe swallows.	Swallowing safety of a bolus based on PAS of each swallow, determined by a VFSS 48 hours after completion of investigational treatment, converted to a trichotomized ordinal response of safe (PAS 1-3), penetration (PAS 4-5), or aspiration (PAS 6-8). Each patient contributes up to 12 post-treatment repeated measurements (PAS) including 6 swallows of thin and 6 swallows of nectar.
Secondary	
To evaluate the efficacy of Phagenyx treatment in improving nutritional management.	Functional Oral Intake Scale (FOIS) at 7 days following the last investigational treatment. Dysphagia Severity Rating Scale (DSRS) at 7 days following the last investigational treatment
Exploratory	

STUDY OBJECTIVES	STUDY ENDPOINTS
To further characterize the efficacy of Phagenyx® treatment in reducing the severity of unsafe swallows. To evaluate the efficacy of Phagenyx® treatment on nutritional management changes.	The severity of unsafe swallows will be further evaluated via: o PAS outcome by each consistency (thin and nectar) o Physiologic measurement obtained using the Modified Barium Swallow Impairment Profile (MBSImP) metrics will be extracted from the thin and nectar swallows by the core lab by using the baseline and follow up VFSS data. These validated and reliable metrics of critical swallowing movements will be explored for their relationship to the primary study endpoint (PAS). o PAS dichotomized as safe (PAS 1-3) or unsafe (PAS 4-8) Nutritional management improvement will be evaluated via: o Dysphagia Severity Rating Scale (DSRS) at 14 days or discharge, whichever is first, and at 11 weeks following the last investigational treatment. o Time from baseline to removal of enteral feeding (i.e., removal of NG tube or PEG or transition to oral feeding, or first diet upgrade) o Functional Oral Intake Scale (FOIS) at 7 days, 14 days or discharge, whichever is first, and 11 weeks following the last investigational treatment
To evaluate the efficacy of Phagenyx® treatment on improving quality of life.	Quality of life (QOL) will be assessed baseline and 11 weeks following the last investigational treatment via the following instruments: o EuroQoL-5 Dimension Questionnaire (EQ-5D) and EuroQoL-Visual Analogue Scale (EQ-VAS)

STUDY OBJECTIVES	STUDY ENDPOINTS
To evaluate the efficacy of Phagenyx® treatment on general stroke health outcomes.	General stroke health outcomes will be assessed by: o Time to discharge from site in which treatment is received o Discharge destination from the site in which treatment is received o Patient location (home, institution) at 11 weeks o Days on antibiotics during hospital stay o NIH Stroke Scale (NIHSS) at baseline and 14 days or discharge, and 11-week follow up o Modified Rankin Scale (mRS) at baseline, 14 days, and 11 week follow up o Barthel Index (BI) at baseline, 14 days or discharge, and 11-week follow up o New onset pneumonia, using a standardized definition adapted from the STROKE-INF study[26] at baseline, 48 hrs, 7 days, and 14 days or discharge o Hospital readmission rate o Number of CXR (related to suspect pneumonia)

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is randomized, sham-controlled, patient-masked, outcome assessor-blinded, prospective, multi-center study designed to support a *de novo* submission and FDA clearance for the Phagenesis Phagenyx® System for treatment of oropharyngeal dysphagia following a stroke. The study will follow an adaptive group sequential design with unblinded sample size re-assessment. To ensure 180 evaluable patients with 7-day data and assuming a 20% dropout rate, 225 patients will be enrolled initially. An interim analysis for futility will occur after the first 60 patients complete their 7-day visit and another interim analysis will be performed for efficacy after 120 patients complete their 7-day visit. The total sample size may be increased up to 338 patients after the second interim analysis to ensure 270 evaluable patients. Up to 15 investigational centers across the US and Europe will participate in this study. The enrollment period is expected to be approximately 24 months and patient participation will last for approximately 11 weeks. Patients will be assessed at the following intervals: baseline,

within 48 hours of treatment, 7 days, 14 days or at discharge, whichever is first, and 11 weeks after completion of study treatments.

Investigational sites will be chosen from centers that have standardized protocols for treating patients with dysphagia post-stroke. Centers will be selected so that US sites represent the majority, with the ability to contribute at least 60% of the total patients. All sites must have speech language therapists/pathologists (SLT/SLP) on staff as well as affiliated VFSS facilities and personnel.

All enrolled patients will have the Phagenyx® Catheter placed and will receive either an active treatment with Pharyngeal Electrical Stimulation or a sham treatment by a HCP who is un-blinded to the treatment assignment.

Randomization will use stratification based on site and baseline PAS. Minimization may also be included to ensure group balance for study site and additional baseline covariates.
Administration of all protocol-specific assessments, other than PES or sham treatments, will be conducted by personnel who are blinded to the treatment assignment, including speech pathologists providing standard dysphagia care (excluding VitalStim and e-Stim). The standard dysphagia care data will be collected on the eCRF.

A core laboratory will be established for analysis of all procedural VFSS. The VFSS core lab will provide standardized baseline and follow-up analyses of the primary endpoint as well as VFSS-related tertiary endpoints. Personnel at the VFSS core lab will also be blinded to patient treatment assignment.

Up to three unblinded, active treatment roll-in patients will first be enrolled at each site in the US. The need for roll-in patients for European sites will be based on experience with the CE-marked device at the site and will be agreed to by Phagenesis and the site investigator. Roll-in patients will enable the site study staff to become fully proficient in the most effective way to administer the Phagenyx® treatment as well as perform other protocol-specific assessments. The sponsor will provide detailed training and education to the site staff in the use of the Phagenyx system and the protocol. The sponsor will provide an on-site representative to oversee and provide aid in the administration of PES during treatment of these roll-in patients. The sponsor will complete the Site Training and Competency Review form during the visit(s). The site will be approved to begin randomizing patients after the site meets the following competency requirements:

- The treatment administrator successfully and confidently completes up to three treatment sessions with little to no prompting or other aid from the sponsor representative,
- The treatment parameters recorded on the Base Station reflect appropriate stimulation levels, and
- Electronic case report forms (eCRFs) for baseline through the acute follow-up visit are completed correctly within 5 days of enrollment then within 5 days of each follow up for the roll-in patients.

A formal review of site competency will be made after one to three roll-in patients have been treated, and the site is competent based on the above parameters. The site investigator and other relevant personnel will meet with sponsor personnel or their designee(s) via teleconference or on site to review the roll-in patient records and answer outstanding questions. The sponsor or their designee will provide approval to begin randomizing patients by controlling access to the randomization module of the study's EDC system. Meeting documentation including recommended actions and decisions will be retained in the eTMF for each site.

Roll-in patients will be analyzed independently from the primary analysis population but will not contribute to the sample size cap.

Dysphagic patients enrolled into the study will continue to receive enteral or oral nutrition via the same manner as prior to study entry and will also have the Phagenyx® Catheter placed as part of the study. In the US, patients may receive feeding through the Phagenyx® Catheter for up to 2 weeks as needed. In Europe, patients may receive feeding through the Phagenyx Catheter for up to 30 days.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Clinical investigation demonstrates that pharyngeal electrical stimulation holds potential for treating patients that are dysphagic following stroke. Based on the founding work reported by Fraser, cortical excitation is directly related to the amplitude of the stimulation signal. The outcome of the STEPS study (Bath et. al.[21]) had a neutral outcome, therefore, this study is designed to overcome some shortcomings that were noted in the STEPS study, including:

- Dysphagia entry criterion has been set to PAS ≥ 4 to limit mild dysphagia;
- Patients will be enrolled at least seven days after their index stroke to omit those with early spontaneous recovery;
- The sham treatment will include Phagenyx Catheter placement but *no* PES to prevent inadvertent treatment.

4.3 CLINICAL EXPERIENCE AND JUSTIFICATION OF PES LEVEL

The Phagenyx® System, or variants thereof, has been studied over a period of 15 years during development and more recent commercial studies in over 30 institutions in five countries. Most clinical studies have demonstrated that patients with dysphagia after stroke experience a clinical benefit associated with pharyngeal electrical stimulation when assessed using standardized measures of swallowing function and performance. Please see the Investigator's Brochure for complete information on these studies.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Age ≥ 18 and ≤ 90 years.
2. Acute ischemic or hemorrhagic cerebral stroke within 7-28 days of baseline VFSS.
3. Score of 0 or 1 on NIHSS question 1a, Level of Consciousness.
4. *Moderate to severe dysphagia (PAS ≥4) on baseline VFSS (Baseline VFSS must meet the threshold criteria of demonstrating a PAS of ≥ 4, in three of the six boli (5 mL/1 tsp/bolus), during swallowing "thin liquid" barium media as assessed by the clinical staff administering the VFSS) unless its deemed too high risk then only 2 swallows will qualify.
5. Willing and able to have the Phagenyx® Catheter placed transnasally.
6. Willing and able to provide informed consent.
7. Stated willingness to comply with all study procedures and availability for the duration of the study.

*Note that the baseline VFSS will include testing with both thin liquids (up to 6 swallows) and nectar liquids (up to 6 swallows). For inclusion criterion 4, only the thin liquid swallows on the baseline VFSS will be considered. However, for descriptive statistics and other analyses, both the thin liquid and nectar liquid swallows on the VFSS will be considered.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Brainstem stroke.
2. Evidence of traumatic brain injury or subarachnoid hemorrhage.
3. Other, non-cerebrovascular, structural brain diseases, including multiple sclerosis or other demyelinating diseases, brain tumors (other than small meningioma), neurodegenerative diseases (including Alzheimer and Parkinson disease), hydrocephalus, and leukodystrophy
4. Dysphagia from conditions other than stroke.
5. Pre-stroke history of swallowing complaints or treatment or history of diseases known to be associated with swallowing problems (other neurological, head and neck cancer.
6. Distorted oropharyngeal anatomy (e.g., pharyngeal pouch, major pharyngeal surgery or head /neck surgery)
7. Currently being treatment for pneumonia.
8. Mute, global aphasia; no usable speech or auditory comprehension (scores 3 on NIHSS question 9, Best Language)
9. NIHSS score of $\geq$25
10. Presence of a tracheostomy
11. Any active implanted device (e.g., cochlear implant, ICD, permanent pacemaker)

12. Any progressive neurological disorder (e.g., Parkinson's Disease, Multiple Sclerosis)
13. Cognitive impairment that prevents compliance with protocol-specific instructions and assessments
14. Unstable cardiopulmonary condition, i.e., not on maintenance therapy.
15. Currently participating in another investigational study
16. Pregnant or planning to become pregnant while participating in the clinical study
17. Known Allergy to oral radiographic contrast media (specifically barium)
18. Any other condition in the opinion of the investigator will prohibit the patient from participation and follow up.

5.3 SCREEN FAILURES

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized to the study intervention or entered in the study. A record of screen failures, along with the reason for failure, will be kept in the database and/or on a Screening Log.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients will be screened and recruited by the investigators and/or coordinators at each site. Eligible patients could be in an inpatient rehabilitation center, having been transferred from the acute care facility in which they had been initially treated for the stroke, or site standard unit for post-acute stroke patients. The length of stay for these patients should be for up to 2 weeks to complete the study requirements for treatment and 14 day (+/- 1 day) follow up.

Stroke patients identified as dysphagic by clinical bedside assessments between the ages of 18 and 90 years, will be screened for study enrollment. The patient or their legal guardian will be eligible to sign the ICF after the study team explains the study and the patient and family have time to read and understand as well as ask all questions. The importance of study compliance will be emphasized throughout the informed consent process.

The length of study participation is approximately 11 weeks, including post treatment follow-up visits at 48 hours (+/- 24 hrs), 7 days (+/- 1 day), 14 days (+/- 1 day) or discharge, whichever is first, and 11 weeks (+/- 1 week).

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

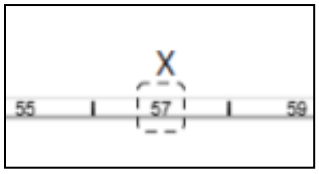
6.1.1 PHAGENYX® CATHETER PLACEMENT

All patients who have met screening and baseline criteria, signed an informed consent, and are enrolled in this study will require transnasal placement of the Phagenyx® Catheter which will remain in place for the minimum time required to complete three consecutive daily treatment sessions of active or sham stimulation. Patients will continue to receive nutrition via the same manner as prior to study entry, and will also have the Phagenyx® Catheter placed. Patients who already have an NGT will need to have it replaced with the Phagenyx® Catheter. Patients may receive feeding through the Phagenyx® Catheter as needed for up to 2 weeks in the US and up to 30 days in Europe.

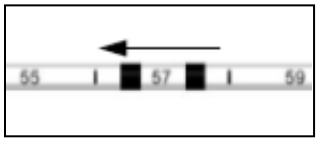
The Phagenyx® Catheter should be configured to fit each patient optimally before it is inserted. This is done to ensure electrodes are in the correct position to deliver stimulation and the distal end of the Phagenyx® Catheter is in the proper position for the delivery of nutrition to the stomach, if being used for feeding. Numbers printed on the exterior of the Phagenyx® Catheter are indexed to align to the correct position in the pharynx based on patient measurements. See Instructions For Use (Phagenyx PNX-100 Catheter IFU) in the eTMF.

1. The distance from nostrils to earlobe to xiphisternum is measured out using the Phagenyx® Catheter with its distal tip positioned at the nostrils.

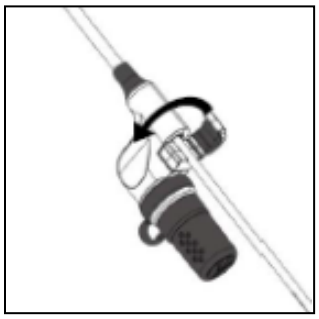
2. The number on the Phagenyx® Catheter printed guide is noted for correct Sleeve positioning so electrodes are properly placed in the pharynx.



3. The Sleeve is then adjusted so that the positioning guide is aligned over the number on the printed guide so that the heavy bars appear on either side of the number.

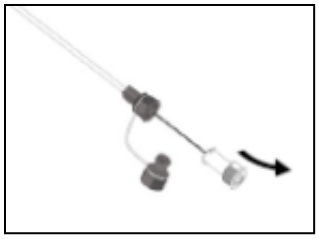


4. The tube clamp on the Sleeve is closed to fix the relative positions of Sleeve and Phagenyx® Catheter components.

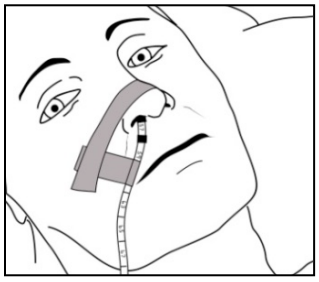


5. The Phagenyx® Catheter is inserted nasally using site standard technique, until the number below the positioning guide is at the patient's nostril. The position of the NGT is verified via standard institutional procedures to ensure the distal end is in the stomach via x-ray of catheter placement; auscultation of air in the stomach injected through the Catheter; and/or aspiration of stomach contents through the Catheter to confirm gastric pH, or per standard at each site.

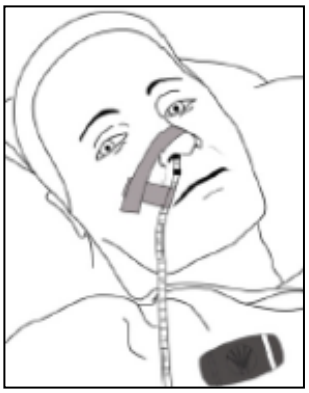
6. The guidewire is removed and disposed of.

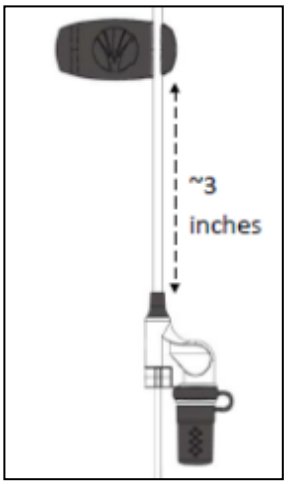


7. The Phagenyx® Catheter is secured in place as per standard practice for NGT placement (medical tape or custom bandage).



8. The Garment clip is attached to the patient and proximal end of the Phagenyx® Catheter inserted into the tube grip for comfort.





If the Phagenyx® Catheter will also be used for feeding, the enteral connector is connected to a suitable enteral feeding set (use of the supplied adaptor, as needed). Prior to NGT feeding, the correct placement of the NGT should be verified to avoid feeding into any space other than the stomach.

6.1.2 VITAL SIGNS MONITORING

Vital signs monitoring is required for approximately the first 20 patients receiving active treatment (including roll-in patients). To maintain the blind, the vital signs will be obtained on all patients including those randomized to sham treatment, until there are data for 20 patients who have received active treatment; this applies to all three days of treatment. Vital signs monitoring includes blood pressure, heart rate, and ECG monitoring. Immediately (within 5 minutes) prior to beginning PES treatment, the user will obtain and record pre-treatment blood pressure and heart rate numbers, as well as a 30-second ECG rhythm strip. Vital signs monitoring will continue throughout the duration of study treatment and any significant changes (i.e. noticeable increases) will be documented for study records. A second ECG rhythm strip is required 5 minutes into the PES treatment, and a third ECG rhythm strip is required immediately (within 5 minutes) post treatment. Immediate post-treatment blood pressure and heart rate numbers will again be obtained and recorded.

6.1.3 STIMULATION LEVEL OPTIMIZATION AND TREATMENT

The user first verifies that the electrodes are correctly positioned by inspecting the positioning guide, and ensuring the same number appears between the heavy bars of the positioning guide (refer to Step 3 above). In the majority of patients, the catheter will not need to be repositioned after it is inserted for the first time. In some patients, it may also be possible to visualize the oral guide in the throat. If the Sleeve is no longer aligned so that the electrodes are in the correct position, the Sleeve tube clamp can be opened and the Sleeve position adjusted until the correct positioning number is visible

between the heavy bars of the positioning guide. Treatment can be carried out after confirming the proper placement.

1. The treatment cable from the Base Station is attached to the Phagenyx® Catheter.
2. The Base Station power is turned on.
3. The study-specific patient identifier is entered upon first treatment, and is re-called for subsequent treatments.
4. The patient's Threshold Level (lowest detectable level of stimulation) is established via incremental current increase from 5mA to 50mA in 1 mA steps. This is repeated three times, and the average of the three readings is used to determine the treatment level of stimulation.
5. The patient's Tolerance Level (highest tolerated level of stimulation) is established via incremental current increase from the Threshold value in 5mA to a maximum of 50mA. This is repeated three times, and the average of the three readings is used to determine the treatment level of stimulation.
6. The Stimulation Level is automatically calculated. This level is tested for eight seconds to ensure patient tolerability, and adjusted as needed.
7. The Stimulation Level is initiated, and lasts for up to 10 minutes. The patient is monitored/supervised throughout.
8. Steps 1-7 are repeated once per day for two subsequent consecutive days approximately 24 hours apart, for a total of three treatments over three days.
9. See the Instructions for Use (Phagenyx Base Station IFU) in the study's eTMF.

6.1.4 DISPOSAL

The Phagenyx® Catheter will become electronically locked once the 3-treatment regimen has been completed to prevent over-treatment or use of the device across multiple patients. If the catheter is not being used for feeding, it is removed after completion of the 3 treatments by a qualified health care provider and should be disposed of in medical waste as per site-specific procedure.

6.2 DEVICE ACCOUNTABILITY, LABELING AND STORAGE

6.2.1 ACCOUNTABILITY

Investigators will maintain accurate records of the receipt and disposition of the investigational device on the Device Disposition Log supplied by Phagenesis. The Log will be used to record device receipt, uses, discards, or returns. Device disposition will be verified by the clinical monitor periodically throughout the study. The investigator shall return the Base Stations, unused devices, and the completed device disposition log at completion of the investigation to Phagenesis or their designee, as directed. The investigator's copy of the Device Disposition Log must document the devices used in study patients as well as the unused devices that are returned to Phagenesis. Use of the Phagenyx System is prohibited outside of this protocol in US centers. In Europe, although the Phagenyx System is CE marked, the devices supplied for the study will be documented on the Device Disposition Log, stored in a secure area away from general stock, and only used for study patients.

6.2.2 LABELING

In the US, the Phagenyx® System (Base Station and Catheters) will be labeled as investigational. In Europe, the device is CE-marked and will not be labeled investigational. The sites outside of the US will be provided an additional Base Station to be used for patients randomized to sham treatment. The Base Stations will be identified in such a manner to maintain the blind.

6.2.3 STORAGE

All Phagenyx® System components are to be stored in an ambient temperature-controlled, dry secure location where only authorized study personnel can access the devices for study use.

The Phagenyx® Base Station requires an overnight connection to an electrical outlet for overnight charging once a month.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All efforts will be taken to maximize treatment assignment blinding of the patient, caregivers, and third-party outcome assessors of clinical endpoints. Sites will be instructed to assign one healthcare professional to each enrolled patient to administer Phagenyx® treatment; this HCP shall not be blinded to the assigned patient's treatment. The designation of this individual will be at the discretion of the site investigator and may be a study nurse, SLP, or staff physician. The individual selected to administer the Phagenyx® treatment may not be an SLP or qualified health care provider who is otherwise involved with care of the study patient. Moreover, rating scales that reflect oral diet progression (e.g., Functional Oral Intake Scale and Dysphagia Severity Rating Scale) will also be completed by an SLP that is blinded to randomization assignment. All persons involved in placement of the catheter, assessments, treatment and follow up will be at the discretion of the investigator based on skill set and site standards, and will be further trained by the sponsor with a competency review completed.

Randomization will use stratification based on site and baseline PAS. minimization may also be included to ensure group balance for study site and additional baseline covariates Administrative permission to access the randomization assignment in the electronic database will be limited to unblinded HCPs who will administer treatment and who will monitor study compliance.

Stimulation parameters for the active treatment sessions will be collected on the eCRF to enable monitoring of the performance of the investigational device as well as to ensure proper treatment administration. Stimulation data will be monitored by a sponsor representative or designee who is uninvolved with the data analysis. The eCRF in which stimulation parameters are recorded will have strict administrative permissions, so that only the individual monitoring the investigational device will be allowed access. This monitor will also be responsible for monitoring compliance with the assigned treatment arm.

Patients will be masked to treatment and will not be told if they receive the active or sham treatment. Some patients randomized to active treatment will have some sensation associated with the pharyngeal stimulation; however, a few with higher sensory thresholds may not feel anything as demonstrated in prior studies. The patients randomized to the sham treatment will not receive any actual stimulation and thus should not have any sensory feeling associated with the sham treatment. The informed consent documentation will advise that the patient "may or may not" feel the pharyngeal stimulation, so that those patients receiving either the active PES treatment of the sham treatment will not necessarily expect to feel anything. All procedural steps will be carried out in a very similar manner for both groups of patients. The only difference in the administration of the two treatments is that no electrical stimulation will be administered during the sham treatment. The way the treatment is administered will not give the patient any idea as to their treatment as there are no light or sound indicators associated with the administration of PES. Moreover, the individual administering treatment will be facing the patient at all times during the delivery of electrical (or sham) stimulations, and the base station will be facing the treatment administrator. The shape of the base station will prevent the patient from seeing what is on the administrator's screen during treatment delivery. The active/sham treatments will also be administered in privacy so that no other study personnel or patient caregivers/family members can observe the treatment or treatment assignment.

For those patients randomized to the sham group, a different Base Station will be used that delivers no electrical current and does not have the ability to treat with PES. This Base Station will have only “demo” software loaded, so the unblinded healthcare professional administering the treatment will have a screen and the ability to adjust the settings, without any changes or current begin delivered.

An assessment of whether the patient remains blinded will be included at the 14-day (+/- 1 day) or discharge whichever is first, follow-up assessment. This will be done via a question to the patient asking them if they believe they received the active or sham treatment and their response will be documented on the eCRF.

Evaluation of the VFSS will be performed by an external core lab that is not part of a study site. VFSS records will be anonymized so that records are only identified by site number, patient number, and type of study (i.e., baseline or follow-up). Core lab personnel will be blinded to the treatment assignment as well as the actual treatment received.

Protection of the blind will be maintained for the interim analyses. Study documents, analysis reports, closed meeting minutes and recommendations made by the Data Monitoring Committee will be maintained in a separate location not accessible by the sponsor or sites.

Patient data monitoring will be performed in a consistent and dynamic manner so that there will be no need to disrupt the normal study conduct to provide data needed for an

interim analysis. Sites will not be told the results of any interim analysis unless the study is to be terminated early for either futility or success.

6.4 STUDY INTERVENTION COMPLIANCE

Investigational site compliance with all study procedures, including randomization assignment and treatment, will be monitored by trained and qualified study sponsor representatives and/or designees.

7 VFSS STOPPING CRITERIA AND PATIENT/SITE/STUDY TERMINATION

7.1 VFSS STOPPING CRITERIA

- If the PAS is ≥ 6 (see below) for three consecutive bolus trials of the same consistency, that consistency should be stopped and the investigator (or trained and authorized designee) can decide if it is safe to move to the next consistency to assess dietary modification, or if the study needs to be stopped.

  Penetration Aspiration Score Definitions:

  - Score = 6: Material enters the airway, passes below the vocal folds and is ejected into the larynx or out of the airway.
  - Score = 7: Material enters the airway, passes below the vocal folds & is not ejected from the trachea despite effort
  - Score = 8: Material enters the airway, passes below the vocal folds & no effort is made to eject

- A 'Stop' may be applied at any time if the Investigator (or trained and authorized designee) feels it is unsafe for the patient to continue.

- If VFSS time exceeds 3 minutes, the procedure must be stopped.

Regardless of completion of the PES treatment, patients will be encouraged to remain in the study until they have completed the protocol-required follow-up period while maintaining respect for all patient rights. Patients are free to withdraw from participation in the study at any time upon request.

7.2 PATIENT TERMINATION

Possible reasons for premature patient termination include but are not limited to the following:

- Withdrawal of consent: The patient decides to withdraw from the study. If a patient withdraws from the clinical investigation, the reason(s), if known, will be

recorded on the eCRF. If withdrawal is due to problems related to the investigational device safety or performance, the investigator shall ask the patient's permission to follow his/her status/condition outside the investigation.

- Lost to follow-up: If a patient has been discharged to inpatient care at another institution, then attempts should be made to retrieve patient records from that institution. Telephone follow-up at 11 weeks (+/- 1 week) should be attempted at least three times. If the patient does not respond to the three telephone calls, then the investigator should send a letter to the patient. All attempts should be documented in the source documents and on the eCRF. A patient will be considered lost to follow up if more than 30 days has elapsed from last contact. Patients who discontinue prematurely will be included in the analysis of results and will not be replaced.

An investigator may discontinue or withdraw a patient from the study for any reason, including the following:

- Pregnancy
- Significant non-compliance with study protocol
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the patient
- Disease progression which requires discontinuation of the study intervention
- If the patient meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for termination from the study will be recorded on the eCRF. Patients who sign the informed consent form and are randomized but do not receive the assigned study intervention (whether sham or treatment) may be replaced to achieve the number of evaluable patients needed for analysis. Patients who receive treatment but discontinue the study prematurely for any reason will not be replaced.

7.3 SITE TERMINATION AND STUDY TERMINATION

The sponsor may suspend or prematurely terminate an individual investigative site or terminate the entire study for the following reasons:

- A decision is made to suspend or discontinue testing, evaluation, or development of the investigational product for any reason
- An individual site may be closed for the following reasons:
  - The investigator fails to enroll patients into the study at an acceptable rate,
  - The investigator fails to comply with pertinent regulations of appropriate regulatory authorities,
  - Site personnel demonstrate insufficient compliance to protocol requirements, and/or
  - Site personnel submit knowingly false information from the research facility to the sponsor, study monitor, or appropriate regulatory authority

An investigator, IRB/EC, or FDA may suspend or prematurely terminate a site's participation in a clinical investigation. The IRB/EC and FDA may suspend an investigation if a suspicion of unacceptable risk to patients arises; the sponsor shall terminate the investigation if an unacceptable risk is confirmed.

If the study is terminated early, all specified follow-up data on patients enrolled prior to termination will be collected and reported.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 STUDY ASSESSMENTS

8.1.1 SCREENING AND BASELINE ASSESSMENTS

In addition to the assessments detailed below, a medical history and demographics data will be collected at the screening visit. The medical history can be obtained from the patient's medical record and the physical assessment is part of standard care. A modified physical exam will be conducted at the baseline visit to establish the patient's current condition, to facilitate the appropriate adjudication of adverse events that may occur during the study. Information obtained from these assessments will be recorded on the eCRF. Informed consent will also be obtained, per standards and guidelines at each site.

8.1.2 NASOPHARYNGEAL EXAMINATION

The patient's nasopharynx will be examined by means of a visual exam using a standard flashlight /penlight at baseline, Day 7 post catheter placement and upon removal of catheter. If there is evidence or symptoms of erosion or trauma, a fiberoptic exam should be done to rule out any adverse events.

8.1.3 VIDEOFLUOROSCOPIC STUDY (VFSS)

The VFSS is a swallow test during which swallowing function is analyzed radiographically. Institutional protocols vary widely with respect to the consistencies of the contrast materials and the volumes of each; hence, a standardized approach will be used for all protocol-specific assessments. Baseline VFSS must meet the threshold criteria of demonstrating a PAS of ≥ 4, in three of the six boli (5 mL/1 tsp/bolus), during swallowing "thin liquid" barium media as assessed by the clinical staff administering the VFSS.

<u>Standardized VFSS Approach</u>

The standardized VFSS examination will be administered using standardized, commercial preparations of barium sulfate media and will be comprised of two distinct phases:

1) Thin liquid: 5 mL/1 tsp/bolus x 6 swallows
2) Nectar liquid: 5 mL/1 tsp/bolus x 6 swallows

Varibar® (Bracco Diagnostics, Inc. Monroe Township, NJ) will be used as the barium sulfate (40% w/V) media across all sites whenever possible to ensure standardization of the VFSS and its interpretation. Varibar is provided in pre-mixed, ready-to-use consistencies, and thus removes the uncertainty that comes with measuring and mixing prior to use. Varibar will be administered by the SLP/SLT personnel at each site per site standard practice. If Varibar is not used at a site, the site may use their standard as long as the consistency and viscosity is similar to that of Varibar.

Refer to section 7.1 for VFSS stopping criteria.

8.1.3.1 Penetration Aspiration Scale (PAS)

The PAS provides a scoring mechanism for airway closure and clearance during the VFSS. The PAS is a validated 8-point ordinal scale that quantifies penetration and aspiration events observed during VFSS[28]. Scores are determined primarily by the depth to which material passes into the airway and the swallower's response to the material passing into the airway. For each swallow task, there may be more than one swallow. Each swallow in a task shall be scored via the PAS by the core lab.

Penetration Aspiration Scale

Score	Description
1	Material does not enter airway
2	Material enters the airway, remains above the vocal folds, and is ejected from airway
3	Material remains above the vocal folds, and is not ejected from airway
4	Material contacts the vocal folds, and is ejected from airway
5	Material contacts the vocal folds, and is not ejected from airway
6	Material passes below the vocal folds [glottis], and is ejected into larynx or out of airway
7	Material passes below the vocal folds [glottis], and is not ejected from trachea despite effort
8	Material enters the airway [passes glottis], and no effort is made to eject it

8.1.4 BARTHEL INDEX

The Barthel Index is a widely-used measure of functional disability and a measurement of quality of life, as it measures the extent to which someone can function independently and has mobility in their activities of daily living (ADL) i.e., feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation and stair climbing. It was developed for use in rehabilitation patients with stroke and other neuromuscular or musculoskeletal disorders. The BI is completed by the patient on the

provided worksheet and the data are entered on the eCRF. It is completed at the baseline, 14-day, and 11-week visits. Details regarding the administration of the BI can be found in the eTMF.

8.1.5 MODIFIED RANKIN SCALE (mRS)

The mRS is a single-item, global outcomes rating scale for patients who are post-stroke. It is used to categorize level of functional independence with reference to pre-stroke activities rather than on the observed performance of a specific task.

The mRS is used to measure the degree of disability in patients who have had a stroke, as follows:

- 0: No symptoms at all
- 1: No significant disability despite symptoms; able to carry out all usual duties and activities
- 2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
- 3: Moderate disability; requiring some help, but able to walk without assistance
- 4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
- 5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention
- 6: Dead

The mRS is administered by qualified and trained study staff. It is completed at the baseline, 14-day, and 11-week visits and the data will be entered on the eCRF. Details regarding the administration of the mRS can be found in the eTMF.

8.1.6 NIH STROKE SCALE (NIHSS)

The NIH Stroke Scale is a widely-used tool that was built to assess the cognitive effects of a stroke. In more scientific terms, it provides a quantitative measure of stroke-related neurologic deficit. Although the NIHSS was first developed as a clinical tool for research on stroke patients, it is now used by health professionals to determine the severity of a stroke. It also helps create a common language between all people involved in a stroke patient's treatment. In a treatment setting, the scale has three major purposes:

- It evaluates the severity of the stroke
- It helps to determine the appropriate treatment
- It predicts patient outcomes

It is completed at the baseline, 14-day, and 11-week visits and the data will be entered on the eCRF. Details for the NHISS can be found in the eTMF.

8.1.7 FUNCTIONAL ORAL INTAKE SCALE (FOIS)

The FOIS was developed to document the functional level of oral intake of food and liquid in stroke patients with dysphagia[30]. It is a 7-point ordinal scale that can easily completed by clinicians based on information contained in medical charts, dietary journals, and/or patient reports. Verification of patient reports may be obtained by a spouse or family members or from a variety of sources for institutionalized patients. The FOIS shows strong criterion validity and cross-validation compared with standard clinical measures of stroke outcome. The FOIS has demonstrated sensitivity in expected increase in functional oral intake over a 6-month recovery period in stroke patients. It is completed at the baseline, 7 day, 14-day, and 11-week visits and the data will be entered on the eCRF. Details regarding the administration of the FOIS can be found in the eTMF.

Functional Oral Intake Scale

Level	Description
1	Nothing by mouth (NPO)
2	Tube dependent with minimal attempts of food or liquid
3	Tube dependent with consistent intake of liquid or food
4	Total oral diet of a single consistency
5	Total oral diet with multiple consistencies but requiring special preparation or compensations.
6	Total oral diet with multiple consistencies without special preparation, but with specific food limitations.
7	Total oral diet with no restriction.

8.1.8 DYSPHAGIA SEVERITY RATING SCALE (DSRS)

The DSRS is composed of a 3-component score[19] that includes feeding independence, but nutrition level and diet modification is split into the components of liquid feeding and overall diet consistency. The DSRS is the sum of the scores of each of the 3 individual components rather than a combination of the three components into an ordinal scale. Moreover, the DSRS scoring is not based on underlying physiology as the DOSS attempts by use of the VFSS, but instead captures only the result of the swallowing dysfunction as does the FOIS. The DSRS has not been formally validated, but it may provide more sensitive or specific information than the FOIS with its 13-point scale. The DSRS has been used in prior studies that have assessed PES, and is thus being used for this study. It is completed at the baseline, 7 day, 14-day, and 11-week visits and the data will be entered on the eCRF. Details regarding the administration of the DSRS can be found in the eTMF.

Dysphagia Severity Rating Scale

Fluids	Score	Diet	Score	Supervision	Score
No oral fluids	4	Non-oral feeding	4	No oral feeding	4

Pudding consistency	3	Puree	3	Therapeutic feeding (SLP/trained staff)	3
Custard consistency	2	Soft, moist diet	2	Feeding by 3rd party (untrained)	2
Syrup consistency	1	Selected textures	1	Eating with supervision	1
Normal fluids	0	Normal	0	Eating independently	0

Notably, the DSRS was developed in Europe where nomenclature for fluid consistency differs from that used in the US. Hence, in order to standardize the DSRS with the modified barium swallow protocol adopted for the MBS/VFSS, the following interpretation will be used:

Normal fluids = Thin Liquid
Syrup consistency = Nectar
Custard = Honey

8.1.9 QUALITY OF LIFE (QOL) INSTRUMENTS: EQ-5D, EQ-VAS

EQ-5D-5L EuroQuality of Life

The EQ-5D-5L is a simple measure that comprises five dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. There are five options (levels) under each domain. It is completed at the baseline and 11-week visits and the data will be entered on the eCRF.

EQ-VAS EuroQoL Visual Analogue Scale

The EQ-VAS is a component of the EQ-5D. It records the respondent's self-rated health on a 20 cm vertical visual analogue scale with the endpoints labelled as "the best health you can imagine" and "the worst health you can imagine." Patients mark an "x" on the scale to indicate how their health is ***on the day of the assessment*** and also to write the number the marked on the scale in the box on the page. It is completed at the baseline and 11-week visits and the data will be entered on the eCRF. See the eTMF for details on administration of the EQ-VAS.

8.1.10 PNEUMONIA ASSESSMENT

A standardized assessment for clinical signs and symptoms associated with pneumonia will be performed over the initial two weeks that patients are enrolled in the study (e.g., baseline through the 14 days or discharge, whichever is first, follow-up. Diagnostic methods are not specified; instead, signs, symptoms, and/or diagnostics test results will be collected on a regular basis (i.e., baseline and post treatment at 48 hours and on days 7, 14 days or discharge, whichever is first, to determine if a standardized diagnosis of pneumonia can be made. Information will be obtained via the patient's medical record

and recorded on the eCRF. A diagnosis of pneumonia must meet the following set of criteria:

Temperature:
a) ≥ 37.5°C or higher on two consecutive measurements *or*
b) ≥38.0°C or higher (only need one measurement)

AND

Respiration:
a) rate ≥ 20 breaths/min or
b) cough AND breathlessness *or*
c) purulent sputum *or*
d) need for oxygen or increase in oxygen flow rate

AND

a) WBC count ≥ 11.0 × 10^9/L *or*
b) Chest infiltrates on radiograph or
c) Positive sputum culture on microbiology *or*
d) Positive blood culture

AND

No other obvious source of infection

If a diagnosis of pneumonia is made, it will be recorded on the AE eCRF and reported as an AE/SAE in accordance with Section 8.2, below.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENT (AE)

An adverse event (AE) is any undesirable experience (sign, symptom, significant laboratory abnormality, illness, or other medical event) occurring to a patient that appears or worsens during this clinical study, regardless of etiology or relatedness to the study device.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENT (SAE)

A serious adverse event (SAE) is any adverse event that leads to:

- Death
- Life-threatening illness or injury
- Inpatient hospitalization or prolonged hospitalization

- Disability or permanent body damage
- Required intervention to prevent permanent impairment or damage
- Other serious, medically significant event

Important medical events that do not meet the above criteria may still be considered an SAE if they seriously jeopardize the patient and require immediate medical or surgical intervention to prevent one of the aforementioned outcomes.

8.2.3 CLASSIFICATION OF ADVERSE EVENTS

8.2.3.1 SEVERITY

The following criteria will be used by the investigator to classify severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the patient's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not equate to "serious."

8.2.3.2 RELATEDNESS

The following criteria will be used by the investigator to classify relatedness to the device and/or procedure:

- **Unrelated** - An AE for which sufficient information exists to indicate that there is no causal connection between the event and the device or procedure. The AE is due to and readily explained by the patient's underlying disease state or is due to concomitant medication or therapy not related to the use of the device or procedure. In addition, the AE may not follow a reasonable temporal sequence following the procedure.
- **Possibly related** - There is a reasonable possibility that the AE may have been primarily caused by the device or procedure. The AE has a reasonable temporal relationship to the use of the device or procedure and follows a known or expected response pattern to device or procedure, but alternative etiology is equally or more likely compared to the potential relationship to the use of the device or procedure.
- **Definitely related** - The AE has a strong causal relationship to the device or procedure. The AE follows a strong temporal relationship to the use of the device or procedure, follows a known response pattern to the device or procedure, and

cannot be reasonably explained by known characteristics of the patient's clinical state or other therapies.

8.2.3.3 ANTICIPATED AND UNANTICIPATED ADVERSE EVENTS

The investigator at each site will be responsible for determining whether an adverse event (AE) is anticipated or unanticipated.

Anticipated AEs associated with the Phagenyx System, along with risks associated with the Phagenyx-related study procedures (i.e., VFSS) include but are not limited to the following:

- Bruising, skin
- Bleed, skin
- Death
- Dyspnea/shortness of breath
- Epistaxis
- Erosion, skin or mucosa
- Esophagitis, reflux
- Facial reflex, gagging
- Gastroesophageal reflux
- Gastrointestinal bleed
- Ileus
- Infection or irritation, tube insertion site or nasopharynx
- Ionizing radiation risks
- Ischemia, intestinal
- Nausea
- Necrosis, skin or mucosa
- Peritonitis
- Pneumonia, aspiration
- Pneumothorax
- Sepsis
- Sinusitis
- Sore throat
- Ulceration, skin or mucosa
- Vomiting

Other Anticipated Adverse Events

Other anticipated AEs, associated with the index stroke or underlying co-morbid conditions associated with stroke, are also be expected to occur. These may include, but are not limited to, the following:

- Agitation
- Anemia
- Angina/myocardial infarction/cardiac ischemia
- Anxiety
- Atrial fibrillation/flutter
- Bradycardia

- Cardiac arrest
- Cardiac dysrhythmia
- Cellulitis
- Cerebral edema
- Cerebral herniation
- Cerebral infarct extension/recurrence
- Coma/diminished level of consciousness
- Confusion
- Congestive heart failure/heart failure
- Constipation
- Death
- Deep venous thrombosis
- Dehydration
- Diarrhea
- Dizziness/vertigo
- Dyspepsia
- Dysphagia
- Dyspnea
- Extracranial bleeding
- Fever
- Gastritis or gastric/duodenal ulcer
- Gastrointestinal bleed
- Headache/migraine
- Hemorrhagic transformation of cerebral infarct
- Hydrocephalus
- Hypokalemia
- Hyperglycemia/hypoglycemia
- Hypoxia
- Insomnia
- Intracerebral hemorrhage expansion
- Intraventricular hemorrhage
- Joint pain (arthralgia)
- Musculoskeletal pain
- Nausea
- Neurologic worsening
- Peripheral vascular disorder
- Peripheral edema
- Pneumonia
- Pressure sore
- Pulmonary edema
- Pulmonary embolism
- Seizure
- Sepsis
- Sleep apnea
- Skin rash
- Limb spasticity

- Transient ischemic attack
- Urinary incontinence
- Urinary tract infection
- Vomiting

Unanticipated Adverse Device Effect (UADE) is defined as any ***serious*** adverse effect on health or safety or any life-threatening problem or death caused by – or associated with – the device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (including documents such as the protocol, Investigator's Brochure, informed consent form or other study-related documents), or any other unanticipated serious problem associated with the device that relates to the rights, safety or welfare of patients.

8.2.4 DEVICE DEFICIENCIES

Device Deficiency
A device deficiency is an inadequacy of a medical device with respect to its integrity, quality, durability, reliability, safety or performance. For the purposes of this study, a device deficiency will be defined as a failure of the device to perform its intended function when used in accordance with the Instructions for Use.

Device deficiencies will be recorded and evaluated for possible untoward effects on the patient. If a significant device deficiency results in an adverse experience in the patient, this adverse experience should be considered an adverse event and recorded on the AE eCRF. Device failures that do not result in a clinically significant adverse effect on the patient will be noted on eCRF regarding device performance, but will not be considered an adverse event.

8.2.5 EVENT ASSESSMENT AND FOLLOW-UP

All AEs and SAEs will be captured on the AE eCRF. Information to be collected includes event description, date of onset, seriousness, classification of severity and relatedness, treatment, and resolution/stabilization of the event. All AEs/SAEs occurring while on study must be documented appropriately regardless of relationship. Adverse events/SAEs will be collected from the time of signing the ICF through the patient's study termination and will be assessed for at each encounter with the patient. Adverse events may be reported by patients, elicited through questioning by an Investigator or designee, or collected via observation by the Investigator. In addition, patients will be instructed to contact the investigator and/or study coordinator if any significant adverse events occur between study evaluation visits.

Any medical condition that is present at the time that the patient is screened will be considered as baseline and not reported as an AE. However, if the patient's condition deteriorates at any time during the study, it will be recorded as an AE.

8.2.6 EVENT REPORTING

All adverse events are to be reported by the site as soon as possible by recording the information on the AE eCRF in the EDC system. De-identified source documents are to be uploaded to the EDC system as soon as possible when they become available. The EDC system will notify the sponsor of all SAEs including Unanticipated Adverse Device Effects (UADEs). The site investigator is responsible for reporting AEs/SAEs to the appropriate IRB/EC as required by the IRB's/EC's requirements.

Unanticipated Adverse Device Effects must be reported to the sponsor and the IRB within ten working days of discovery. The sponsor is responsible for conducting an evaluation of UADE and shall report the results of such evaluation to FDA and all study sites/investigators within ten working days after the sponsor first receives notice of the UADE.

9 STATISTICAL CONSIDERATIONS

See the separate Statistical Analysis Plan (SAP) for details regarding the statistical analyses.

9.1 STATISTICAL HYPOTHESES

The primary efficacy analysis is based on an ordinal logistic model of PAS (1-8 scale) of each bolus, determined by VFSS 48 hours following the last investigational treatment, and converted to a trichotomized response as follows: Safe (PAS 1-3), Penetration (PAS 4-5), or Aspiration (PAS 6-8). Hypothesis testing will be a superiority test on the difference in cumulative log odds between treatment.

9.2 SAMPLE SIZE DETERMINATION

Sample size and power was determined through simulations. The study will follow an adaptive group sequential design with unblinded sample size re-assessment. To ensure 180 evaluable patients with 7-day data and assuming a 20% dropout rate, 225 patients will be enrolled initially. An interim analysis for futility (non-binding stop) will occur after the first 60 patients complete their 7-day visit, and another interim analysis will be performed for efficacy after 120 patients for futility stopping, early efficacy stopping, and SSR (Sample Size Re-assessment). The SSR strategy will be based on both the primary endpoint and DSRS 7 days after last study treatment (key for evaluating nutritional management changes). The total sample size may be increased up to 338 patients after the second interim analysis to assure up to 270 evaluable patients.

Based on prior feasibility studies (Bath et. al.[21]) the primary endpoint is hypothesized to have an odds ratio of approximately 2.2 favoring the PES group. With this effect size, the power is at least 90% for significance on the primary endpoint. Additional simulation results are provided in the Simulation Report.

9.3 POPULATIONS FOR ANALYSES

- The Intent to Treat (ITT) Population will consist of all patients that were randomized, irrespective of their protocol adherence and continued participation in the study.
- The Per Protocol (PP) Population will consist of all randomized patients who completed the full Phagenyx treatment regimen according to their randomization assignment and for whom completed primary endpoint data are also complete.
- The Safety Population will consist of all patients that were enrolled in the study and underwent the pre-procedural VFSS with or without subsequent placement of the Phagenyx Catheter.
- The Roll-In (RI) population will consist of all patients enrolled in a non-blinded roll-in manner and remained eligible to receive the Phagenyx treatment after initial pre-procedural VFSS testing is completed and the PAS is determined to meet entry criterion and no exclusions are found. All patients in whom treatment was attempted, regardless of procedural outcome, will be included in this analysis set.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Tabulations will be produced for appropriate demographic, baseline, efficacy, pharmacokinetic and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the mean, median, standard deviation, minimum and maximum values will be presented. Time to event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as percent of censored observations.

Formal statistical hypothesis testing will be conducted at the 1-sided, 0.025 level of significance.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The primary analysis will be performed on the ITT population. The primary endpoint is trichotomized PAS on each bolus, determined by VFSS 48 hours after completion of PES treatment. The three ordinal PAS categories are defined as Safe (PAS 1-3),

Penetration (PAS 4-5), and Aspiration (PAS 6-8). Each patient contributes 12 measurements to the primary endpoint, of which 6 are from boli of a thin consistency and 6 are from boli of a nectar consistency.

Missing PAS data will be imputed in the primary analysis. PAS values that are missing due to application of VFSS stopping criteria will be assigned the worst (highest) post-treatment PAS value. For patients who have no post-treatment PAS data due to lost-to-follow-up or death, the post-treatment PAS values will be imputed from baseline PAS values and other patient baseline characteristics using multiple imputation. In addition, tipping point analysis will be performed as a sensitivity analysis.

A cumulative logistic model will be used to analyze the primary endpoint, and a sandwich variance estimator via a generalized estimating equations approach will be used to account for correlated PAS outcomes within each patient. Modeling details are specified in the SAP.

9.4.3 ANALYSIS OF THE SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints will be tested for statistical significance sequentially provided the primary endpoint is found to be statistically significant. The ITT population will be used. The first endpoint tested will be FOIS at 7 days following the last investigational treatment. The second endpoint tested will be DSRS at 7 days following the last investigational treatment.

Analysis details are specified in the SAP.

9.4.4 SAFETY ANALYSES

Safety analyses will be conducted using the Safety Population.

Adverse events will be coded by type using a list of anticipated events. Events which do not meet a pre-defined type will be coded as ‘other’ and will require supporting detail.

Adverse events will be summarized by patient incidence rates, therefore, in any tabulation, a patient contributes only once to the count for a given adverse event.

The number and percentage of patients with any adverse events assessed by the Investigator as related to treatment (definite, probable, or possible relationship), and with any serious adverse event, will be summarized by treatment group and overall. In these tabulations, each patient will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

No formal hypothesis-testing analysis of adverse events incidence rates will be performed. All adverse events occurring on study will be listed in patient data listings.

By-patient listings also will be provided for the following: patient deaths, serious adverse events, and adverse events leading to withdrawal.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline demographics and medical history information will be summarized for the ITT, PP, Safety and RI populations using descriptive statistics. Summaries will be provided by treatment group, stratification factors, and other key baseline parameters if applicable. No formal statistical testing will be performed.

9.4.6 PLANNED INTERIM ANALYSES

To ensure 180 evaluable patients with 7-day data and assuming a 20% dropout rate, 225 patients will be enrolled initially. An interim analysis for futility (non-binding) will occur after the first 60 patients complete their 7-day visit, and another interim analysis will be performed for efficacy after 120 patients complete their 7-day visit. The total sample size may be increased up to 338 patients after the second interim analysis to ensure 270 evaluable patients.

The interim analysis will be performed by an unblinded Independent Statistical Center (ISC) and the recommendation for adaptation or early stopping will be made by the DMC. An electronic file exchange platform capable of secure storage of documents with audited access will be used to control flow of information during the study.

Details on the interim statistical analysis and decision rules are described in the SAP.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT

The investigator (or designee) is responsible for performing consent procedures in accordance with 21 CFR 50 and ISO 14155 for each patient enrolled in the study. The template ICF will be provided to the site by Phagenesis for review and approval by the governing IRB/EC. Modifications requested by local IRB/EC must be approved by Phagenesis prior to first use. Each investigator is responsible for ensuring that enrollment at his/her site does not commence until Phagenesis and IRB/EC approval of the ICF has been obtained and the site training activities have been successfully completed.

Consent forms describing in detail the study intervention, study procedures, and risks are given to the patient and written documentation of informed consent is required prior to starting intervention/administering study assessment or intervention.

10.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. The investigator (or designee if allowed) will explain the research study to the patient and answer any questions that may arise. A verbal explanation will be provided in terms suited to the patient's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research patients. Patients will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patients should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The patient or legally authorized representative (if allowed) will sign the ICF prior to any procedures being done specifically for the study. Patients must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the patients for their records. The informed consent process will be conducted and documented in the source document. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.3 STUDY DISCONTINUATION AND CLOSURE

The study may be suspended or discontinued early by the sponsor for reasons that include but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The sponsor may terminate investigator and site participation in the study if there is evidence of an investigator's failure to maintain adequate clinical standards or evidence of an investigator or staff's failure to comply with the protocol.

If the study is prematurely terminated or suspended, the investigator will promptly inform study patients, the IRB/EC and sponsor and will provide the reason(s) for the termination or suspension. Study patients will be contacted, as applicable, and be informed of changes to study visit schedule.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB/EC and/or FDA.

10.1.4 CONFIDENTIALITY AND PRIVACY

Patient confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. The study protocol, documentation, data, and all other information generated will be held in strict confidence to the extent allowed by law, including Protected Health Information (PHI). No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The investigator will ensure protection of patient personal data and that all reports, publications, and any other disclosures, except where required by law are identified only by the patient identification number and site identification number to maintain patient confidentiality. All patient study records will be kept safely in an access-controlled area. Identification code lists linking patient names to patient identification numbers are to be stored separate from patient records. In case of data transfer, the sponsor, designees and sites will maintain high standards of confidentiality and protection of patient personal data. Clinical information will not be released without the written permission of the patient, except for monitoring by regulatory authorities, and the sponsor and their designees.

The patient's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long at least two years (or per regulations) after the study is closed, the Phagenyx System receives market clearance, whichever is longer. Records cannot be archived or destroyed by the site without prior written permission from Phagenesis, regardless of when the study closed.

Study patient research data will be transmitted to and stored at RCRI via the EDC system and eTMF. The study data entry and study management systems used by clinical sites and by RCRI will be secured and password protected.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB/EC, and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Phagenesis Limited is the Study Sponsor, and has the overall responsibility for the conduct and safety of the study, including assurance that the study meets the regulatory requirements of the FDA and governing IRBs/ECs. The Sponsor will have certain direct responsibilities and will coordinate other responsibilities to the specified committees, core labs and other support services as necessary.

Phagenesis or its designee will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the clinical trial as appropriate.

Phagenesis or its designee will submit all reports required by FDA and governing IRBs.

The Steering Committee will be responsible for general oversight of the study. This committee will meet periodically to monitor clinical site progress and protocol compliance. The committee will be responsible for reviewing the final results and may help determine authorship per standard rules/guidelines. The committee will be comprised of qualified professionals (e.g. stroke neurologists, physiatrists, speech language pathologist), and at least one sponsor representative. Members of the Steering Committee may also be study investigators.

The independent Data Monitoring Committee (DMC) will act as the appropriate entity to recommend all pre-specified study adaptation decisions. Recommendations are expected to be primarily based on efficacy; however, the DMC will also monitor safety events (see Section 10.1.6 of this protocol) The DMC members will be independent of Phagenesis and any study site.

10.1.6 SAFETY OVERSIGHT

The Medical Monitor (MM), will be responsible for reviewing pre-specified safety events, including all SAEs as well as being available to help with any protocol questions and inclusion or exclusion criteria if needed. The MM will be independent of Phagenesis and any study site. Details regarding the MM's roles and responsibilities are detailed in the Safety Management Plan.

A DMC will be established by Phagenesis for the purposes of this study. The DMC is responsible for monitoring aggregate safety information and the impact of adverse events on the safety and well-being of the patients, particularly as events relate to the investigational device and study procedures. The DMC may recommend that the sponsor modify or stop the study based on safety information. The final decision regarding modification or stopping the study is the responsibility of the sponsor.

At the recommendation of the DMC the following actions may be taken at the second interim analysis:

- Stop the study for futility
- Stop the study for efficacy

- Increase the final sample size up to a maximum of 338 patients
- Continue the study as planned until reaching 225 patients

Details regarding the DMC's roles and responsibilities are detailed in the DMC Charter.

10.2 CORE LABORATORY

A core laboratory will be established for VFSS analysis. Standardized protocols for acquiring, transmitting, and analyzing electronic records will be developed and documented prior to study initiation. Protocols for the transmission of electronic media files will strip personal identifiers from the media. The core laboratory will maintain copies of correspondence, data, and other records related to the clinical study as appropriate. Refer to the Core Lab Manual of Operations for specific information.

10.2.1 CLINICAL MONITORING

Clinical site monitoring will be conducted to help ensure that the rights and well-being of patients are protected, that the reported study data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol/amendment(s), with ICH GCPs, and with applicable regulatory requirement(s) including federal (US) regulations and ISO 14155.

The sponsor or designee will monitor the study throughout its duration. Study monitors will visit each site at appropriate intervals to review clinical data for accuracy and completeness and to help ensure compliance with the protocol. The study monitor may inspect all documents and required records maintained by the investigator, including medical records (office, clinic, or hospital) for patients enrolled in this study. The investigator will allocate adequate time for such monitoring activities. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

A study termination (close-out) monitoring visit will be conducted at the completion of the study. Clinical study documentation is to be properly documented and stored for a minimum of two years following study completion or FDA market clearance, whichever is later. The sponsor or designee will notify each site during the closeout visit of the current data storage requirements.

If a monitor becomes aware that an investigator is not complying with the signed Investigator Agreement, the protocol, or any conditions of approval imposed by the regulatory authorities, the sponsor or designee will immediately attempt to secure compliance, suspend enrollment at the site, remove devices from the site, or discontinue shipments of the device to the Investigator until compliance is achieved and guaranteed. The sponsor may terminate an investigator's participation in the study at

the sponsor's discretion. The investigator will be required to return all unused devices to the sponsor unless this action would jeopardize the rights, safety or welfare of a patient.

Details of clinical site monitoring are documented in the study-specific Clinical Monitoring Plan (CMP). The CMP describes who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.2.2 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control procedures will be implemented beginning with the data entry system and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following Regulatory and Clinical Research Institute's (RCRI) standard operating procedures (SOPs), the monitors will verify that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH GCPs, and applicable regulatory requirements.

The investigational site will provide direct access to all study-related source data/documents, and reports for the purpose of monitoring and auditing by the sponsor or designee, and inspection by local and regulatory authorities.

10.2.3 DATA HANDLING AND RECORD KEEPING

10.2.3.1 STUDY RECORDS RETENTION

Study documents must be maintained by the investigator and sponsor for the duration of the study and for a period of at least two years (or per regulations) after market clearance or after the study has been formally closed, whichever is later. Documents cannot be archived or destroyed unless prior written approval is granted to the site by the sponsor.

10.2.3.2 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

This study will be performed using an EDC system with password protection. The investigator and study site staff will receive training and support on the use of the EDC system and will be granted specific user privileges. All eCRF data are to be completed by the investigator, study coordinator, or other designated site personnel. The investigator will perform a final review and sign-off of all eCRFs in a timely manner.

Designated site personnel will be trained to enter data into the web-based EDC system. Completed eCRFs will be monitored against the medical record by a monitor during the onsite and remote data review. The EDC system will be a closed system, allowing for tracking all the data elements and any changes made (audit trail).

The sponsor and RCRI will work with the investigational sites mange the electronic Trial Master File (eTMF) to house essential documents including:

- Signed protocol and amendments,
- Signed Investigator Agreement,
- Financial Disclosures
- IRB/EC approval letters, consent forms and correspondence,
- Investigator and sponsor reports,
- Relevant correspondence between the Investigator and Sponsor,
- Notification to sponsor and IRB/EC of UADEs (and SAEs, if applicable)
- Device Accountability Records,
- Administrative Tracking Logs (Monitoring Visits, Training Logs, etc.).

Study documents must be maintained by the investigator and sponsor for the duration of the study and for a period of at least two years after FDA market clearance or after the study has been formally closed, whichever is later. Documents cannot be archived or destroyed unless prior written approval is granted to the site by the sponsor.

10.3 SOURCE DOCUMENTS

Source data are all information, original records of clinical findings, observations, or other activities from a clinical study necessary for the reconstruction and evaluation of the study. Examples of these original documents, and data records include but are not limited to: medical records, clinic and office charts, x-rays, laboratory notes, and study specific worksheets.

Regulations require that the investigator maintain information in the patients' medical/hospital records that corroborates data collected for the study. In order to comply with these regulatory requirements, at a minimum, the following is a list of information that should be maintained.

- Medical history/general physical condition of the patient before involvement in the study of a sufficient nature to verify the protocol eligibility criteria,
- Dated and signed study/progress notes on the date of entry into the study documenting the following:
  - The general health of the patient,
  - A statement that the patient has reviewed, signed and received a copy of the patient informed consent form.
  - Adverse events reported and their continuation or resolution, including, supporting documents such as discharge summaries, x-ray reports and other test reports,

- Patient's general health and medical condition upon completion of or withdrawal from the study.

Patient confidentiality will be maintained throughout the clinical study in a manner that helps ensure data can be traced back to the source documents. Additionally, patient information will be managed according to HIPAA and European confidential requirements specific to the country the patient is enrolled in.

In the event that the patient revokes authorization, the investigator retains the ability to use all information collected prior to the revocation. The investigator should attempt to obtain permission to collect at least vital status, i.e., that the patient is alive, at the time of patient authorization revocation.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents are to be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets may be provided for use as source document worksheets for recording data for each patient enrolled in the study. Data recorded in the eCRF derived from source documents must be consistent with the data recorded on the source documents.

10.4 PROTOCOL DEVIATIONS

A protocol deviation is defined as an event when the investigator or site personnel deviate from the study protocol or study procedures. It is the investigator's responsibility to ensure that there are no deviations from the protocol without prior notification and approval of the sponsor or sponsor's designee, and in full compliance with all established procedures and conditions of the reviewing IRB/EC.

The investigator may deviate from the protocol without prior written approval from the sponsor or sponsor's designee in cases of medical emergencies, when the deviation is necessary to eliminate an apparent immediate hazard to the patient. In that event, the investigator will notify the sponsor or sponsor's designee immediately by phone or electronic communication, notify the reviewing IRB/EC and confirm notification to the sponsor or designee in writing. Prior deviation approval is generally not expected in situations where unforeseen circumstances are beyond the investigator's control, for example, the patient was not available for a scheduled follow-up office visit. These events, although outside the investigator's control, are still required to be reported on the appropriate protocol deviation form in order to ensure that all deviations from the standard patient population are adequately documented and reported. The investigator

will inform the sponsor or sponsor's designee of all deviations, and the reviewing IRB/EC of all protocol deviations as per the IRB/EC requirements for this study.

The occurrence of protocol deviations will be monitored by the sponsor or sponsor's designee for evaluation of investigator compliance to the protocol, ICH GCPs, and regulatory requirements.

10.5 PUBLICATION AND DATA SHARING POLICY

The publication policy will follow International Committee of Medical Journal Editors (ICJME) guidelines. The Steering Committee will help adjudicate authorship per standard rules/guidelines.

10.6 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed.

10.7 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	26 January 2018	N/A	Initial release

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