This supplement contains the following items:

1. Original protocol (Page 2-47), Final protocol (Page 48-98), Summary of changes (Page 99-103).

2. Original statistical analysis plan (Page 104-115), Final statistical analysis plan (Page 116-128), Summary of changes (Page 129-133).
Background, Rationale and Study Design

1.1. Background

Stroke is the main cause of disability and the third most common cause of death in the United Kingdom (NHS, 2011). Of those that suffer a stroke, 50–78% will be affected by swallowing problems (known as oropharyngeal dysphagia), within one-week of the event, as a result from damage to swallowing specific regions of the brain (Jayasekeran, et al., 2010). Some of these patients will recover partial swallowing ability within the first months after stroke and others may over time recover more of this function. However, conflicting evidence regarding the effects of proposed treatments and their regimens still remains with recent research demonstrating that up to 40% of stroke patients remain dysphagic a year later. In addition to this a significant proportion of patients will remain chronically dysphagic, requiring feeding through a nasogastric (NG) or percutaneous gastrostomy (stomach) tube (PEG) with an increased likelihood of institutionalised care (Jayasekeran, et al., 2010). Moreover and despite of interventions, these patients are still at a 3-fold increased risk of contracting pneumonia as a result of aspiration of substances into the lungs.

The diagnosis of dysphagia is most often based upon a bedside swallowing assessment conducted by dysphagia trained Speech and Language Therapists (SLTs). Typical assessment entails cranial nerve examination, airway protection testing (e.g. cough reflex), and swallow bolus trials of fluids and foods of various consistencies (e.g. water, nectar, smooth yogurt, banana, biscuit) with and without swallow strategies (e.g. chin tuck) if deemed appropriate. Instrumental assessments by means of VFS or FEES are sometimes used to confirm dysphagia (Kelly, Hydes, McLaughlin, & Wallace, 2007), although other practices can lead to the same valid conclusion: oesophagoscopy, laryngoscopy, ultrasonography, CT-scan, MRI, chest X-ray.

In addition the underlying neurological condition can be worsened by certain medication (anaesthetics, sedatives, neuroleptica etc.). The severity of dysphagia can also be altered by medication which is most often linked to the underlying disease, but medication is also known to cause dysphagia.

SLT therapy is commenced upon diagnosis of dysphagia. Often alternative diets, compensatory strategies and postural changes are applied separately or in tandem with a variety of stimulation strategies to treat dysphagia. Therapies are often applied at the discretion of the SLT and little or no scientific evidence is available to predict the outcome of the therapy nor the effect of the SLT therapy on the outcome of PES (Bath, Bath-Hextall, & Smithard, 1999) (Greeganage, Beavan, Ellender, & Bath, 2012). In worst cases, enteral feeding is required or even surgical interventions can be applied to help prevent unintentional aspiration.

In stroke-patients, PES has been shown to enhance brain plasticity (Fraser, et al., 2002), improve swallowing and feeding status, and reduce time in hospital (Jayasekeran, et al., 2010). Based on these data, the treatment of neurogenic dysphagia as a result of stroke was the subject of the investigation in the (Phagenesis sponsored) STEPS study (AHE01 - A multi-centre, double blind, randomised controlled Clinical Investigation to validate the EPS1 device as a treatment for stroke-induced dysphagia: A Study of Swallowing Treatment using Electrical Pharyngeal Stimulation).

Research into electrical stimulation for the treatment of dysphagia is expanding and several clinical studies are currently on going (most often in acute or post-stroke patients) to demonstrate the benefit of direct or percutaneous electrical stimulation in association or not with standard SLT-therapies for dysphagia (not restrictive list from ClinicalTrial.gov):

- NCT01971320: Evaluation of transcutaneous electrical stimulation in post-stroke dysphagia (TENSDEG),
- NCT01970384: Transcranial direct current stimulation for dysphagia therapy in acute stroke patients,

1 VFS = videofluoroscopic swallow study also known as the modified barium swallow.
2 FEES = Fiberoptic endoscopic evaluation of swallowing.
3 SLT = Speech and Language Therapist.
- NCT01956175: Electrical pharyngeal stimulation for dysphagia therapy in tracheotomised stroke patients,
- NCT01777672: Effect of afferent oropharyngeal pharmacological and electrical stimulation on swallow response and on activation of human cortex in stroke patients with oropharyngeal dysphagia,
- NCT01723358: Neuromuscular electrical stimulation (NMES) treatment technique therapy in the management of young infants with severe dysphagia,
- NCT02007759: Neuromuscular electrical stimulation (NMES) for dysphagia in neonates,
- NCT01697891: A pilot study of ALTENS in improving dysphagia induced by IMRT for head and neck cancers,
- NCT01731847: Combined NMES, FEES and traditional swallowing rehabilitation in the treatment of stroke-related dysphagia.

Pilot data from one such study (NCT01956175: Electrical pharyngeal stimulation for dysphagia therapy in tracheostomised stroke patients) suggests that PES treatment has beneficial effects on airway safety that can allow for early decannulation of tracheotomised stroke patients residing within an ICU. The main results, observed but not yet published by Dr Dziewas, can be summarized in the graph hereunder where the effect of a PES-treatment can be seen as compared to a control group where no PES treatment was offered. In this study 30 patients, who were weaned from ventilation and tracheotomised, were randomised 2:1 to the treatment or control arm. A total difference of 55% between the treatment and control arm was observed. This created the basis for the current PHAST-TRAC study.

![Graph showing percentage of patients requiring a cannula with and without PES treatment.](image)

**Figure 1: Main results of Dr Dziewas unpublished research.**

Tracheotomy is reported as one of the most frequently performed surgical procedures within the ICU patient population, with as many as 10% of patients who require at least 3 days of mechanical ventilation eventually receiving a tracheotomy for prolonged mechanical ventilation or airway support. While prolonged respiratory failure is probably the most common reason for performing tracheotomy, there are generally four reasons for tracheotomy insertion:

- To relieve upper-airway obstruction due to tumor, surgery, trauma, foreign body, or infection (ventilator-acquired pneumonia),
- To prevent laryngeal and upper airway damage due to prolonged translaryngeal intubation (orotracheal intubation),
- To allow easy or frequent access to the lower airway for suctioning and secretion removal,
- To provide a stable airway in a patient who requires prolonged mechanical ventilation or oxygenation support due to respiratory failure or risk of aspiration due to dysphagia.

Indeed it is reported that between 10–43% of patients hospitalised because of a major brain trauma (e.g. ischaemic or haemorrhagic strokes, ischaemic brain injuries and others) require a tracheotomy, which

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4 ICU = Intensive Care Unit.
increases to 50–70% in patients with the low Glasgow Coma Scale (GCS)\(^5\) scores (Mackiewics-Nartowics, et al., 2008). Despite the advantages of tracheotomy in the setting of prolonged mechanical ventilation, optimal timing for tracheotomy is controversial, with strong arguments for both early\(^6\) and late tracheotomy insertion (Bittner & Schmidt, 2012) (Durbin, 2010).

Airway related complications in ICU patients are reported to be the most frequent complication with presence of dysphagia and increased risk of aspiration as the main reasons for patients to remain tracheotomised once successfully weaned from artificial ventilation (Bösel, 2014). The frequency of swallowing disorders in tracheotomised patients is reported to vary from 50-83% depending on the assessment method (Garut, et al., 2014) however, intubation with mechanical ventilation is known to have negative effects on laryngeal competence and swallowing physiology (Kumar, et al., 2014).

Timing of tracheotomy decannulation is also a highly controversial topic with decisions to decannulate often dependent on the physician’s individual experience because evidence-based practice guidelines are not available (Warnecke, et al., 2013). Timely decannulation after weaning from mechanical ventilation is reported to be favorable because the prolonged presence of a tracheotomy tube can delay rehabilitation, reduces patient comfort, and is associated with higher costs due to longer hospitalisation periods (Choate, Barbetii, & Currey, 2009) (Leung, MacGregor, Campbell, & Berkowitz, 2003). Research also suggests that a tracheotomy tube in place on discharge from the ICU can increase patient mortality (Martinez, et al., 2009) whereas removing the tracheotomy tube too early can also pose a significant threat to patients and therefore must be avoided. (Warnecke, et al., 2013) recently established criteria that permit safe and efficient decannulation of critically ill neurological ICU patients using a FEES decision flow protocol. Using this protocol, the authors report increased sensitivity of the FEES decision flow protocol to safely decannulate patients when compared with a standard clinical bedside swallow examination (54 vs 29 patients respectively) and only a low failure (recannulation) rate of 1.9% (1 patient) suggesting the endoscopic protocol is safe, efficient, and an objective bedside tool to guide decannulation decisions.

### 1.2. Rationale of study design

This is a prospective, single (assessor)-blinded randomised controlled interventional and international clinical study of PES in tracheotomised patients after supratentorial stroke. Given that the assessor of the decannulation remains blinded to the treatment, but that the patients who receive PES treatment do feel without undue discomfort the electrical stimulation, we can identify the study as a single, but not a double blinded trial. In addition, there is a blinded Independent Review Committee that will independently re-assess the primary end-point, one can also identify the ‘blinded end-point assessment’, as is common in PROBE-designed trials, however this Independent assessment does not influence the actual treatment of the patient nor the first primary end-point assessment of the study.

The data collected will be used to support a new application/extend of the current CE Mark of the Phagenesis Phagenyx device in accordance with the Medical Device Directive 93/42/EEC. The clinical investigation will conform to ISO14155:2011 requirements. The data may also be used to support a marketing application in the United States of America; the investigation therefore includes additional requirements to support such an application in line with the Code of Federal Regulations.

The Clinical Investigation Plan (CIP) is designed to be prospective to ensure that the population is representative of the populations for which the Phagenesis device is intended to treat. The CIP objectives, eligibility criteria, procedure and follow-up period will draw upon the design of clinical study protocols evaluating the safety and performance of PES in the particular setting of this study.

The patients included in this study will be tracheotomised patients with supratentorial stroke that have been successfully weaned from artificial ventilation, but who are still tracheotomised to minimise the risk of...

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\(^5\) The GCS is a reliable, objective and practical method for healthcare professionals to assess impairment of conscious level in (traumatic brain injury) patients in response to defined stimuli. It has value in predicting a patient’s ultimate outcome by assessing three types of response: best motor response (scored 1-4), best verbal response (scored 1-5) and best eye response (scored 1-6). Severe = GCS 3-8 (you cannot score lower than a 3.), Moderate = GCS 9-12 and Mild = GCS 13-15.

\(^6\) The definition of early tracheotomy differs between studies. A review of papers published over 10 years by Cheung et al. (Respir Care 2014;59(6):895–919) reports that early was generally defined as within 3–10 d of mechanical ventilation, whereas late was variously defined as any time outside the early period, within 7–14 d, 14–28 d, or >28 d after initiation of mechanical ventilation.

\(^7\) PROBE trial: prospective randomised open-label blinded end-point trial
aspiration. A comparison of the clinical success rate of early decannulation will be made post-PES treatment for patients treated versus patients not treated over the same time period.

In addition, patients initially serving as ‘control’ patients to assess the difference in success rate of early decannulation with patients receiving the PES-treatment, will also receive the same standard PES treatment but some 5 days later. Differences in success rates of decannulation between EARLY and LATE treatment (control) groups will be assessed in combination with the occurrence of adverse (device) effects to establish the safety and performance evaluation leading to a potential extension of the current CE labelling.

Finally, patients failing to be decannulated after a first PES, will be subjected to a second exposure of the same standard therapy. The success rate of decannulation after a second PES will be compared to the rate observed after the first PES, again potentially leading to an extension of the CE label.

1.3. Rationale of PES

Dysphagia represents a major therapeutic challenge; however, conflicting evidence regarding the effects of proposed treatments and their regimens still remain. In addition, there is, as yet, no well-established evidence for the current therapies for dysphagia used by SLTs, which include a variety of compensatory and treatment-swallowing techniques in combination with texture-modified diets, pharmacologic therapies and stimulations strategies (Greeganage, Beavan, Ellender, & Bath, 2012) (Bath, Bath, & Smithard, 2000)

PES treatment is a novel intervention designed to optimise the recovery processes responsible for the restoration of safer swallowing function in dysphagic patients. PES treatment has been shown to improve swallowing and feeding status, and reduce time of care in the hospital. The Phagenyx device has been optimised to reduce risk, improve ease of use and also has the potential to reduce respiratory chest infections and improve mortality rates in these populations. Pilot data also suggests that PES treatment has beneficial effects on airway safety that can allow for early decannulation of tracheotomised stroke patients residing within an ICU.

1.4. Conduct of Clinical Investigation to Reduce Bias

The following are incorporated into this CIP to minimise the effects of bias:

- Patients are recruited according to the criteria outlined in the CIP.
- The circumstances when individual patients withdraw prior to the planned completion of the study are specified in this CIP.
- Suitability of patients for decannulation will be assessed with FEES following the decannulation decision flow protocol of (Warnecke, et al., 2013) by suitably experienced health professionals who will not be actively recruiting subjects and who are blinded to the PES-treatment of patients.
- Training of the research staff will be identical and the procedures as well as healthcare professional performance will be tested prior to delivering PES to patients.
- The outcome of the ability assessment for a decannulation will be assessed in parallel to the investigator’s judgement by a blinded independent central group of physicians/SLT’s, experienced in this process and using copies of the anonymised FEES-video recordings at the time of decannulation assessment.

1.5. The study design.

Patients will be selected according strict in- and exclusion criteria. Those patients fulfilling these criteria will be requested to voluntarily participate in the trial. After signing the Patient Informed Consent form, the patient will be randomised to either the ‘EARLY’ or the ‘LATE treatment’ group, where the patients in the ‘EARLY TREATMENT’ group get the standard PES-treatment immediately (0-24 hrs) after randomisation and where patients from both groups are subjected to a first decannulation attempt at around the same time point after randomisation. All patients who failed to be decannulated at that time point will be subjected within 24-72 hrs to the standard PES-treatment prior a second attempt (within 24-72 hrs after the last PES-treatment is applied) to decannulate the tracheotomised patients.

This design can be graphically represented as:

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8 Patients included in the study might not be all the time conscious. The Glasgow Coma Scale is not used in the selection of patients, as verbal communication is hard to judge in some of the patients potentially eligible for study inclusion. Therefore the Richmond Agitation and Sedation Scale (RASS) is used to identify potential patients for study enrollment.
Figure 2: Essential study design elements. The control group (A) is identified in the CIP as “LATE TREATMENT” group and the treatment group (B) is referred to as “EARLY TREATMENT”; nomenclature is linked to the timing of PES treatment versus the time point of randomisation.

All patients will be followed up for up to 30 days or until hospital discharge, whatever occurs first. During this time period the improvement of swallowing is assessed using standardized questionnaires.

2. Device Used in the Clinical Investigation

5.1 The Base Station, Its Stimulation Catheters and Electrical Stimulation

The device used as part of this clinical investigation is the CE-marked Phagenyx Base Station (EPS1) and Phagenyx Catheter. These are commercially available for treatment of neurogenic dysphagia and apply a standard electrical stimulation treatment at 5 Hz via the Phagenyx Catheter which is in essence a standard nasogastric feeding tube provided with built-in stimulation electrodes. The intensity of stimulation is optimised for each treatment by the Base Station software and operator input by setting the intensity at 75% of the tolerable limit above sensory threshold. The catheter has internal electronic controls that mean that once the regime of 3 consecutive treatments is delivered the unit can no longer be used to deliver any further treatments. It is recommended to execute the calibration and 10 minutes stimulation at about the same time point during the three consecutive days.

5.2. The CE label and the status of investigational device.

The CE-mark indicates the Phagenyx products are for the treatment of neurogenic dysphagia by means of the above-described PES method. The method involves the application of a fixed regime of 3 treatment sessions in total. However the study protocol requires that this series of 3 treatment sessions is then re-applied to patients who failed to be decannulated after being treated with the first regime of 3 treatments. As this second application of PES treatment is outside the scope of the CE-label, the devices (both catheter and base station) are considered non-CE labelled and will be labelled ‘FOR CLINICAL TRIAL USE ONLY’. The software provided in the current version of the Phagenyx device does not allow the delivery of more than one series of 3 x 10 min of electrical stimulation. The device or the device software will NOT be adjusted for the needs of this study protocol. The devices will be labelled “FOR CLINICAL TRIAL USE ONLY” only to reflect the fact that supplementary instructions will be provided to allow the device to deliver the 2nd therapy to the same patient. This will be achieved through a change in the patient identifier information between the two treatment regimes and the replacement of the catheter between the treatment regimes.

Safety evidence for multiple applications has been obtained during the research and product development phase and is included in the Clinical Evaluation document within the current Technical Product Dossier. Delivery of more than one set of 3 treatments was carried out within this research without any adverse effects seen. The application of the additional regime of 3 treatment sessions is not considered to involve any additional treatment related risks. The CE label may be adjusted in the future depending on the clinical data justification (including the data from this study).

5.3. Device Accountability
As mentioned above, the devices used in this clinical investigation are considered investigational devices; they are for the purpose of the study labelled as ‘FOR CLINICAL TRIAL USE ONLY’ and their distribution will be appropriately tracked during the trial. That said, the devices are exactly the same as those which are commercially available for treatment of neurogenic dysphagia and which are CE labelled for this purpose. Each catheter used will be identified by a unique number and recorded on the appropriate data forms and will be uniquely labelled for study purposes; the Base Stations remain unmodified during the study, but devices can already be present in the hospital to support commercial post-market uses of the system. During the study, a non-CE labelled base station will be provided to the investigational sites for the duration and the purpose of the study.

5.4. Risks and Benefits of the Product and Clinical Investigation

The investigator brochure (IB) which is provided to each of the investigators of this study, lists all considerations that were made to reduce and limit risks to the patient and users. This assessment, together with the current knowledge from the STEPS study, has created the basis for the listing of anticipated adverse device effects (ADEs) which are provided in Appendix A.1.9

No unacceptable risks are associated with the treatment; patients may benefit from the PES treatment and experience an improvement of the swallowing difficulties post-PES treatment. The purpose of this study is to demonstrate the benefit of PES in terms of an earlier decannulation of tracheotomised patients.

It has been demonstrated in earlier research (Jayasekeran, et al., 2010) that repeated PES-treatments during one day or for more than 3 consecutive days don’t pose additional risks to the person receiving the treatment and don’t result in any other adverse event; as such it is deemed safe, also for those patients from the EARLY treatment arm, who failed to be decannulated after the first PES and who are being exposed to the second series of PES. The potential benefit of this second series of PES is, obviously, to increase the potential to be decannulated thereafter and thus improve the swallowing function and the comfort of the patient. As no additional risks are to be expected this second treatment is considered only offering potential benefits to the patient.

This clinical trial does not require any special clinical procedure that is not standard applied to the patients deemed eligible for study participation. As such there are no additional risks for the patient posed by the clinical study.

3. Objectives and end-points of the study.

3.1. Hypothesis

The hypothesis of the study is formulated as:

“At least 25% more tracheotomised patients after supratentorial stroke can be decannulated after a first period of pharyngeal electrical stimulation (PES) treatment and following a standardised assessment scheme executed by the local blinded assessor/investigator at 24-72 hrs after the PES-treatment has been completed as compared to control patients who only get standard therapy over the same time period.”

3.2. Primary Objective

The primary objective is to assess the proportion of tracheotomised patients after supratentorial stroke that benefit from and have an earlier removal of the tracheal tube at the first attempt between 24 and 72 hrs after completion of the PES treatment as compared to the proportion of patients who only get standard therapy.

3.3. Secondary Objectives

Secondary objectives are to:
- Measure the severity of dysphagia at the time of decannulation, and during the follow up period in terms of standard assessment scores;

9 Appendices indicated with “A” refer to study specific documents, forms etc., while appendices referring to “B” sections refer to standard, public domain documents, forms etc.
- Assess the proportion of patients who benefit from a first PES treatment but at a later time period of standard therapy in the ‘LATE TREATMENT’ (control) group, i.e. 170-288 hrs after the initial randomisation;
- Assess the proportion of patients who benefit from a second PES treatment after failing a first attempt to decannulate the patient in the EARLY treatment arm;
- Assess the severity level of stroke at different time points after PES treatment up to three months;
- Measure the number of days a patient stays on a given ward/ICU;
- Assess the amount of recannulations over a time period of 30 days (or until hospital discharge) after the preceding decannulation;
- Assess the occurrence of severe adverse events during the observation period up to 30 days (or hospital discharge) after decannulation or a second failure to decannulate;
- Assess the optimal treatment parameters (threshold, tolerance, intensity of stimulation);
- Document the SLT management plan and its execution.

3.4. Primary Endpoint

The primary end-point is to assess the ability to remove the tracheal tube in a time period of 24 to 72 hrs after the last PES-treatment is applied and according a standard dichotomised decision flow program as applied by the local blinded assessor/investigator. In the LATE TREATMENT group the assessment is done at an equivalent time point, i.e. 3-6 days after the randomisation time point:

![Diagram](image)

Figure 3: Timing of the separate sessions of 10 min of PES treatment immediately after the randomisation time point and of the timing of the first decannulation attempt.

3.5. Secondary Endpoints

The secondary endpoints will focus on the assessment of:
- The proportion of patients that can be decannulated after a (second) PES-treatment in the time period between 170-288 hrs after the randomisation time point: the PES-treatment will be the first one to apply in the ‘LATE TREATMENT’ group, but it will be the second application in those patients of the ‘EARLY TREATMENT’ group that failed to be decannulation at the first attempt (i.e. 24-72 hrs after the end of the first PES treatment);
- Severity of dysphagia over a time period of 30 days (or until hospital discharge) after decannulation by means of relevant standard assessment scales (DSRS\(^{10}\) and FOIS\(^{11}\)): every 48 hrs during the first 10 days and every 5 days thereafter until hospital discharge or maximum 30 days, the severity of

\(^{10}\) DSRS = Dysphagia Severity Rating Scale
\(^{11}\) FOIS = Functional Oral Intake Scale
dysphagia is measured and compared with the patient’s own condition at the time of baseline and of
decannulation attempts;
- the treatment optimisation parameters (threshold, tolerance and intensity of the electrical
stimulation);
- Severity of level of stroke at baseline, at 72-144 hrs after randomisation, at hospital discharge and at
3 months post-PES treatment by means of standard scoring scales (NIHSS\textsuperscript{12} and modified Rankin
Scale);

In addition, following parameters will be documented:
- Demographics, symptoms and description of underlying dysphagia causes;
- SLT\textsuperscript{13}-management plan and execution during the identified distinct time points of the clinical study;
- Adverse Events (AEs) and device deficiencies
- Health economics: duration of ICU-stay/hospitalisation/ stay at different care giving units until 30 days
FU or until hospital discharge, whatever comes first.

4. Patient Selection

4.1. Target Population

The target population encompass patients who suffer(ed) from a supratentorial stroke event (both
haemorrhagic and ischemic stroke), who are successfully weaned from mechanical ventilation support but
who are still tracheotomised to minimise the risks of penetration/aspiration and ceased from sedatives for a
minimum period of 72 hours. These patients failed a first attempt to be decannulated at a minimum of 10 days
after the stroke event, and failed a second decannulation attempt 24-72 hrs after the first one. Patients
fulfilling these criteria are potential candidates to be included in the study:

Figure 4: illustration of the separate inclusion criteria required to make a patient eligible for study inclusion.

Patients (or their legal representatives or close relatives) must be willing to sign per the local procedure a
standard EC\textsuperscript{14}-approved Informed Consent Form explaining the conditions of study participation. Elected
patients must be compliant with the inclusion and exclusion criteria before they can be considered enrolled in
the study.

4.2. Inclusion Criteria

Patients are eligible for study participation if they:
- Experienced a haemorrhagic or ischemic stroke; AND
- Experienced a supratentorial stroke; AND
- Were mechanically ventilated for a minimum of 48 hrs after the stroke event; AND
- Were subsequently tracheotomised for any reason; AND
- Were weaned from mechanical ventilation – thus being able to sustain own respiration; AND
- Are free from sedatives for a minimum of 3 days prior the first decannulation attempt; AND
- Were found ineligible for decannulation minimally 10 days after the stroke event; AND

\textsuperscript{12} NIHSS = National Institutes of Health Stroke Scale
\textsuperscript{13} SLT = Speech and Language Therapist
\textsuperscript{14} EC = Ethics Committee
- Were found ineligible for decannulation minimally 24 and maximally 72 hrs after the first decannulation attempt; AND
- Cannot receive oral food (thus DRS5=12 and/or FOIS = 1); AND
- Have a score of > - 1 on the Richmond Agitation and Sedation Scale (RASS); AND
- Are over 18 years old; AND
- Give themselves (or have legal relatives/authorities representing themselves per the local practice to give) voluntary written informed consent;

And if they do not meet any of the exclusion criteria listed hereunder.

4.3. Exclusion Criteria
Patients are excluded from study participation if they;
- Have an undefined date of stroke causing the dysphagia (but not excluding stroke occurring during the night, for which the date will be the morning the stroke was observed); or
- Have a infratentorial stroke; or
- Suffer from pre-existing neurogenic dysphagia or a disease linked to that symptom (for example Parkinson Disorder); or
- Suffer from non-neurogenic dysphagia (e.g. cancer); or
- Suffer from neuromuscular disorders (e.g. myasthenia gravis, motor neuron disease); or
- Participate in any other study potentially influencing the outcome of PES, both medicinal or medical device product related and for which the patient signed a consent form for his/her study participation; or
- Receive or have received within one month prior to the intended PES treatment any other type of standard cranial or percutaneous electrical stimulation therapy to treat dysphagia; or
- Have a cardiac pacemaker or a cardioverter defibrillator implanted unless the device can be switched off completely at the time of treatment delivery; or
- Have experienced an oesophageal perforation, or have an oesophageal stricture or pouch; or
- Have an unstable cardiopulmonary status; or
- Have severe pneumonia that cannot be stabilized by medication and prevents the patient to be decannulated; or
- Receive continuous oxygen treatment or have the equipment for such treatment permanently in place preventing the positioning of the Phagenyx Catheter (this does not exclude patients that can have the oxygen treatment temporarily stopped and equipment removed during PES-treatment\textsuperscript{15}); or
- Are pregnant or nursing women; or
- Require emergency treatment, preventing appropriate conduct of the subject informed consent process; or
- Have a life expectancy less than the duration of the patient’s follow up period, i.e. less than three months.

4.4. Sample size
On average 72 patients will be enrolled in the study with a 1:1 randomisation scheme to demonstrate a 25% difference between two treatment groups (see 10.4 Sample Size Determination):
- Group ‘LATE Rx’ (Late Treatment, control group) will comprise half of the patient randomised patients who will each receive during the first 3-6 consecutive days after randomisation only standard therapy, but on the 4\textsuperscript{th} – 9\textsuperscript{th} day will start the 3 days of PES Treatment;

\textsuperscript{15} It is the treating physicians responsibility to ensure that continuous oxygen is stopped and equipment is removed prior to starting the PES-treatment.
- Group ‘EARLY Rx’ (Early Treatment) will comprise half of the patients randomised patients who will each receive 3 days of PES treatment starting within 24 hrs after randomisation.

Upon receipt of primary end-point data of each batch of 10 patients and interim analysis will be performed to assess the level of significance of the difference in proportions of patients that can be decannulated in both study arms. Patient enrolment will cease once a significant difference is achieved or when it becomes evident that it is very unlikely that the expected difference is real.

4.5. Patient Enrolment and Withdrawal Criteria

A signed (by the patient or a legal representative) Informed Consent Form, approved by the EC, is required prior to performing any study related procedure. Patients are not considered as enrolled in the study until a valid signature on the Patent Informed Consent form is obtained and a catheter placement is confirmed by at least a first attempt to prepare the patient to receive the PES intervention by the Phagenyx Catheter insertion; patients not considered enrolled in the study may be replaced.

Patients may withdraw from the investigation for any reason, at any time without their standard of care being affected. Patients that withdraw after receiving the PES-intervention are considered as being enrolled in the study; they will not be replaced upon voluntary withdrawal. All discontinuations will be documented along with the reason for withdrawal. Patient data collected up to the point of voluntary withdrawal will still be used.

4.6. Patient transfer from one treatment unit to another

A patient who is enrolled in the study in one study centre e.g. treatment unit and who is subsequently discharged to another centre/unit might get ‘lost-to-follow-up’. To limit the number of patients lost-to-follow-up, their follow-up is continued within the same centre/different unit under the responsibility of the original investigator. All discontinuations will be documented along with the reason for withdrawal.
5. Study Design

The overall study design can be graphically represented as:

**Figure 5**: Graphical representation of the total study design, from screening of patients until entry into the follow-up period.

During the follow up period, clinical data will be collected at following time points:

- **SLT management documentation**
- **Severity of dysphagia assessment**
- **Severity of stroke assessment**

**Figure 6**: Identification of time points to assess secondary end-points during the follow up period.

Finally, at a 3-month time point after the last PES treatment, the DSRS and mRS will be re-assessed by means of a telephone call to the patient by a medical staff member.
5.1. Investigational Sites

The centres can be identified and might be located in Europe, Middle-East, Africa and Canada (EMEAC-region). Centres can participate after an assessment of appropriate ability to contribute to the study. This assessment will be documented.

A maximum of 10 centres will be invited to participate in the study. A list of participating study centres is kept current at the sponsor’s site.

5.2. Identification and Selection

A list of investigational sites is available at the sponsor’s site. The selection criteria are based on experience and a willingness to adequately support the study execution and its progress. Criteria include:

- Centres that have participated in the STEPS or PHADER study;
- Centres that provide evidence of experience by having used the Phagenyx devices as part of their standard/routine medical care (as demonstrated by using the products in at least three patients);
- Centres that provide confirmation that a minimum of five patients will be enrolled in the PHAST TRAC over a maximum period of 12 months;
- Centres that are willing to comply with the requirements of the CIP such as, but not limited to, accurate and complete data collection on applied standard clinical processes using investigational product, obtaining Ethics Committee approval for the study, signing a CDA and CA, complying with the requirements for patient enrolment and follow-up, knowing and applying ISO 14155 requirements, complying with monitoring and auditing requirements etc.
- Centres having a ‘clinical study team’ available that is able to support the conduct of the study as confirmed upfront by the investigator.

5.3. Ethics Committee Approval

Each centre must obtain formal Ethics Committee approval prior to the start of the study and thus prior to enrolment of any patient. This approval must be forwarded to the sponsor who will provide at that time, access to the electronic data capture system. Submission documents from the sponsor are provided and additional support to apply for Ethics Committee approval can be provided upon request. The documents that are delivered to the investigator for this purpose are:

- Clinical Investigational Plan (CIP),
- Investigator Brochure (IB) – Amendment 5,
- Participant Information Sheet and Informed Consent Form provided in local language (see Appendix A.2. for an English template version),
- Clinical Agreement specifying the proposed compensation for study execution (see Appendix A.3. for an explanation on the standard template document – a template provided and accepted by the local investigation site might be added to the dossier for Ethic Committee submission, if available),
- Evidence of clinical investigation insurance (see Appendix A.4.),
- The structure of the database and data collection priority (see Appendix A.5.) and draft case report forms (CRF), i.e. indication of data collection blocks, to be used to document the clinical information (see Appendix A.6.),
- The SLT management plan questionnaire (see Appendix A.7)

5.4. Competent Authority Approval.

The Phagenyx device will always be applied according to its current labelling and in compliance with the CE-label. However, in some patients the PES treatment will be offered a second time, i.e. in those patients randomised to the “EARLY TREATMENT” group who failed to be decannulated at the first attempt. The application of the therapy a second time in the same patient is currently not covered under the CE-label (see The CE label and the status of investigational device)

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16 CDA and CA: Confidentiality Disclosure Agreement and Clinical Agreement.
Therefor the catheter products will be offered under the ‘FOR CLINICAL TRIAL USE ONLY’ label and the Phagenyx device becomes an investigational device for the purpose of the second treatment application as part of this study.

The use of investigational devices requires also oversight National Competent Authority approval prior to the start of the study. The sponsor will look after the communication with the Competent Authority and look for its approval. Receipt of approval is condition to allow start up of the study, aside from other local regulatory requirements such as EC approval and Investigator Agreement sign off.

5.5. Site Activation
A clinical investigation centre can only start enrolling patients in the study after having obtained the required approvals and after the study staff has been appropriately trained on the different aspects of the CIP by the sponsor. Training records will be appropriately maintained both at the sponsor’s and investigational site. A formal approval for site activation is provided by the sponsor to the investigator after which access to the electronic data collection system will be granted.

5.6. Patient Discharge to Another Treatment Unit or to Home
Patient treatment and data collection do not pose a problem as long as a patient is treated within one care giving centre; transfer from one unit to another within the same hospital can be documented while the patient remains in the clinical study under supervision of the original investigator.

When a patient is discharged to another care giving centre at a time point earlier than one month (30 days) following the first successful or second decannulation attempt, this will be considered a ‘Hospital Discharge’, after which the patient exists from the study; yet, it is documented to which care giving centre the patient is discharged.

At the 3 month FU period DRSR and mRS will be attempted to be assessed by phone call to patients residing at home or at another care given centre.

6. Investigation Procedures
This prospective, single (assessor)-blinded randomised controlled interventional clinical study will be executed in compliance with the ISO 14155 (version 2011) and must be approved by the local Ethics Committee prior to commencement in the investigational centre. The voluntary participation of each patient, after being well informed, must be documented in writing.

The following table gives an overview of the investigation procedures applied in this study.
Table 1: Overview of the study procedures.

<table>
<thead>
<tr>
<th>Screening</th>
<th>Enrollment</th>
<th>Randomization point (DAY 0)</th>
<th>Every PES-treatment</th>
<th>Each Decannulation attempt</th>
<th>Initial FU (every 48 hrs ≤ 10 days)</th>
<th>Extended FU (every 5 days &lt; 30 days/HD)</th>
<th>Last (3M) FU Patient exit from study</th>
</tr>
</thead>
<tbody>
<tr>
<td>In/Exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NG catheter insertion</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>SLT management</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PES-Rx parameters</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity dysphagia</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSSR/FOIS</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Severity stroke</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>NIH SS/ Rankin scale</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE/SAE/ADE/death</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

6.1. Screening of patients.

Post-stroke patients, residing on the ICU and requiring mechanical ventilation support, are 24 hrs a day under medical supervision. Over a time period of minimally 10 days the progress of healing is continuously assessed and offers a potential to evaluate – as part of routine care application - if the patient could meet the inclusion criteria with respect to transfer from the oral intubation to a tracheotomy, the weaning from mechanical ventilation support, the use of sedatives and the attempts to decannulate the patient. (see 4.1 Target Population)

The investigator is requested to maintain an overview of potential patients for study inclusion. Only those, who demonstrate to be willing to participate on a voluntary basis, can be further considered for study enrolment.

6.2. Informed Consent

Every patient who is considered for enrolment in the study must be informed appropriately about the study intentions and their rights prior any further study related activity can be executed. The procedures, study objectives and assessment tools/timing should be explained by the investigator in layman’s terms. The sponsor provides a (Patient) Participant Information Sheet providing all the relevant information (see Appendix A.2 for a template that can be used for local translation\[17\]). All questions from the patient in relation to the study should be appropriately addressed. After having sufficient time to decide whether they wish to participate, the formal Informed Consent Form (provided by the sponsor to the investigator in the local language and to be approved by the local Ethics Committee prior use by the investigator – see Appendix A.2) will be signed by the patient, a close relative or by his/her legally authorised representative, e.g. in case of unconscious patients or less conscious patients, as specified by local regulations and practice.

Only patients with an appropriately signed Informed Consent Form can be considered for further study participation. Upon signing the Informed Consent Form, the patient will be issued a unique study participation number.

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\[17\] Local Ethics Committee’s might want to impose specific forms or specifications into the Information Sheet. If so, this will be documented and implemented.
The investigator will retain the original signed Informed Consent Form in the study site file.

**Vulnerable populations (ISO 14155 § 4.6 and §4.7.3.3).**

Some of the patients, potentially eligible for study enrolment, might be less conscious post-stroke (ref to the RASS of “-1”, see Appendix B.5). Their recovery might allow them to understand the physician’s explanations of the study and might allow them to decide themselves and independently from anyone else to voluntarily participate in the study. If however, the level of consciousness would be inadequate, local EC procedures to enrol such patients in a study will apply. These might encompass the involvement of other legal representatives, witnesses and/or special documentation/approval aspects. These aspects will be followed and documented as part of the clinical trial. No emergency treatments can be considered as part of the clinical trial.

6.3. Patient Eligibility

All inclusion and none of the exclusion criteria must be fulfilled in order to assign a patient as eligible for study inclusion, otherwise the patient will not advance any further into this clinical investigation and will exit the study. If the patient fullfills all of the inclusion and none of the exclusion criteria, he/she is invited to participate in the study and to sign the Informed Consent form.

6.4. Assessment and Randomisation Prior to Treatment

6.4.1. Randomisation

Upon entry into the study, a nasogastric Phagenyx catheter will be positioned. When a nasogastric feeding tube which is in use at this time point, it needs to be replaced by the Phagenyx catheter. Upon successful positioning of the catheter, a randomised group assignment will be obtained for the patient via an independent IWRS\(^\text{18}\) that is provided by the sponsor. This IWRS access is limited and restricted to the medical staff member applying the PES-treatments. No-one else of the medical staff nor the patient him/herself should be informed about the randomisation assignment: all should remain blinded.

6.4.2. Baseline assessment upon entry in the study.

At study entry, a series of clinical data will be recorded which – all together – completes the baseline assessment. Baseline assessment should be completed within 24 hrs after the randomisation time point. The following baseline data will be collected:

Demographic data
- Age,
- sex,
- distance from the entrance to the nostrils to the ear lobes and the distance from the ear lobe to the laryngeal prominence (Adam’s apple).

Dysphagia causal event documentation

Timing of stroke event, location in the brain, severity of event... will be retrospectively documented based upon the patient’s chart information. To estimate the severity of the stroke, the NIH SS (Appendix B.1) and ‘modified Rankin scale’ (Appendix B.2) are applied.

Dysphagia assessment

The level of severity of dysphagia will be assessed by means of:
- Dysphagia Severity Rating Scale (DSRS);

The applicable questionnaire for DSRS is listed respectively in Appendix B.3

Feeding status assessment

Feeding status should be assessed by means of the Functional Oral Intake Scale – FOIS (Crary, Carnaby-Mann, & Gorher, 2005). The applicable questionnaire is listed in Appendix B.4. In addition, the use of a nasogastric feeding tube, PEG, radiologically inserted gastrostomy (RIG) or potentially the execution of

\(^{18}\) IWRS = Interactive Web Response System.
other surgical interventions (e.g. to avoid dehydration) should be documented. Consistency of fluids, types of diets, amounts of food intake, duration of feeding sessions and need for supervision during feeding should also be documented. Initially all patients will be orally fed, however this condition might improve and should be documented.

**Ventilation status assessment**

Type, purpose and duration of artificial ventilation and/or tracheostomy should be documented retrospectively. Timing of and reason for removal of ventilation tube should also be recorded.

**SLT management**

The SLT management plan assessment is similar to the one applied in the STEPS and PHADER studies, sponsored by Phagenesis. As such results can be more easily compared.

The clinical assessment used to create the SLT management plan may be an SLT bedside swallow assessment, an objective (instrumental) swallow assessment such as a clinical FEES, or another local procedure that must be specified. However, the type of clinical assessment used to inform the SLT management plan must remain consistent at all time points for each patient throughout the study, i.e. should a patient swallow be assessed by SLT bedside assessment at baseline, usual SLT practice for conducting the assessment would be followed and this also would need to be the swallow assessment used to inform the remainder of the patient’s SLT management plan at the subsequent periods of this investigation (up to one month maximum). To clarify, the swallow assessment type may vary between two different patients in the same hospital, but should not vary at different time points for the same patient during the study.

For reasons of consistency of management, it is also important that where a clinical led FEES local protocol is not used as standard, that the same named SLT conducts the patient swallow assessments and determines the management plan for a patient throughout the study. To clarify, more than one SLT may take part in this investigation but each SLT must be assigned consistently to a single patient throughout.

The SLT assessments and management plan should be carried out at baseline (retrospective documentation, current planning), and the actuals documented at the time of PES treatment and at distinct time points throughout the one-month follow-up period. The SLT plan will be recorded in the study files and provided case report forms.

The applicable questions are listed in Appendix A.7

### 6.5. PES-Treatment Procedure

Patients randomised to the ‘EARLY TREATMENT’ arm of the study will receive within 24 hrs after randomisation the first of the 3-day session of the PES-treatment. During the following 2 days the second and third session of 10 min of electrical stimulation is delivered, preferably at the same time point during the day.

The applied treatment is the standard PES treatment as described in the ‘Instructions For Use’ provided with the Phagenyx products. In brief:

- Optimisation of the treatment parameters is conducted; sensory threshold and maximum tolerable limits are assessed by using the Phagenyx Base Station by which the difference is calculated between the tolerable stimulation intensity and the lower threshold and where stimulation levels are set at 75% of this difference above the lower threshold;

- The standard treatment regime is delivered; this is fixed to three consecutive days of 10 minutes of PES at 5 Hz at the determined stimulation level.

Typically, upon diagnosis of dysphagia, the SLT will help determine the best therapy for a given patient to recover the swallowing functionality. This might take place early or later after the dysphagia causing event. As part of this investigation, it is important to document the planned and actual SLT treatments (see above) in addition to the planned and actual PES treatment.
Timing of PES treatment vis-à-vis the dysphagia causing event will be an important parameter to document alongside the treatment outcome as assessed by means of DSRS and FOIS.

The Phagenyx Catheter is intended to be for single patient use. It is possible that during use, the catheter is accidentally or intentionally removed. Repositioning, but eventually use of a new catheter, might be appropriate. The number of catheters used, the timing of placement and duration of use should be recorded as part of this study, in addition to the technical settings of stimulation levels and effective application of the PES treatment.

**Single blinded approach of the clinical trial.**

Patients randomised to the “LATE TREATMENT” arm of the study will need to be kept blinded for the PES-procedure prior to the first decannulation attempt. For this reason all patients have a nasogastric catheter inserted prior to randomisation and training will be locally implemented to help assure that only the person who applies the treatment is unblinded. The medical staff member applying the treatment should execute the same handling as if the patient was going to receive a true PES treatment, however the patient cable is not effectively connected to the Base Station and thus will not deliver any electrical stimulation to the patient. Optimal procedures will be worked out on an investigational site basis. Patients receiving the PES treatment do feel the stimulation as the level is set above threshold, therefore the study cannot be called “double blinded”. Yet, as all medical staff except the person delivering the treatment, remain blinded including the assessor (person assessing the decannulation) - one can call the study a single-blinded trial.

6.6. **First Decannulation Attempt.**

A standard protocol is followed to assess the possibility to decannulate the patient. The assessor of the decannulation needs to remain blinded to randomisation of the patient to one of the treatment arms in the study. The applied steps are the first 3 steps of those mentioned in the article of (Warnecke, et al., 2013) and can be represented as follows:

![Figure 7: Graphic representation of decision flow to support the decannulation protocol.](image)

A dedicated training session will be provided to the blinded assessor applying this protocol for decannulation to help assure consistent applications across study centres. It remains at all times the responsibility of the
“assessor” of the decannulation to decide based on medical grounds if the patient can be decannulated or not. This is a safety decision. His/her decision will be implemented subsequently, irrespective of the assessment made by the Independent Review Board that runs in parallel.

Patients from both study arms will be assessed at about the same time point after the randomisation time point (considered time 0), i.e. in the time period between 72 and 144 hrs after the randomisation assignment.

Patients who are able to be successfully decannulated, will enter the follow up period immediately; those who fail to be decannulated, will receive a second PES-treatment. Once the determination is made using the FEES protocol above, whether or not the patient is suitable for decannulation, it is left to the discretion of the physician (assessor) to leave the cannula for another 24 hrs but deflate the cuff to bridge a time period of weaning from the tracheal tube, which allows easy and fast switch to re-install the airway protection/ventilation if necessary. The timing of effective removal of the tracheal tube will be recorded.

6.7. LATE or Second PES-Treatment and Second Decannulation Attempt.
In a time period between 24 to 72 hrs patients who failed to be decannulated (see above) will receive PES-treatment: this will be the first PES-treatment offered to patients who were assigned to the “LATE TREATMENT” group, but it will be the second PES-treatment for those patients randomised to the “EARLY TREATMENT” group.

For those patients who will receive their second PES-treatment a new nasogastric Phagenyx catheter will need to be inserted. The model numbers will be documented.

Within a time period of minimally 24 to maximally 72 hrs after the 3rd session of this PES-treatment has been delivered, a second attempt to decannulate the patient will be executed. This process is similar to the one applied earlier. Also in this case, once the conclusion is reached that the patient can be decannulated, it is left to the discretion of the physician (assessor) to leave the cannula for another 24 hrs but deflate the cuff to bridge a time period of weaning from the tracheal tube, which allows easy and fast switch to re-install the airway protection/ventilation if necessary. After this, all patients will enter into the follow up period.

6.8. Follow-up Evaluations during Follow Up Period.
The follow-up period will start as indicated above:
- For those patients who are successfully decannulated: at the time of decannulation;
- For all other patients: at the time of the second attempt to decannulate.

Follow-Up Assessments
A follow up scheme has been presented above (see 5. Study Design). It is the intention to observe and document the progression of healing with respect to severity of stroke and swallowing. For this, a continuous documentation of SLT-management is essential and during the first 10 days of the follow up period, this will be done every 48 hrs (+ 12 hrs), and during the subsequent 20 days every 5 days (+ 24 hrs). At day 30, or when the patient is discharged to home or to another rehabilitation centre/ward, an FU-session is scheduled. Finally, at 3-months post PES treatment (interval 60-120 days) medical staff will attempt to contact the patient via telephone to assess the DSRS and mRS at that time.

The severity of swallowing is assessed through the DSRS and FOIS scores; the severity of stroke is assessed through the NIH SS (Appendix B.1) and ‘modified Rankin scores’ (Appendix B.2).

7. Adverse Events (AEs)
This clinical investigation is executed in accordance with the ISO 14155 (2011). The definitions of AEs listed in this standard apply to the study (see Appendix A.1).
All adverse events shall be documented in a timely manner throughout the clinical investigation.
Reporting requirements to EC and Competent Authorities are restricted to:
- All serious adverse device effects (SADEs) and non-device related AEs observed in a patient enrolled in the study;
- All unexpected adverse device effects (UADEs) observed in a patient enrolled in the study;
- All device deficiencies observed during the clinical trial period;
Any patient death, whatever the cause might be.

For clarity, general non-serious non-device related AEs are documented in the study and will be reported as part of the study report. From the regulatory reportable AEs, sufficient information will be obtained so as to permit 1) an adequate determination of the outcome of the event (i.e. whether the effect should be classified as an SAE) and; 2) an assessment of the causal relationship between the AE and the Phagenyx devices. The following information will be collected for those AEs that require regulatory reporting:

- Title of Event
- Start date of event
- Intensity of event
- Frequency
- Outcome
- Relationship to Device/Procedure
- Seriousness Criteria
- Action Taken

Instructions will be given to the local study team with respect to the contact person at Phagenesis in case of observation of SAES, SADEs and/or unanticipated AEs (see also Appendix A.1).

AEs occurring in any patient, who signed the informed consent form, will need to be documented during a subsequent period of one month as part of this study, and whether or not the patient was ultimately enrolled in the study (e.g. a patient who signed the informed consent, but decided not to participate prior the nasogastric catheter is positioned). If the patient was enrolled in the study, AE’s will be documented during a one-month follow-up period. All SAE’s, SADE’s or unanticipated AE’s will be reviewed by the Chairman of the Scientific Committee, the Coordinating Investigator and a representative of the sponsor to decide on complete documentation, device relatedness and impact on risk assessment. Recommendations to reduce the risk will be made and documented. Appropriate measures will be implemented by the sponsor as based on the recommendations received.

8. Data Management

8.1. Electronic data collection system

A validated electronic data collection system will collect the clinical data. Access to the system will be granted to the investigation site by the sponsor after appropriate training of involved staff members and after the site has obtained and provided the sponsor with the proof of the local Ethics Committee approval and of the signed Investigator Agreement.

8.2. Data Collection

For every identified section of data collection there are a series of mandatory questions to be completed and a series of additional questions that can be completed on a voluntary basis. The basic/mandatory tier of data collection refers to the essentials allowing to assess the primary and secondary objectives by data collection of parameters listed as ‘end-points’-parameters.

The investigator is responsible to ensure that data collection is timely, is accurate and is as complete as possible.

In addition, section of the eCRF related to the randomisation and PES treatment will only be accessible by the person delivering the PES treatment, while other medical staff will have access to the other portions of the eCRF. This is to assure blinding of the clinical data.


During the FEES assessment of the decannulation activities, video recordings are performed. These are anonymized. The video-recordings will be used by a central, blinded, Independent Review Board to assess the appropriateness of the decannulation procedure at a given time. To keep the blinding a)
recordings remain anonymized, and b) all patients receive the nasogastric catheter required to deliver
the PES treatment and which is visible on the video-recordings.

The decision on appropriateness of decannulation will be used in parallel of the decision made by the
local investigator but only for purposes of data analysis not for medical reasons and/or to manage the
patient situation.

8.4. Monitoring, Auditing and Inspection
A clinical monitoring plan, based on risk assessments and focussed on the adverse device related events,
on the primary and on the secondary objectives, is in place at the sponsor’s site. This will be executed
during the conduct of the study. At regular time intervals, monitoring will be executed either via
electronic review of data completion, via electronic automated or manual queries, or at the site via
source document verification during personal site visits.

Site visits will be scheduled at the time of site initiation, in the time period between the first and fifth
patient enrolment and at study closure. Additional site visits will be planned based upon a risk
assessment approach. Monitoring will be done by qualified people as assigned by the sponsor.

The sponsor might plan to also execute a number of audits in selected centres to further help assure
complete and accurate data collection, but also to help assure adherence to regulatory requirements.

Inspections can be executed unexpectedly by regulatory authorities at any of the participating study
centres. In such an event, the investigator will explicitly allow these authorities to have access to the
(patient) source data to allow review of the clinical study conduct per the current CIP. The patient
Informed Consent Form will also refer to this access modality and the originals will be kept at hand
during the total duration of the clinical trial.

8.5. Data Review, Cleaning and Queries
Data will be reviewed by either sponsor’s personnel or by assigned people from qualified clinical
research organisations. Based on the review of the mandatory clinical data, queries will be generated
to further request any missing information. This will help to complete (clean) the database prior to any
major analysis being performed.

Especially for the primary end-point and in view of the sequential analysis a fast transfer of minimal
essential clinical data is required in order not to hamper swift statistical assessment of the level of
significance of the difference in proportions of the populations that can be successfully decannulated
between the ‘EARLY’ and ‘LATE TREATMENT’ groups.

To assure adequate data review and to help assure complete data sets, the sponsor’s personnel is not
blinded to any of the eCRF data.

8.6. Data Retention
Clinical data collected in this investigation are for the purpose to obtain regulatory approval to extend
the labelling of the Phagenyx device towards allowing a second application of the standard PES
treatment, not to bring the product to market as the device is granted already with CE-label to treat
patients with neurogenic dysphagia.

In that perspective clinical data should be retained at the site and at the sponsor’s premises for a
minimum of five (5) years after completion of the clinical study; prior this date, no study related clinical
data may be destroyed without prior written approval from the sponsor. A formal indication of the
study closure date will be provided by the sponsor at the end of the investigation. A reference is made
to §7.4 of the ISO 14155, but also to Code of Federal Regulation, § 21CFR312.57 and 312.62 where a
time period of 2 yrs after approval of the marketing application is specified. Retaining the study data
for 5 yrs is deemed more than sufficient to comply with the regulatory requirements.
In case the investigator moves/retires, or otherwise leaves their post, they will provide Phagenesis with the name and address of the person assuming responsibility for records relating to this clinical investigation.

9. **Suspension, Termination and Close-out of Clinical Investigation**

Phagenesis may suspend or prematurely terminate either the clinical investigation in an individual investigation site or the entire clinical investigation for which the reasons will be documented. Reasons for suspension or premature termination at an investigation site may include incidences where monitoring or auditing identifies serious or repeated deviations from the protocol on the part of an investigator, but also unexpected low enrolment rates jeopardising the proper conduct of the study within the foreseen time windows. Phagenesis will ensure that the Ethics Committee (and if applicable, regulatory agency) is notified of any suspension or early termination of the clinical investigation, it will also notify all other principal investigators in the event that the suspension or termination was due to safety issues.

A principal investigator, Ethics Committee, or regulatory authority may suspend or prematurely terminate participation in the clinical investigation at the investigation sites for which they are responsible.

If suspicion of an unacceptable risk to patients arises during the clinical investigation, or when so instructed by the Ethics Committee or regulatory authorities, Phagenesis will suspend the clinical investigation while the associated risk is assessed. The sponsor will terminate the clinical investigation if an unacceptable risk is confirmed. Should the risk not be confirmed Phagenesis will, in accordance with regulations, supply relevant persons with justification and data supporting the decision to resume the clinical investigation.

Routine close-out procedures will be conducted ensuring that the Investigator’s records are complete, all documents needed for the sponsor files are retrieved, and previously identified issues have been resolved.

Enrolment of patients in the study might be suspended when the sequential data analysis demonstrates a statistical significant level of difference in proportions between study groups, or alternatively, when the analysis demonstrates that the difference is too small to reach ever a significant level. Such a decision is to be made by the Scientific Committee.

Enrolment of patients (with a given indication) in a single centre might be suspended if the centre contributes 50% of the target patients in the study.

10. **Statistics and Data Analysis**

10.1. **Randomisation and stratification**

Patients will be randomised in blocks of 4 within centres. The statistical analysis will be stratified according to centre.

10.2. **Data Analysis and Presentation**

Normally distributed continuous outcome variables will be summarized by their mean and s.d.; categorical variables will be summarized as proportions.

10.3. **Statistical Analysis of Primary End-point**

**Sequential monitoring: general aspects**

Interim analyses or group sequential monitoring of cumulative patient data will be performed on the primary outcome data in successive groups of 10 patients.

The main reason for interim analyses on efficacy is to determine whether EARLY PES treatment is significantly better than LATE treatment or whether there is no significant difference between the two. In both cases, when enough evidence has been gathered, the trial can be stopped early and patients can be offered the best treatment available (Whitehead, 1997 (rev 2nd Ed)).
Sequential analysis in PHAST TRAC and hypothesis testing.

For the control [LATE] treatment, the probability of successful decannulation is estimated as 20% [unpublished data of Dr Dziewas]. For the EARLY PES treatment, a probability of at least 45% is expected for successful decannulation: this is a 25 % improvement over the control group [actually 75%, not 45% success was achieved in the study of Dr Dziewas – unpublished data]. Based on these probabilities, a two-sided type I error of 0.05 and a power of 80%, monitoring boundaries can be specified (see Figure 8). Two test statistics, Z and V, are calculated after each new group of 10 patient outcomes. Test statistic V stands for the cumulative amount of information and is a function of the number of patients; test statistic Z is equal to the difference between the observed and the expected (for a proportion successes of 0.20) number of successful decannulations for the EARLY treatment. When the (Z,V)-statistic based on the cumulative data crosses the upper red boundary, the null hypothesis of no difference will be rejected. When the lower dashed boundary is crossed, the null hypothesis will be accepted. PEST 4 software (PEST 4, 2000) will be used for implementation of the sequential analysis.

![Figure 8: Illustration of upper and lower boundaries of acceptance levels.](image)

10.4. Sample Size Determination

The fixed sample size to detect a difference of at least 25 % is at least 102 patients, excl. drop-outs. With a sequential analysis, on average 71 to 73 patients will be needed to detect this or no difference. If the treatment difference turns out to be less than the expected 25%, 85 to 126 patients or more will have to be included and treated. However if the treatment difference turns out to be more than 30% 51 to 54 patients would need to be included.

10.5. Implementation of sequential analysis in PHAST TRAC

Each time, a group of 10 successive patients has reached their confirmed primary endpoints, the total cumulative data will be transferred to the statistician for a new group sequential analysis. The statistician will advise the members of the Scientific Committee (see 11. Reports and Publications) on continuing or stopping the study.

When the study is stopped, the estimates of the difference in proportion successful decannulation and of its 95%-confidence interval will be adjusted for the cumulative monitoring (PEST 4, 2000) (Whitehead, 1997 (rev 2nd Ed)).

The statistical analysis will take place conform the intention-to-treat principle. A Statistical Analysis Plan will be developed and finalized prior first patient enrolment in the study. This plan will be executed subsequently. Study results will be all reported in the final study report.
11. Reports and Publications

Scientific Committee

A Scientific Committee is established, chaired by Professor S. Hamdy, Manchester, and assisted by the Coordinating Investigator, Dr. R. Dziwes, Münster. Other investigators might be appointed to participate in the Scientific Committee as needed and as appropriate. This committee will address the intended data collection as specified in this study. This group supervises the data analysis and primarily decides on the outcome of interim data analyses to conclude patient enrolment. The members of the committee also agree on the publication policy and will inform other investigators accordingly.

Prof. I. van der Tweel (UMC Utrecht, Department of Biostatistics & Research Support, Julius Centre, The Netherlands) is a member of the Scientific Committee and supervises the statistical analyses. She published on the nature of sequential analysis (van der Tweel & Roes, 2013)

The Clinical Research Manager is a member of the Scientific Committee. A list of the other Scientific Committee members (investigators) is available at the sponsor’s site.

11.1. Interim Report
No formal interim reports are foreseen other than those describing the progress of the study (enrolment, data collection, monitoring etc.), unless identified ad-hoc by the Scientific Committee.

11.2. Final Report
A final report will be created per the ISO 14155 guidelines. This final report will be reviewed by the Scientific Committee members and approved by all investigators.

11.3. Publications and Publication Policy
A publication policy will be created by the members of the Scientific Committee, defining the content and the timing of specific publications addressing the relevant symptoms, diagnosis, therapy and treatment outcome in the total patient population and in the ‘EARLY’ and ‘LATE TREATMENT’ subgroup of patients defined in this study. Authorship rules will also be defined in that policy and will consider the numerical and scientific contribution to the study (e.g. enrolment rates, timing of data collection, compliance to data collection requirements etc.). No publications other than those specified and approved by the members of the Scientific Committee are allowed to be published or presented in any kind during the conduct of the clinical study until the final report is approved and the investigation formally closed. Each investigator will be informed about the policy prior first enrolment of a patient in the study at the investigator’s site and agrees formally with this approach by signing the Investigator Agreement.

12. Ethical Considerations

12.1. Declaration of Helsinki
The study is executed in line with the relevant articles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in 1964 and as revised repeatedly and lately in Seoul (2008).

12.2. Ethics Committee Approval
At a minimum the local Ethics Committee must formally approve the conduct of the study in the investigator’s centre, unless local regulations dictate a different procedure. For this, the appropriate documents must be submitted and the investigator must provide the sponsor with a signed and dated letter granting approval from the local Ethic Committee.

12.3. Informed Consent and Patient Information
Each patient will be appropriately informed about the study purpose and their voluntary participation will be documented in writing by signing the provided Informed Consent Form (see Appendix A.2). This document also states that all clinical data collected from a patient will be remain confidential, irrespective of the fact that the sponsor, delegates of the sponsor, and/or regulatory authority personnel can have direct access to the source data. It will also specify the duration of the clinical data retention, incl. the video-recordings.
12.4. **Patient compensation for study participation**
No compensation is provided to the patients for study participation. Travel costs, if any, are reimbursed via the investigator’s study centre upon provision of the receipts.

12.5. **Subject Insurance – Indemnity / Patient Pay-Outs**
The sponsor recognises its liability in law to compensate for any injury sustained by a patient participating in this clinical investigation when the injury directly evolves from the malfunctioning of the medical device (device deficiency) when correctly applied and used per the Instructions For Use or from the application of any study related procedure, more specifically from the application of the second PES-treatment in certain patients, which procedure establishes the only difference from the already CE-labeled application for which product liability coverage is offered. The insurance will comply with local and national guidelines.

13. **Good Clinical Practice (GCP) Compliance**

13.1. **Professional Conduct of the Clinical Study**
Only well identified study centres can participate in the study. The centre selection criteria are specified to assure that appropriate medical, technical and clinical investigator expertise is present prior approval of study participation. Prior the start of the study, the investigator will sign the CIP demonstrating the willingness to conduct the study according the specifications of the CIP.

13.2. **Training Provided by Sponsor**
Specific technical training to use the Phagenyx devices is not part of this study, given that the device is CE-marked and that availability of technical expertise is a requirement to participate in the study. Training is however provided by the sponsor to the investigator on the GCP aspects, on the CIP and as outlined in the ISO 14155.

13.3. **ISO 14155 (version 2011)**
The ISO 14155 describes the good clinical practices for conduct of clinical investigations in humans with medical devices. The study is set-up and is implemented according to these guidelines. Each centre will be trained on or should demonstrate acquaintance on the relevant elements of this standard prior first enrolment of a patient.
15. Appendices:

Series A appendices are study specific, Series B appendices are general/standard in nature and can be used for multiple studies.

Series A: Study Specific Documents.

A.1. Adverse event definition and handling
A.2. Patient Information Sheet and Informed Consent Form
A.3. Template Investigator Agreement
A.4. Insurance statement
A.5. Structure of database
A.6. Draft CRFs
A.7. Speech and Language Therapy management plan

Series B: General Documents (Questionnaires).

B.1 National Institute of Health Stroke Scale (NIHSS)
B.2 Modified Rankin Scale
B.3 Dysphagia Severity Ranking Scale (DSRS)
B.4 Functional Oral Intake Score (FOIS)
B.5 Richmond Agitation and Sedation Scale

If there are any non-substantial changes to any of these appendices or required changes by a local authority (e.g. Ethics Committee or Research Office), this would not require a revision of the CIP.
## A.1: Adverse Event (AE) definitions and handling

### Definitions

| ADE  | Adverse Device Effect: AE related to the use of an investigational medical device. This includes:  
A. any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.  
B. any event that is a result of a use error or intentional misuse. |
|------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| AE   | Adverse Event: Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in patients, users or other persons whether or not related to the investigational medical device.  
This includes:  
A. events related to the investigational device or the comparator.  
B. events related to the procedures involved (any procedure in the clinical investigation plan).  
C. events related to the investigational medical device by users. |
| SAE  | Serious Adverse Event: AE that:  
A. led to a death,  
B. led to a serious deterioration in health that either:  
1. resulted in a life-threatening illness or injury, or  
2. resulted in a permanent impairment of a body structure or a body function, or  
3. required in-patient hospitalization or prolongation of existing hospitalization, or  
4. resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function. |
| SADE | Serious Adverse Device Effect: ADE that has resulted in any of the consequences characteristic of a SAE. |
| USADE| Unanticipated serious adverse device effect: AE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. |
| Anticipated serious adverse device effects | An AE that is listed as a potential issue in the Risk Analysis of the company.  
The identified anticipated SADES are listed in this Appendix. |
| Device Deficiency | An inadequacy of the medical device with respect to its identity, quality, durability, reliability, safety or performance. This includes malfunctions, use errors, and inadequate labelling. Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence:  
a) if either suitable action had not been taken,  
b) if intervention had not been made, or  
c) if circumstances had been less fortunate, |
shall be reported to the Ethics Committee.

**Handling**

During the period of the investigation the handling of adverse events will occur per the guidelines given by the European Commission on clinical investigations\(^\text{19}\). As such new findings/updates in relation to already reported events are considered reportable events.

All relevant AE’s, SAEs, SADEs, unanticipated adverse effects, device deficiencies (previously called ‘incidents’) and new findings/updates in relation to already reported events must be reported to the sponsor. In case of death or SAE’s requiring urgent medical interventions: by telephone within 24 hours of the investigator becoming aware of the SAE.

The investigator should institute appropriate therapeutic and follow-up measures in accordance with good medical practice but should notify the monitor of such actions and record them in the patient’s case report form. Each telephone reported event must be documented in writing to Phagenesis Limited within three (3) working days of the event.

Safety reporting to Ethics Committees, responsibilities and timelines are detailed hereunder. Where national law differs from this CIP, the national law for that country will take precedence.

All SAEs, SADEs and/or UADEs will be followed-up until they are resolved or for 30 days after the patient's participation in the clinical investigation ends.

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<td>Sponsor</td>
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<td>AE report form</td>
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| reported event |  |  |  |
Anticipated Adverse Device Effects

Based on the Investigator Brochure, where the details of an extensive literature search are listed and based on the Instructions for Use, the following warnings and/or contra-indications are mentioned that potentially could lead to AEs which can be considered anticipated:

- difficulty or inability to position the Phagenyx Catheter in patients with anatomical abnormalities that preclude passage of the catheter (or any other feeding tube);

- as the use of the Phagenyx Catheter is contra-indicated to be used in patients with oral intubation20, history of oesophageal perforation, stricture or pouch, the use of the device is those patients can lead to complications;

- use of the Phagenyx Catheter should be avoided in patients with cardiac or respiratory condition that might render the insertion of a catheter into the throat unsafe;

- use of the Phagenyx device should be avoided in patients implanted with a pacemaker or a cardioverter defibrillator as interference between electrical stimulation and dysfunction of the device might result;

- when the patient is to receive an magnetic resonance imaging (MRI) scan, the Phagenyx Catheter should not be left in place to prevent generation of electrical current by the magnetic field in the metal leads;

- pharyngeal electrical stimulation should not be carried out in patients receiving oxygen therapy whilst the supply is in place or in operation and be in contact with the electrodes;

- pharyngeal electrical stimulation should not be carried out in female patients who are pregnant or who are nursing;

- when applying PES, distortions or anomalies in electrical encephalogram (EEG) or in electrocardiogram (ECG) recordings might occur when recorded in parallel to the PES by the applied current;

- the Base Station should be used as indicated, no other devices should at any time be connected to the Base Station than Phagenesis approved USB sticks or catheters;

- damage to the packaging might lead to unsterile catheter products – in such a case the catheter should not be used;

- the catheter is indicated for single patient use – using the product in multiple patients is contraindicated and must be avoided;

- use of the catheter is indicated for a single patient for up to 30 days – thereafter it must be removed and disposed of in clinical waste;

- the electrodes of the catheter should never be handled/touched when the catheter is connected to Base Station – connection to the Base Station should only be done after the catheter has been inserted into the patient;

- the catheter should be checked before and after feeding to ensure there are no leaks;

- if changes in performance of the catheter are observed, it should not be used further;

- connection of the catheter to enteral feeding systems can occur but only via a stepped enteral connector and to enteral feeding sets and/or feeding pumps designed to deliver nutrition via an 8Fr feeding tube.

20 The wording "oral intubation" is intended to indicate those conditions where the presence of equipment for mechanical ventilation would prevent the use of Phagenyx Catheter and circumstances where electrical stimulation would occur in spaces with high oxygen concentration. Patients receiving continuous oxygen treatment that can have the oxygen treatment temporarily stopped and equipment removed during PES-treatment can still be included in the study. It is the treating physicians responsibility to ensure that the continuous oxygen is stopped and equipment is removed prior to starting the PES-treatment.
No additional device related AEs were currently observed in the STEPS study.

In case of emergency, the following contact details should be used:

Name: Jaak Minten
Telephone number: +32 (0) 475-923-149

In addition, the study is executed under the supervision of a physician, who also co-reviews each SAE and ADE. The outcome of each review is documented in the files of the clinical study at Phagenesis.
A.2: Patient Information Sheet

Benefit of PHAryngeal electrical STimulation for early de-cannulation in TRACHEotomised stroke patients with neurogenic dysphagia: a prospective randomised single-blinded interventional study (PHAST-TRAC study)

Why you have been chosen for this study

You have been diagnosed with or are suffering from ‘neurogenic dysphagia’ which makes your swallowing difficult. A variety of conditions such as Stroke, in combination with (artificial) mechanical ventilation or not, can lead to difficult swallowing. A common problem caused by difficult swallowing is that food or drinks may go down the wrong way and end up in your lungs. This can cause serious chest infections. All this might make your recovery more cumbersome and often alternative feeding methods are proposed as a therapy. Your oral ventilation tube has also been replaced with a direct access ventilation tube (known as a tracheotomy tube) to prevent complication linked with swallowing difficulties. To treat the symptoms of difficult swallowing, special training or swallowing techniques might have been explained to you by your care team. Unfortunately, current treatment methods are not always effective and some patients end up needing long-term feeding via a tube inserted in the nose or surgically placed in their stomach.

Description of the treatment device

There are alternative treatments. One of these is called ‘Pharyngeal Electrical Stimulation’ (PES), which is a simple and harmless technique for treating difficult swallowing. PES treatment is delivered by a medical device that is commercially available and that can be used by your care team on a routine basis at your bedside. The device is made up of a control unit and a small tube placed through your nose down your throat and into your stomach. It is very similar to the type of tube used to temporarily feed people with swallowing difficulty. It can also be used to give you medicine and liquids if you need them. The tube is this thick: ø (3mm) and is used to stimulate nerves in your throat (pharynx) for 10 minutes each day for 3 days in a row to improve your swallowing function. The intensity of the stimulation is adjusted on each day so that it is at the right level for you.

A minimum of 50 and a maximum of 126 patients will take part in this study which will take about 18 months in total to be completed. Your participation may last up to 6 weeks but every patient that takes part in the study will receive the same PES treatment. Some patients will receive the treatment sooner than others and some patients will receive the treatment twice. Apart from when you receive the PES treatment, you will otherwise be treated as recommended by your care team which is the standard practice when using this treatment.

Previous scientific research on this treatment

Scientific research on PES shows that it can help improve swallowing function. This previous research has mainly been performed in stroke patients. This study is designed to help understand the potential benefit (or lack of benefit) PES treatment can have in stroke patients who were mechanically ventilated and have a tracheotomy tube in place for swallowing difficulties. During previous studies, no new or unanticipated adverse events were observed; as such, the treatment can be described as safe.

Purpose of this clinical study

The purpose of this clinical study is to assess if the PES treatment can help stroke patients with a tracheotomy tube in place, have the tube removed earlier as compared to patients who do not receive the treatment at the same time point. The study will involve observing how the devices work and documenting the outcome of the treatment. Apart from the PES treatment, no additional specific medical interventions are required by this clinical study and you will continue to receive standard care as recommended by your care team.

As such, there is actually no “experimental” part of this study other than that some patients will receive the standard PES treatment two times. The intent is to collect clinical data related to the PES treatment and its effects on the ability to remove your tracheotomy tube, but also on the improvement of your swallowing function and severity of stroke.
Although the standard PES treatment is “safe”, it is not impossible that an unanticipated risk may occur during the clinical study, but the chances of this happening are small and we have taken steps to make sure it is as safe as possible for you to take part.

**What is involved?**

Before you participate in this study, your doctor will carefully check if you are able to take part and if you might benefit from the PES-treatment. For this you will be asked a series of questions and some medical checks will be made. There are certain conditions that make it unsafe for you to take part such as having a pacemaker, being pregnant or requiring continuous oxygen therapy. Your care team will check this and let you know if you can take part.

The ability to remove your tracheotomy tube will be assessed several times by your doctor using a standard tube removal camera test (endoscope). For the purposes of this study only, some extra documentation of video-recordings will be made during these camera tests. These recordings will be anonymised which means they will not contain any information that can personally identify you.

The severity of your swallowing difficulties will be measured by standard medical tests which would be routinely performed by your care team. They will explain these tests to you. Some of the tests will involve specific instruments, but the majority of observations will be made through the use of questionnaires completed either by you, the nurse or the doctor. This information or ‘data’ will be documented before, during and after the PES-treatment for up to a maximum time period of one month. These data can be collected while you are in the hospital or in a rehabilitation home. It is planned to publish the results of the study in scientific journals and to talk about it at scientific meetings. This will be done without affecting the confidential nature of your personal data, however it requires the storage of your clinical data (including the anonymised video-recordings) for up to a maximum period of 5 years after the end of the study.

**Assignment to the study groups.** Patients participating in this study, will be assigned (a process called ‘randomisation’) either to the “EARLY” or the “LATE” treatment group. The time difference between groups is 4-6 days only. You will have an equal chance of being assigned to either group, but all patients participating in the study will receive the same standard PES treatment. Once the standard PES treatments have finished, your doctor will attempt to remove the tracheotomy tube. If the tube cannot be removed successfully, you will given another standard period of PES treatment after which your doctor will retry to remove the tracheotomy tube a few days later.

**Blinding of study activities.** In order not to influence yourself nor the doctor who is going to perform the tube removal tests, you and all other members of the medical staff (except one person) will not be told about when the PES treatment is delivered to you. Only one person will know when and how the PES treatment was delivered. This standard study process is called “blinding”.

**Your study participation**

Taking part in this study is completely voluntary and you will continue to receive the standard treatments for swallowing difficulty even if you do not participate. In the case that you decide not to take part you will still receive the best possible treatment which might still include the same standard PES treatment. If you decide to participate, you will have to sign a ‘Patient Informed Consent Form’.

All the clinical data that is collected from you during the study will remain strictly confidential. In order to use and analyse your data, we will need to access your clinical records. Only people involved with the study, such as the clinical staff, those assigned by the study sponsor, and potentially some from government regulatory authorities (Europe, U.S.A., Asia) who collect information to check that the study is being run properly will have access to your data. The data collected will be maintained for a long time (maximally 5 years after study closure), but will remain strictly confidential and none of your personal data will be disclosed to inappropriate parties. By taking part in the study, and by signing the Informed Consent Form, you grant these persons/organisations access to your personal medical records and data. Please note that all your medical records are kept strictly confidential and that outside the hospital, only anonymised data is used and
stored securely: this means your information will be labelled with a code/number and no information with your name or other identifiable information will leave the hospital.

You will be informed if any new information becomes available through the conduct of this study, or if the study concept changes by which your study participation could be jeopardised.

There are no expenses or compensation for taking part in this study. You will however be insured by the sponsor in the event of an injury arising from taking part in this clinical investigation. For any injury caused by taking part in this study, we will provide compensation in accordance with the local, national guidelines, e.g. those of the Association of the British Healthcare Industry (ABHI). We will pay compensation where the injury resulted from i) device being tested or administered as part of the research or ii) any test or procedure you received as part of the study.

Compensation will be paid regardless of whether you are able to prove that the company has been negligent or that the product is defective (please ask if you would like more information on this). We would not be bound by these guidelines to pay compensation where i) the injury resulted from a device or procedure outside the study protocol and/or ii) the protocol was not followed.

As your study participation is completely voluntary, you may withdraw from the study at any time without any consequence to your continued care. The same also applies if the sponsor decides to stop the clinical investigation early.

Sponsor and contact details

The study is set-up and sponsored by the manufacturer of the PES treatment, Phagenesis Limited, located in Manchester, United Kingdom. The sponsor’s representative in this hospital is:

__________________________________________ (name of investigator, title)
__________________________________________ (telephone number)

He/she is responsible for the correct conduct of the clinical study at this hospital. If you wish to take part or have any remaining questions about the study or about your rights, or in the case of an injury arising from taking part in this study, please contact this person. If you agree to take part in the study and if you wish, the investigator will inform your personal doctor (general practitioner) that you are taking part in this clinical study.
# PATIENT INFORMED CONSENT FORM

**Study Title:** Benefit of PHaryngeal electrical STimulation for early de-cannulation in TRAcheotomised stroke patients with neurogenic dysphagia: a prospective randomised single-blinded interventional study (PHAST TRAC study)

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<th>Name of Investigator: [input name of PI]</th>
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<tr>
<td>1. I confirm that I have read and understand the information sheet dated 5 February 2015 (Version 1.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.</td>
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<td>2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.</td>
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<td>3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from/on behalf of Phagenesis Limited, from regulatory authorities, the hospital, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records and data.</td>
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<tr>
<td>4. I agree that data collected from me in this study may be used as described in the information sheet, including transfer to countries outside the European Union submission to regulatory bodies (for example the Food and Drug Administration of America).</td>
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<td>5. I agree to my GP and other relevant health professionals involved in my care being informed of my participation in the study and for them to be notified if changes in my care are deemed appropriate or any abnormal findings are detected during the assessments of this study.</td>
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<td>6. I agree to take part in this study.</td>
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<th>Name of Patient</th>
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<tr>
<td>OR Name of Legal Representative</td>
<td>Date</td>
<td>Signature</td>
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<tr>
<td>Name of Person taking consent</td>
<td>Date</td>
<td>Signature</td>
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Complete: 1 original wet-ink consent form. Original copy to be kept in study file, 1 copy in medical notes and give 1 copy to the patient.

PHAST-TRAC: Patient Informed Consent Form  Version 1.0 | FEB 2015  Page 1 of 1
A.3: Investigator Agreement: Standard Template
Phagenesis has a standard English version of the Investigator Agreement. Together with the CIP, the appropriate template translation or the English version of the agreement is added to the dossier.

The Investigator Agreement comprises two parts:

- One part specifies the duties of sponsor and investigator
- The second part specifies the compensation that is due for completion of clinical study activities.

On the contrary, if a local hospital investigator agreement template is available that can be approved by Phagenesis Limited’s legal department, then preferably that agreement will be used as part of the study.

A copy of the standard template can be obtained upon request.

A.4: Evidence of Clinical Investigation Insurance
Phagenesis Limited has brought the Phagenyx devices onto the market: these bear the CE mark and the company is liable for the product’s performance. The product is used as is, however in some patient a second application of the same standard PES treatment is applied. Based on this single element, the devices used in the clinical trial are assigned a “FOR CLINICAL INVESTIGATION ONLY” label.

Phagenesis agrees to abide by the local guidelines in a European country and to establish an appropriate patient insurance. A copy of the insurance policy can be obtained from the sponsor.

A.5: Structure of Data Forms/Database
An electronic data capture system will be created and validated. It will be made available to the investigators when the site is appropriately trained to use the database, when all required approvals for executing the study are obtained (ethics committee, national competent authority) and when the appropriate members of the medical staff (study team) are trained on the conduct of the clinical trial and on ISO 14155 / ICH GCP relevant aspects.

The database contains the questions as they appear on the Case Report Forms and collects the following main data sets:

- CRF01: Patient Data: match with in/exclusion criteria
- CRF02: Patient Baseline Data: assessment of dysphagia, stroke severity, ventilation status, feeding status
- CRF03: PES treatment form
- CRF04: Decannulation attempt outcome form
- CRF05: Patient follow up form
- CRF06: Lost-to-follow up, patient study exit form

In addition there is an Adverse Event form and a SLT-management form.
The electronic database is an interactive database that allows immediate feedback on the presence/absence and correctness of entered data. Appropriate training will be provided to the study team that supports the data collection.

The system will also allow for access to the IWRS system that provides immediate feedback to the certified requestor on the randomisation status of a certain patient. Only certified people will have access to this information, all others, including those performing data entry or monitoring the data will not have access to such information. This approach supports the maintenance of the blinding of patient and assessor of the decannulation process.

It will be requested to complete the information per patient as soon as it becomes available, especially the information on the outcome of the primary end-point. The database is on-line accessible by the Biostatistical department Utrecht, where the sequential analysis is executed under supervision of Prof I van der Tweel and where analysis reports will be generated after the primary end-point data are received and analysed from every batch of 10 patients (data will be continuously accumulated).

This report will be discussed between the members of the Scientific Board, where the decision to (dis)continue the study enrolment will be made. A decision on discontinuation will be communicated within 5 working days to all investigators.

A.6. Draft CRFs

Copies of the Case Report Forms (CRFs) are available and a set is provided to the investigator at the time of the protocol delivery. These dataforms serve as the backbone to construct the electronic data base system. Additional copies can be obtained upon request.

Appropriate training will be provided to the medical staff on the use of the eCRFs prior study start in the given centre.
A.7: Speech and Language Therapy Management

The following information will be recorded on the electronic data collection system. A paper copy will also be kept in the study files for source documentation verification.

Screening, Baseline, Follow up-Visit 1 (1-2 weeks), Follow up-Visit 2 (2 weeks-discharge) and Follow up-Visit 3 (8-16 weeks)

If the patient has had a further SLT assessment since that documented previously and there is new information to populate this pro-forma as a result of this, please complete the following information. N.B. If there has not been a further SLT assessment or any change in the information since the previous visits, please confirm this in the case report forms and in the source data.

3.B.8.1. Swallow assessment:
N.B: this assessment must be consistently done at all time points by the same person for this patient.

Patient’s Speech and Language Therapist’s Name:………………………………………………………………………………

Date of swallow assessment: (dd/mmm/yyyy) …………………………………………. _ _ / _ _ _ / _ _ _ _

Indicate on the following scale the severity of swallowing as assessed by the SLT:
Where 1 = no problem at all to swallow fluids or any food;
Where 7 = unable to swallow and requires instrumentation.

- Retrospective assessment at the time of start of SLT-management (this hospitalisation period):
  1 2 3 4 5 6 7 N/A
- Current assessment at the time of baseline:
  1 2 3 4 5 6 7 N/A

3.B.8.2. Further Assessments:

1. Was an SLT management plan set-up since the dysphagia causing event? ………………………………………………………………………………………
   If YES,
   a. When was it started up? (dd/mmm/yyyy) …………………………………………………………………………………………… _ _ / _ _ _ / _ _ _ _

2. Was the SLT management plan considered successful? …………………
   If YES,
   a. Did swallowing ability improve considerably? …………………
   b. Was diet adjusted towards a more normal diet? …………………
   c. Was fluid intake adjusted towards a more regular pattern? ………………………………………………………………………………………

3. Was the SLT management plan considered completed with no further follow-up treatments scheduled? ………………………………………
3.B.8.3. Current SLT Management

1. The current SLT Management plan is based on information from:
   a. SLT led bedside swallow assessment? ..............................................................
   b. Clinical videofluoroscopy (i.e. local SLT practitioner protocol or radiology led; VFS)? .............................................................
   c. Fibreoptic Endoscopic Evaluation of Swallowing (FEES)? ................................
   d. Other (Please specify): .............................................................................
      .............................................................................................................

2. Diet recommendations (tick as appropriate):
   a. None? ........................................................................................................
   b. Normal? ....................................................................................................
   c. Normal avoiding challenging textures? .....................................................
   d. Soft? ..........................................................................................................
   e. Soft-mashed? ............................................................................................
   f. Puree? ........................................................................................................
   g. Nil oral diet? ...............................................................................................  
   h. Other (e.g. puree trials, please specify): ...................................................
      .................................................................................................................

3. Current fluid recommendations (tick as appropriate):
   a. None? ........................................................................................................
   b. Normal? ....................................................................................................
   c. Syrup? .......................................................................................................  
   d. Custard? ....................................................................................................
   e. Pudding? ....................................................................................................
   f. Nil oral fluids? ............................................................................................
   g. Other (Please specify): .............................................................................
      .................................................................................................................

4. Specific instrumentation that have currently been installed to manage the patients dysphagia: (tick as appropriate):
   a. None, no supplementary or alternative feeding is being given? ...............  
   b. PEG? ..........................................................................................................  
   c. Nasogastric (NG) tube? .............................................................................
   d. Other (Please specify): .............................................................................
      .................................................................................................................

5. Additional advice given to the patient in relation to feeding: (tick as appropriate):
   a. None? ........................................................................................................
   b. Assistance to feed? ....................................................................................
   c. Supervision & prompts re: bolus size or speed? .......................................  
   d. Restrictions in quantity of oral intake per sitting? ....................................
   e. Altered frequency of oral intake? .............................................................
   f. Specified body position during oral intake? .............................................
   g. Use of specialist equipment or utensils? ...................................................
   h. Specified regime or oral hygiene? ............................................................
   i. Specified patient/care education? ............................................................
   j. Other (Please specify): .............................................................................
      .................................................................................................................
B.1. National Institute of Health Stroke Scale (NIH SS)

The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

<table>
<thead>
<tr>
<th>Score</th>
<th>Stroke Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Stroke Symptoms</td>
</tr>
<tr>
<td>1-4</td>
<td>Minor Stroke</td>
</tr>
<tr>
<td>5-15</td>
<td>Moderate Stroke</td>
</tr>
<tr>
<td>16-20</td>
<td>Moderate to Severe Stroke</td>
</tr>
<tr>
<td>21-42</td>
<td>Severe Stroke</td>
</tr>
</tbody>
</table>

1. Level of Consciousness (LOC)

Level of consciousness testing is divided into three sections. The first LOC items test for the patient's responsiveness. The second LOC item is based on the patient's ability to answer questions that are verbally presented by the examiner. The final LOC sub-section is based on the patient's ability to follow verbal commands to perform simple task. Although this item is broken into three parts, each sub-section is added to the final score as if it is its own item.

A) LOC Responsiveness

Scores for this item are assigned by a medical practitioner based on the stimuli required to arouse patient. The examiner should first assess if the patient is fully alert to his or her surroundings. If the patient is not completely alert, the examiner should attempt a verbal stimulus to arouse the patient. Failure of verbal stimuli indicates an attempt to arouse the patient via repeated physical stimuli. If none of these stimuli are successful in eliciting a response, the patient can be considered totally unresponsive.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Alert; Responsive</td>
</tr>
<tr>
<td>1</td>
<td>Not alert; Verbally arousable or aroused by minor stimulation to obey, answer, or respond.</td>
</tr>
<tr>
<td>2</td>
<td>Not alert; Only responsive to repeated or strong and painful stimuli</td>
</tr>
<tr>
<td>3</td>
<td>Totally unresponsive; Responds only with reflexes or is a-reflexic</td>
</tr>
</tbody>
</table>

B) LOC Question

Patient is verbally asked his or her age and for the name of the current month.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Correctly answers both questions</td>
</tr>
<tr>
<td>1</td>
<td>Correctly answers one question</td>
</tr>
<tr>
<td>2</td>
<td>Does not correctly answer either question</td>
</tr>
</tbody>
</table>
C) LOC Commands
The patient is instructed to first open and close his or her eyes and then grip and release his or her hand

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Correctly performs both tasks</td>
</tr>
<tr>
<td>1</td>
<td>Correctly performs 1 task</td>
</tr>
<tr>
<td>2</td>
<td>Does not correctly perform either task</td>
</tr>
</tbody>
</table>

2. Horizontal Eye Movement
Assesses ability for patient to track a pen or finger from side to side only using his or her eyes. This is designed to assess motor ability to gaze towards the hemisphere opposite of injury. This item is tested because Conjugated eye deviation is present in approximately 20% of stroke cases. CED is more common in right hemispheric strokes and typically in lesions affecting the basal ganglia and temporoparietal cortex. Damage to these areas can result in decreased spatial attention and reduced control of eye movements.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal; Able to follow pen or finger to both sides</td>
</tr>
<tr>
<td>1</td>
<td>Partial gaze palsy; gaze is abnormal in one or both eyes, but gaze is not totally paralyzed. Patient can gaze towards hemisphere of infarct, but can't go past midline</td>
</tr>
<tr>
<td>2</td>
<td>Total gaze paresis; gaze is fixed to one side</td>
</tr>
</tbody>
</table>

3. Visual field test
Assess the patient's vision in each visual fields. Each eye is tested individually, by covering one eye and then the other. Each upper and lower quadrant is tested by asking the patient to indicate how many fingers the investigator is presenting in each quadrant. The investigator should instruct the patient to maintain eye contact throughout this test, and not allow the patient to realign focus towards each stimulus. With the first eye covered, place a random number of fingers in each quadrant and ask the patient how many fingers are being presented. Repeat this testing for the opposite eye.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No vision loss</td>
</tr>
<tr>
<td>1</td>
<td>Partial hemianopia or complete quadrantanopia; patient recognizes no visual stimulus in one specific quadrant</td>
</tr>
<tr>
<td>2</td>
<td>Complete hemianopia; patient recognizes no visual stimulus in one half of the visual field</td>
</tr>
<tr>
<td>3</td>
<td>Bilateral Blindness, including blindness from any cause</td>
</tr>
</tbody>
</table>
4. Facial Palsy

Facial palsy is partial or complete paralysis of portions of the face. Typically this paralysis is most pronounced in the lower half of one facial side. However, depending on lesion location the paralysis may be present in other facial regions. While inspecting the symmetry of each facial expression the examiner should first instruct patient to show his or her teeth (or gums). Second, the patient should be asked to squeeze his or her eyes closed as hard as possible. After reopening his or her eyes, the patient is then instructed to raise his or her eyebrows.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal and symmetrical movement</td>
</tr>
<tr>
<td>1</td>
<td>Minor paralysis; function is less than clearly normal, such as flattened nasolabial fold or minor asymmetry in smile</td>
</tr>
<tr>
<td>2</td>
<td>Partial paralysis; particularly paralysis in lower face</td>
</tr>
<tr>
<td>3</td>
<td>Complete facial Hemiparesis, total paralysis in upper and lower portions of one face side</td>
</tr>
</tbody>
</table>

5. Motor Arm

With palm facing downwards, have the patient extend one arm 90 degrees out in front if the patient is sitting, and 45 degrees out in front if the patient is lying down. If necessary, help the patient get into the correct position. As soon as the patient’s arm is in position the investigator should begin verbally counting down from 10 while simultaneously counting down on his or her fingers in full view of the patient. Observe to detect any downward arm drift prior to the end of the 10 seconds. Downward movement that occurs directly after the investigator places the patient’s arm in position should not be considered downward drift. Repeat this test for the opposite arm. This item should be scored for the right and left arm individually, denoted as item 5a and 5b.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No arm drift; the arm remains in the initial position for the full 10 seconds</td>
</tr>
<tr>
<td>1</td>
<td>Drift; the arm drifts to an intermediate position prior to the end of the full 10 seconds, but not at any point relies on a support</td>
</tr>
<tr>
<td>2</td>
<td>Limited effort against gravity; the arm is able to obtain the starting position, but drifts down from the initial position to a physical support prior to the end of the 10 seconds</td>
</tr>
<tr>
<td>3</td>
<td>No effort against gravity; the arm falls immediately after being helped to the initial position, however the patient is able to move the arm in some form (e.g. shoulder shrug)</td>
</tr>
<tr>
<td>4</td>
<td>No movement; patient has no ability to enact voluntary movement in this arm</td>
</tr>
</tbody>
</table>
6. Motor Leg

With the patient in the supine position, one leg is placed 30 degrees above horizontal. As soon as the patient's leg is in position the investigator should begin verbally counting down from 5 while simultaneously counting down on his or her fingers in full view of the patient. Observe any downward leg drift prior to the end of the 5 seconds. Downward movement that occurs directly after the investigator places the patient's leg in position should not be considered downward drift. Repeat this test for the opposite leg. Scores for this section should be recorded separately as 6a and 6b for the left and right legs respectively.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No leg drift; the leg remains in the initial position for the full 5 seconds</td>
</tr>
<tr>
<td>1</td>
<td>Drift; the leg drifts to an intermediate position prior to the end of the full 5 seconds, but at no point touches the bed for support</td>
</tr>
<tr>
<td>2</td>
<td>Limited effort against gravity; the leg is able to obtain the starting position, but drifts down from the initial position to a physical support prior to the end of the 5 seconds</td>
</tr>
<tr>
<td>3</td>
<td>No effort against gravity; the leg falls immediately after being helped to the initial position, however the patient is able to move the leg in some form (e.g. hip flex)</td>
</tr>
<tr>
<td>4</td>
<td>No movement; patient has no ability to enact voluntary movement in this leg</td>
</tr>
</tbody>
</table>

7. Limb Ataxia

This test for the presence of a unilateral cerebellar lesion, and distinguishes a difference between general weakness and incoordination. The patient should be instructed to first touch his or her finger to the examiner’s finger then move that finger back to his or her nose, repeat this movement 3-4 times for each hand. Next the patient should be instructed to move his or her heel up and down the shin of his or her opposite leg. This test should be repeated for the other leg as well.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal coordination; smooth and accurate movement</td>
</tr>
<tr>
<td>1</td>
<td>Ataxia present in 1 limb; rigid and inaccurate movement in one limb</td>
</tr>
<tr>
<td>2</td>
<td>Ataxia present in 2 or more limbs: rigid and inaccurate movement in both limbs on one side</td>
</tr>
</tbody>
</table>

8. Sensory

Sensory testing is performed via pinpricks in the proximal portion of all four limbs. While applying pinpricks, the investigator should ask whether or not the patient feels the pricks, and if he or she feels the pricks differently on one side when compared to the other side.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of sensory loss</td>
</tr>
<tr>
<td>1</td>
<td>Mild-to-Moderate sensory loss; patient feels the pinprick, however he or she feels as if it is duller on one side</td>
</tr>
<tr>
<td>2</td>
<td>Severe to total sensory loss on one side; patient is not aware he or she is being touched in all unilateral extremities</td>
</tr>
</tbody>
</table>
9. Language

This item measures the patient's language skills. After completing items 1-8 it is likely the investigator has gained an approximation of the patient's language skills; however it is important to confirm this measurement at this time. The stroke scale includes a picture of a picture of a scenario, a list of simple sentences, a figure of assorted random objects, and a list of words. The patient should be asked to explain the scenario depicted in the first figure. Next, he or she should read the list of sentences and name each of the objects depicted in the next figure. The scoring for this item should be based on both the results from the test performed in this item in addition to the language skills demonstrated up to this point in the stroke scale.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal; no obvious speech deficit</td>
</tr>
<tr>
<td>1</td>
<td>Mild-to-moderate aphasia; detectable loss in fluency, however, the examiner should still be able to extract information from patient's speech</td>
</tr>
<tr>
<td>2</td>
<td>Severe aphasia; all speech is fragmented, and examiner is unable to extract the figure's content from the patients speech.</td>
</tr>
<tr>
<td>3</td>
<td>Unable to speak or understand speech</td>
</tr>
</tbody>
</table>

10. Speech

Dysarthria is the lack of motor skills required to produce understandable speech. Dysarthria is strictly a motor problem, and is not related to the patient's ability to comprehend speech. Strokes that cause dysarthria typically affect areas such as the anterior opercular, medial prefrontal and premotor, and anterior cingulate regions. These brain regions are vital in coordinating motor control of the tongue, throat, lips, and lungs. To perform this item the patient is be asked to read from the list of words provided with the stroke scale while the examiner observes the patients articulation and clarity of speech.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal; clear and smooth speech</td>
</tr>
<tr>
<td>1</td>
<td>Mild-to-moderate dysarthria; some slurring of speech, however the patient can be understood</td>
</tr>
<tr>
<td>2</td>
<td>Severe dysarthria; speech is so slurred that he or she cannot be understood, or patients that cannot produce any speech</td>
</tr>
</tbody>
</table>

11. Extinction and Inattention

Sufficient information regarding this item may have been obtained by the examiner in items 1-10 to properly score the patient. However, if any ambiguity exist the examiner should test this item via a technique referred to as "double simultaneous stimulation". This is performed by having the patient close his or her eyes and asking him or her to identify the side on which they are being touched by the examiner. During this time the examiner is alternating between touching the patient on the right and left side. Next, the examiner touches the patient on both sides at the same time. This should be repeated on the patients face, arms, and legs. To test extinction in vision, the examiner should hold up one finger in front of each of the patient's eyes and ask the patient to determine which finger is wiggling or if both are wiggling. The examiner should then alternate between wiggling each finger and wiggling both fingers at the same time.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal; patient correctly answers all questions</td>
</tr>
<tr>
<td>1</td>
<td>Inattention on one side in one modality; visual, tactile, auditory, or spatial</td>
</tr>
<tr>
<td>2</td>
<td>Hemi-inattention; does not recognize stimuli in more than one modality on the same side</td>
</tr>
</tbody>
</table>
### B.2. Modified Rankin Scale

*(From Van Swieten et al. '1998)*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms: able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability: requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability: bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>
B.3. Dysphagia Severity Ranking Scale (DSRS)
A score from 0 to 4 is given for three different elements (fluids, diet, and supervision):

**FLUIDS:**
0. Normal fluids
1. Syrup consistency
2. Custard consistency
3. Pudding consistency
4. No oral fluids

**DIET:**
0. Normal
1. Selected textures
2. Soft, moist diet
3. Puree
4. Non-oral feeding

**SUPERVISION**
0. Eating orally completely independently
1. Eating with supervision
2. Feeding by third party (untrained)
3. Therapeutic feeding (SLT / trained staff)
4. No oral feeding

Note: A score of 4 or higher is considered unsafe; a score between 9 and 12 is considered severe.

B.4: Functional Oral Intake Scale (FOIS)\(^2\)

**TUBE DEPENDENT** (levels 1-3)

1. No oral intake
2. Tube dependent with minimal/inconsistent oral intake
3. Tube supplements with consistent oral intake

**TOTAL ORAL INTAKE** (levels 4-7)

4. Total oral intake of a single consistency
5. Total oral intake of multiple consistencies requiring special preparation
6. Total oral intake with no special preparation, but must avoid specific foods or liquid items
7. Total oral intake with no restrictions

---
B.5. Richmond Agitation Sedation Scale (RASS) ²²

Score Term Description

<table>
<thead>
<tr>
<th>Score</th>
<th>Term Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Combative: overtly combative, violent, immediate danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated: pulls or removes tube(s) or catheter(s); aggressive</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated: frequent non-purposeful movement, fights ventilator</td>
</tr>
<tr>
<td>+1</td>
<td>Restless: anxious but movements not aggressive, vigorous</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy: not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (&gt;10 seconds)</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation: briefly awakens with eye contact to voice (&lt;10 seconds)</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation: movement or eye opening to voice (but no eye contact)</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation: no response to voice, but movement or eye opening to physical stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>Unarousable: no response to voice or physical stimulation</td>
</tr>
</tbody>
</table>

The scores -1 to -3 are observed under verbal stimulation, the scores -4 and -5 under physical stimulation.

Procedure for RASS Assessment

1. Observe patient
   a. Patient is alert, restless, or agitated. (score 0 to +4)
2. If not alert, state patient’s name and say to open eyes and look at speaker.
   b. Patient awakens with sustained eye opening and eye contact. (score -1)
   c. Patient awakens with eye opening and eye contact, but not sustained. (score -2)
   d. Patient has any movement in response to voice but no eye contact. (score -3)
3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.
   e. Patient has any movement to physical stimulation. (score -4)
   f. Patient has no response to any stimulation. (score -5)


1. Background, Rationale and Study Design

1.1. Background

Stroke is the main cause of disability and the third most common cause of death in the United Kingdom (NHS, 2011). Of those that suffer a stroke, 50-78% will be affected by swallowing problems (known as oropharyngeal dysphagia), within one-week of the event, as a result from damage to swallowing specific regions of the brain (Jayasekeran, et al., 2010). Some of these patients will recover partial swallowing ability within the first months after stroke and others may over time recover more of this function. However, conflicting evidence regarding the effects of proposed treatments and their regimens still remains with recent research demonstrating that up to 40% of stroke patients remain dysphagic a year later. In addition to this a significant proportion of patients will remain chronically dysphagic, requiring feeding through a nasogastric (NG) or percutaneous gastrostomy (stomach) tube (PEG) with an increased likelihood of institutionalised care (Jayasekeran, et al., 2010). Even with interventions, these patients are still at a 3-fold increased risk of contracting pneumonia as a result of aspiration of substances into the lungs.

The diagnosis of dysphagia is most often based upon a bedside swallowing assessment conducted by dysphagia trained Speech and Language Therapists (SLTs). Typical assessment entails cranial nerve examination, airway protection testing (e.g. cough reflex), and swallowing bolus trials of fluids and foods of various consistencies (e.g. water, nectar, smooth yogurt, banana, biscuit) with and without swallow strategies (e.g. chin tuck) if deemed appropriate. Instrumental assessments by means of VFS\(^{23}\) or FEES are sometimes used to confirm dysphagia (Kelly, Hydes, McLaughlin, & Wallace, 2007)\(^{24}\), although other practices can lead to the same valid conclusion: oesophagoscopy, laryngoscopy, ultrasonography, CT-scan, MRI, chest X-ray.

In addition the underlying neurological condition can be worsened by certain medication (anaesthetics, sedatives, neuroleptica etc.). The severity of dysphagia can also be altered by medication which is most often linked to the underlying disease, but medication is also known to cause dysphagia.

SLT\(^{25}\) therapy is commenced upon diagnosis of dysphagia. Often alternative diets, compensatory strategies and postural changes are applied separately or in tandem with a variety of stimulation strategies to treat dysphagia. Therapies are often applied at the discretion of the SLT and little or no scientific evidence is available to predict the outcome of the therapy nor the effect of the SLT therapy on the outcome of PES (Bath, Bath-Hextall, & Smithard, 1999) (Greeganage, Beavan, Ellender, & Bath, 2012). In worst cases, enteral feeding is required or even surgical interventions can be applied to help prevent unintentional aspiration.

In stroke-patients, PES has been shown to enhance brain plasticity (Fraser, et al., 2002), improve swallowing and feeding status, and reduce time in hospital (Jayasekeran, et al., 2010). Based on these data, the treatment of neurogenic dysphagia as a result of stroke was the subject of the investigation in the (Phagenesis sponsored) STEPS study (AHE01 - A multi-centre, double blind, randomised controlled Clinical Investigation to validate the EPS1 device as a treatment for stroke-induced dysphagia: A Study of Swallowing Treatment using Electrical Pharyngeal Stimulation).

Research into electrical stimulation for the treatment of dysphagia is expanding and several clinical studies are currently on going (most often in acute or post-stroke patients) to demonstrate the benefit of direct or percutaneous electrical stimulation in association or not with standard SLT-therapies for dysphagia (not restrictive list from ClinicalTrials.gov):

- NCT01971320: Evaluation of transcutaneous electrical stimulation in post-stroke dysphagia (TENSDEG),
- NCT01970384: Transcranial direct current stimulation for dysphagia therapy in acute stroke patients,

\(^{23}\) VFS = videofluoroscopic swallow study also known as the modified barium swallow.

\(^{24}\) FEES = Fiberoptic endoscopic evaluation of swallowing.

\(^{25}\) SLT = Speech and Language Therapist.
- NCT01956175: Electrical pharyngeal stimulation for dysphagia therapy in tracheotomised stroke patients,
- NCT01777672: Effect of afferent oropharyngeal pharmacological and electrical stimulation on swallow response and on activation of human cortex in stroke patients with oropharyngeal dysphagia,
- NCT01723358: Neuromuscular electrical stimulation (NMES) treatment technique therapy in the management of young infants with severe dysphagia,
- NCT02007759: Neuromuscular electrical stimulation (NMES) for dysphagia in neonates,
- NCT01697891: A pilot study of ALTENS in improving dysphagia induced by IMRT for head and neck cancers,
- NCNT01731847: Combined NMES, FEES and traditional swallowing rehabilitation in the treatment of stroke-related dysphagia.

Pilot data from one such study (NCT01956175: Electrical pharyngeal stimulation for dysphagia therapy in tracheostomised stroke patients) suggests that PES treatment has beneficial effects on airway safety that can allow for early decannulation of tracheotomised stroke patients residing within an ICU\textsuperscript{26} (Suntrup, et al., 2015).

The main results, published by the group of Prof R. Dziewas and colleagues (Suntrup, et al., 2015), can be summarized in the graph hereunder where the effect of a PES-treatment can be seen as compared to a control group where no PES treatment was offered. In this study 30 patients, who were weaned from ventilation and tracheotomised, were randomised 2:1 to the treatment or control arm. A total difference of 55% between the treatment and control arm was observed. This created the basis for the current PHAST-TRAC study.

![Figure 9: Main results of Dr Dziewas’ research group on decannulation outcome.](image)

Tracheotomy is reported as one of the most frequently performed surgical procedures within the ICU patient population, with as many as 10% of patients who require at least 3 days of mechanical ventilation eventually receiving a tracheotomy for prolonged mechanical ventilation or airway support. While prolonged respiratory failure is probably the most common reason for performing tracheotomy, there are generally four reasons for tracheotomy insertion:

- To relieve upper-airway obstruction due to tumor, surgery, trauma, foreign body, or infection (ventilator-acquired pneumonia),
- To prevent laryngeal and upper airway damage due to prolonged translaryngeal intubation (orotracheal intubation),
- To allow easy or frequent access to the lower airway for suctioning and secretion removal,
- To provide a stable airway in a patient who requires prolonged mechanical ventilation or oxygenation support due to respiratory failure or risk of aspiration due to dysphagia.

Indeed it is reported that between 10–43% of patients hospitalised because of a major brain trauma (e.g. ischaemic or haemorrhagic strokes, ischaemic brain injuries and others) require a tracheotomy, which

\textsuperscript{26} ICU = Intensive Care Unit.
increases to 50–70% in patients with the low Glasgow Coma Scale (GCS)\textsuperscript{27} scores (Mackiewics-Nartowics, et al., 2008). Despite the advantages of tracheotomy in the setting of prolonged mechanical ventilation, optimal timing for tracheotomy is controversial, with strong arguments for both early\textsuperscript{28} and late tracheotomy insertion (Bittner & Schmidt, 2012) (Durbin, 2010).

Airway related complications in ICU patients are reported to be the most frequent complication with presence of dysphagia and increased risk of aspiration as the main reasons for patients to remain tracheotomised once successfully weaned from artificial ventilation (Bösel, 2014). The frequency of swallowing disorders in tracheotomised patients is reported to vary from 50-83% depending on the assessment method (Garuti, et al., 2014) however, intubation with mechanical ventilation is known to have negative effects on laryngeal competence and swallowing physiology (Kumar, et al., 2014).

Timing of tracheotomy decannulation is also a highly controversial topic with decisions to decannulate often dependent on the physician’s individual experience because evidence-based practice guidelines are not available (Warnecke, et al., 2013). Timely decannulation after weaning from mechanical ventilation is reported to be favorable because the prolonged presence of a tracheotomy tube can delay rehabilitation, reduces patient comfort, and is associated with higher costs due to longer hospitalisation periods (Choate, Barbetti, & Currey, 2009) (Leung, MacGregor, Campbell, & Berkowitz, 2003). Research also suggests that a tracheotomy tube in place on discharge from the ICU can increase patient mortality (Martinez, et al., 2009) whereas removing the tracheotomy tube too early can also pose a significant threat to patients and therefore must be avoided. (Warnecke, et al., 2013) recently established criteria that permit safe and efficient decannulation of critically ill neurological ICU patients using a FEES decision flow protocol. Using this protocol, the authors report increased sensitivity of the FEES decision flow protocol to safely decannulate patients when compared with a standard clinical bedside swallow examination (54 vs 29 patients respectively) and only a low failure (recannulation) rate of 1.9% (1 patient) suggesting the endoscopic protocol is safe, efficient, and an objective bedside tool to guide decannulation decisions.

1.2. Rationale of study design

This is a prospective, single (assessor)-blinded randomised controlled interventional and international clinical study of PES in tracheotomised patients after supratentorial stroke. Given that the assessor of the decannulation remains blinded to the treatment, but that the patients who receive PES treatment do feel without undue discomfort the electrical stimulation, we can identify the study as a single, but not a double blinded trial. In addition, there is a blinded Independent Review Committee that will independently re-assess the primary end-point, one can also identify the ‘blinded end-point assessment’, as is common in PROBE-designed\textsuperscript{29} trials, however this Independent assessment does not influence the actual treatment of the patient nor the first primary end-point assessment of the study.

The data collected will be used to support an extension to the indications for the current CE Mark of the Phagenesis Phagenyx device in accordance with the Medical Device Directive 93/42/EEC. The clinical investigation will conform to ISO14155:2011 requirements. The data may also be used to support a marketing application in the United States of America; the investigation therefore includes additional requirements to support such an application in line with the Code of Federal Regulations.

The Clinical Investigation Plan (CIP) is designed to be prospective to ensure that the population is representative of the populations for which the Phagenyx device is intended to treat. The CIP objectives, eligibility criteria, procedure and follow-up period will draw upon the design of clinical study protocols evaluating the safety and performance of PES in the particular setting of this study.

The patients included in this study will be tracheotomised patients with supratentorial stroke that have been successfully weaned from artificial ventilation, but who are still tracheotomised to

\textsuperscript{27} The GCS is a reliable, objective and practical method for healthcare professionals to assess impairment of conscious level in (traumatic brain injury) patients in response to defined stimuli. It has value in predicting a patient’s ultimate outcome by assessing three types of response: best motor response (scored 1-4), best verbal response (scored 1-5) and best eye response (scored 1-6). Severe= GCS 3-8 (you cannot score lower than a 3.), Moderate = GCS 9-12 and Mild = GCS 13-15.

\textsuperscript{28} The definition of early tracheostomy differs between studies. A review of papers published over 10 years by Cheung et al. (Respir Care 2014;59(6):895–919) reports that early was generally defined as within 3–10 d of mechanical ventilation, whereas late was variously defined as any time outside the early period, within 7–14 d, 14–28 d, or >28 d after initiation of mechanical ventilation.

\textsuperscript{29} PROBE trial: prospective randomised open-label blinded end-point trial
aspiration. A comparison of the clinical success rate of early decannulation will be made post-PES treatment for patients treated versus patients not treated over the same time period.

In addition, patients initially serving as ‘control’ patients to assess the difference in success rate of early decannulation with patients receiving the PES-treatment, will also receive the same standard PES treatment but some 5 days later. Differences in success rates of decannulation between EARLY and LATE treatment (control) groups will be assessed in combination with the occurrence of adverse (device) effects to establish the safety and performance evaluation leading to a potential extension of the current CE labelling.

Finally, patients failing to be decannulated after a first PES, will be subjected to a second exposure of the same standard therapy. The success rate of decannulation after a second PES will be compared to the rate observed after the first PES, again potentially leading to an extension of the CE label.

1.3. Rationale of PES
Dysphagia represents a major therapeutic challenge; however, conflicting evidence regarding the effects of proposed treatments and their regimens still remain. In addition, there is, as yet, no well-established evidence for the current therapies for dysphagia used by SLTs, which include a variety of compensatory and treatment-swallowing techniques in combination with texture-modified diets, pharmacologic therapies and stimulations strategies (Greeganage, Beavan, Ellender, & Bath, 2012) (Bath, Bath, & Smithard, 2000).

PES treatment is a novel intervention designed to optimise the recovery processes responsible for the restoration of safer swallowing function in dysphagic patients. PES treatment has been shown to improve swallowing and feeding status, and reduce time of care in the hospital. The Phagenyx device has been optimised to reduce risk, improve ease of use and also has the potential to reduce respiratory chest infections and improve mortality rates in these populations. Pilot data also suggests that PES treatment has beneficial effects on airway safety that can allow for early decannulation of tracheotomised stroke patients residing within an ICU.

1.4. Conduct of Clinical Investigation to Reduce Bias
The following are incorporated into this CIP to minimise the effects of bias:

- Patients are recruited according to the criteria outlined in the CIP.
- The circumstances when individual patients withdraw prior to the planned completion of the study are specified in this CIP.
- Suitability of patients for decannulation will be assessed with FEES following the decannulation decision flow protocol of (Warnecke, et al., 2013) by suitably experienced health professionals who are blinded to the PES-treatment of patients.
- Training of the research staff will be identical and the procedures as well as healthcare professional performance will be tested prior to delivering PES to patients. During the study, adequate control measures on delivering the standard PES will assure appropriate treatment of patients.
- The outcome of the ability assessment for a decannulation will be assessed in parallel to the investigator’s judgement by a blinded independent central group of physicians/SLT’s, experienced in this process and using copies of the anonymised FEES-video recordings at the time of decannulation assessment.

1.5. The study design
Patients will be selected strictly according to the in- and exclusion criteria. Those patients fulfilling these criteria will be requested to voluntarily participate in the trial. After signing the Patient Informed Consent form, the presence of dysphagia is assessed by applying the FEES decannulation protocol (see section 9 on Screening and Decannulation procedures). The dysphagia prevents the decannulation of the patient. The stability of dysphagia is re-assessed 24-72 hrs later. Only patients who demonstrate twice the inability to be decannulated, prove to have stable dysphagia and are eligible to be enrolled in the study. First the Phagenyx nasogastric catheter is positioned. Subsequent randomization will assign a patient to either the ‘EARLY’ or the ‘LATE treatment’ group, where the patients in the ‘EARLY TREATMENT’ group receive the standard PES-treatment immediately (0-24 hrs) after randomisation and where patients from both groups are subjected to a first

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30 Patients included in the study might not be all the time conscious. The Glasgow Coma Scale is not used in the selection of patients, as verbal communication is hard to judge in some of the patients potentially eligible for study inclusion. Therefor the Richmond Agitation and Sedation Scale (RASS) is used to identify potential patients for study enrolment.
decannulation attempt at the same time point after randomisation. All patients who failed to be decannulated at that time point will be subjected within 48-72 hrs to the standard PES-treatment prior a second attempt (within 24-72 hrs after the last PES-treatment is applied) to decannulate the tracheotomised patients.

For purposes of consistency and to limit variability of performance, centres participating in the PHAST TRAC without previous experience with the Phagenyx PES treatment or the FEES decannulation protocol, will be offered training opportunities. In countries where the local language labelling is appropriately implemented, training is achieved through use of commercially available products; in countries where local language labelling is not yet fully implemented, training occurs as part of the clinical trial by using “For Clinical Trial Use Only” labelled products in patients who are appropriately enrolled in the study. The first three (3) patients are excluded from data analysis in centres without appropriate experience with the PES-technology. The need for training is assessed on a per centre basis and is documented prior the start of the study.

This design can be graphically represented as:

![Figure 10: Essential study design elements. The control group (A) is identified in the CIP as “LATE TREATMENT” group and the treatment group (B) is referred to as “EARLY TREATMENT”; nomenclature is linked to the timing of PES treatment versus the time point of randomisation.](image)

All randomised patients will be followed up for up to 30 days or until hospital discharge, whatever occurs first. During this time period the improvement of swallowing is assessed using standardized questionnaires.

1.6. Definition of “decannulation”

The patients enrolled in the study are patients who have been weaned from mechanical ventilation but have a tracheal tube inserted to prevent saliva aspiration into the lungs because of inadequate swallowing function (airway protection).

A standardised endoscopic swallowing (FEES) evaluation is applied to assess the readiness of the patient to be decannulated (Suntrup, et al., 2015). In the context of this clinical trial, where the improvement of swallowing function as a result of PES-delivery is tested, the action of “decannulation” can be achieved in two manners:

a) Effective tracheal tube removal. In this case the tracheal tube is actually removed from the patient; the tracheal opening is closed. This action leads to the continuous exposure of the patient to the risk of saliva aspiration. In case of aspiration due to insufficiently recovered swallowing function, it requires the opening of the trachea and re-insertion of the tube.

b) Deflation of the tube-cuff. Rather than removing the tube, the cuff, inflated to close the airway and fixate the tube, can be deflated. This action leads to the continuous exposure of the patient to the risk of saliva aspiration, similar to the situation after removal of the tracheal tube. In case of aspiration due to insufficiently recovered swallowing function, it requires only to re-inflate the cuff to create a safe situation again for the patient.

The stability over time of the patient’s “decannulated” condition is important, therefore the status of decannulation is to be checked regularly. It is foreseen in this study to perform this check and to document the outcome every 48 hrs during the first 14 days after the primary end-point assessment. The FEES is not required at this stage of ‘checking’ as it will be determined by the clinical interventions done.
FEES is however applied during screening procedures to assure consistent assessment over time of the dysphagia status until the primary end-point assessment.

2. Device Used in the Clinical Investigation

2.1. The Base Station and Stimulation Catheters
The device used as part of this clinical investigation is the CE-marked Phagenyx Base Station (EPS1) and Phagenyx Catheter. These are commercially available for treatment of neurogenic dysphagia and apply a standard electrical stimulation treatment at 5 Hz via the Phagenyx Catheter which is in essence a standard nasogastric feeding tube provided with built-in stimulation electrodes. The intensity of stimulation is optimised for each treatment by the Base Station software and operator input by setting the intensity at 75% of the tolerable limit above sensory threshold. The catheter has internal electronic controls that mean that once the regime of 3 consecutive treatments is delivered the unit can no longer be used to deliver any further treatments. It is recommended to execute the calibration and 10 minutes stimulation at about the same time point during the three consecutive days.

2.2. The CE label and the status of investigational device
The CE-mark indicates the Phagenyx products are for the treatment of neurogenic dysphagia by means of the above-described PES method. The method involves the application of a fixed regime of 3 treatment sessions in total. However the study protocol requires that this series of 3 treatment sessions is then re-applied to patients who failed to be decannulated after being treated with the first regime of 3 treatments. As this second application of PES treatment is outside the scope of the indication of the CE-mark, the devices (both catheter and base station) are considered non-CE labelled and will be labelled 'FOR CLINICAL TRIAL USE ONLY'.

The software provided in the current version of the Phagenyx device does not allow the delivery of more than one series of 3 x 10 min of electrical stimulation. The device or the device software will NOT be adjusted for the needs of this study protocol. The devices will be labelled “FOR CLINICAL TRIAL USE ONLY” only to reflect the fact that supplementary instructions will be provided to allow the device to deliver the 2nd therapy to the same patient. This will be achieved through a change in the patient identifier information between the two treatment regimens and the replacement of the catheter between the treatment regimes.

Safety evidence for multiple applications has been obtained during the research and product development phase and is included in the Clinical Evaluation document within the current Technical Product Dossier. Delivery of more than one set of 3 treatments was carried out within this research without any adverse effects seen. The application of the additional regime of 3 treatment sessions is not considered to involve any additional treatment related risks. The CE label may be adjusted in the future depending on the clinical data justification (including the data from this study).

2.3. Device Accountability
As mentioned above, the devices used in this clinical investigation are considered investigational devices; they are for the purpose of the study labelled as ‘FOR CLINICAL TRIAL USE ONLY’ and their distribution will be appropriately tracked during the trial. That said, the devices are exactly the same as those which are commercially available for treatment of neurogenic dysphagia and which are CE labelled for this purpose. Each catheter used will be identified by a unique number and recorded on the appropriate data forms and will be uniquely labelled for study purposes; the Base Stations remain unmodified during the study, but devices can already be present in the hospital to support commercial post-market uses of the system. During the study, a non-CE labelled base station will be provided to the investigational sites for the duration and the purpose of the study.

2.4. Risks and Benefits of the Product and Clinical Investigation
The investigator brochure (IB) which is provided to each of the investigators of this study, lists all considerations that were made to reduce and limit risks to the patient and users. This assessment, together with the current knowledge from the STEPS study, has created the basis for the listing of anticipated adverse device effects (ADEs) which are provided in Appendix A.1.31

31 Appendices indicated with “A” refer to study specific documents, forms etc., while appendices referring to “B” sections refer to standard, public domain documents, forms etc.
No unacceptable risks are associated with the treatment; patients may benefit from the PES treatment and experience an improvement of the swallowing difficulties post-PES treatment. The purpose of this study is to demonstrate the benefit of PES in terms of an earlier decannulation of tracheotomised patients.

It has been demonstrated in earlier research (Jayasekeran, et al., 2010) that repeated PES-treatments during one day or for more than 3 consecutive days do not pose additional risks to the person receiving the treatment and don’t result in any other adverse event; as such it is deemed safe, also for those patients from the EARLY treatment arm, who failed to be decannulated after the first PES and who are being exposed to the second series of PES. The potential benefit of this second series of PES is, obviously, to increase the potential to be decannulated thereafter and thus improve the swallowing function and the comfort of the patient. As no additional risks are to be expected this second treatment is considered only offering potential benefits to the patient.

This clinical trial does not require any special clinical procedure that is not standard applied to the patients deemed eligible for study participation. As such there are no additional risks for the patient posed by the clinical study.

3. Objectives and end-points of the study.

3.1. Hypothesis
The hypothesis of the study is formulated as:
“A significantly larger proportion of tracheotomised patients after supratentorial stroke can be decannulated after a first period of pharyngeal electrical stimulation (PES) treatment and following a standardised assessment scheme executed by the local blinded assessor/investigator at 24-72 hrs after the PES-treatment has been completed as compared to control patients who only get standard therapy over the same time period.”

3.2. Primary Objective
The primary objective is to assess the proportion of tracheotomised patients after supratentorial stroke that benefit from PES treatment and have an earlier removal of the tracheal tube at the first attempt between 24 and 72 hrs after completion of the PES treatment as compared to the proportion of patients who only get standard therapy.

3.3. Secondary Objectives
Secondary objectives are to:
- Measure the severity of dysphagia at the time of decannulation, and during the follow up period in terms of standard assessment scores;
- Assess the proportion of patients who benefit from a first PES treatment but at a later time period of standard therapy in the ‘LATE TREATMENT’ (control) group, i.e. 170-288 hrs after the initial randomisation;
- Assess the proportion of patients who benefit from a second PES treatment after failing a first attempt to decannulate the patient in the EARLY treatment arm;
- Assess the severity level of stroke at different time points after PES treatment up to three months;
- Measure the number of days a patient stays on a given ward/ICU;
- Assess the amount of recannulations over a time period of 30 days (or until hospital discharge) after the preceding decannulation;
- Assess the occurrence of severe adverse events during the observation period up to 30 days (or hospital discharge) after decannulation or a second failure to decannulate;
- Assess the optimal treatment parameters (threshold, tolerance, intensity of stimulation);
- Document the SLT management plan and its execution.

3.4. Primary Endpoint
The primary end-point is to assess the ability to remove the tracheal tube in a time period of 24 to 72 hrs after the last PES-treatment is applied and according a standard dichotomised decision flow program (the FEES
decannulation protocol) as applied by the local blinded assessor/investigator. In the LATE TREATMENT group the assessment is done at an equivalent time point, i.e. 3-6 days after the point of randomisation:

In this study, the readiness for decannulation of the patient is used as the primary end-point. Based on this assessment, the ability to remove the tracheal tube, either executed by the effective removal of the tracheal tube or by deflation of the tube-cuff, is used as the surrogate measure for the improved swallowing function of the patient. The timing of this assessment is referred to as time 0. Additional assessments (every 48 hrs during first 14 days) are documented.

3.5. Secondary Endpoints
The secondary endpoints will focus on the assessment of:
- The proportion of patients that can be decannulated after a (second) PES-treatment in the time period between 170-288 hrs after the randomisation time point: the PES-treatment will be the first one to apply in the ‘LATE TREATMENT’ group, but it will be the second application in those patients of the ‘EARLY TREATMENT’ group that failed to be decannulation at the first attempt (i.e. 24-72 hrs after the end of the first PES treatment);
- Severity of dysphagia over a time period of 30 days (or until hospital discharge) after decannulation by means of relevant standard assessment scales (DSRS\textsuperscript{32} and FOIS\textsuperscript{33}): every 48 hrs during the first 10 days and every 5 days thereafter until hospital discharge or maximum 30 days, the severity of dysphagia is measured and compared with the patient’s own condition at the time of baseline and of decannulation attempts;
- The treatment optimisation parameters (threshold, tolerance and intensity of the electrical stimulation);
- Severity of level of stroke at baseline, at follow up Day2, at hospital discharge/day 30 (whichever occurs first) by means of standard scoring scales (NIHSS\textsuperscript{34} and modified Rankin Scale - mRS), and at 3 months post-PES treatment by using the mRS.

In addition, following parameters will be documented:
- Demographics, symptoms and description of underlying dysphagia causes;
- SLT\textsuperscript{35}-management plan and execution during the identified distinct time points of the clinical study;
- Adverse Events (AEs) and device deficiencies
- Health economics: duration of ICU-stay/hospitalisation/ stay at different care giving units until 30 days FU or until hospital discharge, whatever comes first.

4. Patient Selection

4.1. Target Population
The target population encompass patients who suffer(ed) from a supratentorial stroke event (both haemorrhagic and ischemic stroke), who are successfully weaned from mechanical ventilation support but who are still tracheotomised to minimise the risks of penetration/aspiration and ceased from sedatives for a minimum period of 72 hours. Patients fulfilling these criteria are potential candidates to be included in the study and can be considered to obtain Informed Consent from:

![Figure 12: Illustration of the separate inclusion criteria required to make a patient eligible for study inclusion.](image)

Patients (or their legal representatives or close relatives) must be willing to sign per the local procedure a standard EC\textsuperscript{36}-approved Informed Consent Form explaining the conditions of study participation. Elected patients must be compliant with the inclusion and exclusion criteria before they can be considered enrolled in the study.

4.2. Inclusion Criteria
Patients are eligible for study participation if they:

\textsuperscript{32} DSRS = Dysphagia Severity Rating Scale
\textsuperscript{33} FOIS = Functional Oral Intake Scale
\textsuperscript{34} NIHSS = National Institutes of Health Stroke Scale
\textsuperscript{35} SLT = Speech and Language Therapist
\textsuperscript{36} EC = Ethics Committee
- Experienced a haemorrhagic or ischemic stroke; AND
- Experienced a supratentorial stroke; AND
- Were mechanically ventilated for a minimum of 48 hrs after the stroke event; AND
- Were subsequently tracheotomised for any reason; AND
- Were weaned from mechanical ventilation – thus being able to sustain own respiration; AND
- Are free from sedatives for a minimum of 3 days prior the first decannulation attempt; AND
- Were found ineligible for decannulation minimally 10 days after the stroke event; AND
- Were found ineligible for decannulation minimally 24 and maximally 72 hrs after the first decannulation attempt; AND
- Are over 18 years old; AND
- Give themselves (or have legal relatives/authorities representing themselves per the local practice to give) voluntary written informed consent.

And if they do not meet any of the exclusion criteria listed hereunder.

4.3. Exclusion Criteria

Patients are excluded from study participation if they;
- Have an undefined date of stroke causing the dysphagia (but not excluding stroke occurring during the night, for which the date will be the morning the stroke was observed); or
- Have a infratentorial stroke; or
- Suffer from pre-existing neurogenic dysphagia or a disease linked to that symptom (for example Parkinson Disorder); or
- Suffer from non-neurogenic dysphagia (e.g. cancer); or
- Suffer from neuromuscular disorders (e.g. myasthenia gravis, motor neuron disease); or
- Participate in any other study potentially influencing the outcome of PES, both medicinal or medical device product related and for which the patient signed a consent form for his/her study participation; or
- Receive or have received within one month prior to the intended PES treatment any other type of standard cranial or percutaneous electrical stimulation therapy to treat dysphagia; or
- Have a pacemaker or an implantable defibrillator; or
- Have a nasal anatomical deformity, nasal airway obstruction, have had oesophageal surgery or any other circumstance where placement of a standard NG feeding tube would be deemed unsafe; or
- Have a cardiac or respiratory condition that might render the insertion of the catheter into the throat unsafe; or
- Receive oxygen therapy whilst the oxygen supply is in place or in operation; or
- Are pregnant or nursing women; or
- Require emergency treatment, preventing appropriate conduct of the subject informed consent process; or
- Have a life expectancy less than the duration of the patient’s follow up period, i.e. less than three months.

4.4. Screening procedures

Patients fulfilling the above listed in- and exclusion criteria (with exception of the inability to be decannulated) will undergo screening procedures to demonstrate the stability of dysphagia. The screening procedures refer to the application of the FEES decannulation protocol to demonstrate dysphagia and the inability to decannulate the patient at that time:

17 The FEES decannulation protocol is to be followed to assess this criterion.
18 The FEES decannulation protocol is to be followed to assess this criterion.
Only patients with stable dysphagia are eligible for consideration to further participate in the study.

4.5. Sample size

Based on the study results of Dr Dziewas’ publication (Suntrup, et al., 2015), the sample size calculation assumes a minimum difference of 25% in decannulation success between groups, a two-sided type I error of 5% and a power of 80%. The corresponding fixed sample size to detect this difference is at least 102 patients. Sequential analysis will, on average, require less patients to include. A minimum of 80 patients will be enrolled in the study with a 1:1 randomisation scheme (see 10.4 Sample Size Determination) unless futility is demonstrated after 50 pts were enrolled.

Interim analyses will be performed to assess the level of significance of the difference in proportions of patients that can be decannulated in both study arms upon receipt of primary end-point data from pre-determined numbers of patients. Patient enrolment will cease once futility is statistically demonstrated or once PES treatment demonstrated superior outcome. If none of both can be demonstrated using the pre-determined sample sizes, patient enrolment will continue until one of the decision boundaries is crossed. The 90th percentile of the required number of patients is 126.

4.6. Patient Enrolment and Withdrawal Criteria

A signed (by the patient or a legal representative) Informed Consent Form, approved by the EC, is required prior to performing any study related procedure. Patients are not considered as enrolled in the study until a valid signature on the Patent Informed Consent form is obtained, stable dysphagia has been demonstrated and a catheter placement is confirmed by at least a first attempt to prepare the patient to receive the PES intervention by the Phagenyx Catheter insertion; patients not considered enrolled in the study may be replaced. Patients may withdraw from the investigation for any reason, at any time without their standard of care being affected. Patients that withdraw after receiving the PES-intervention are considered as being enrolled in the study; they will not be replaced upon voluntary withdrawal. All discontinuations will be documented along with the reason for withdrawal. Patient data collected up to the point of voluntary withdrawal will still be used.

4.7. Patient transfer from one treatment unit to another

A patient who is enrolled in the study in one study centre e.g. treatment unit and who is subsequently discharged to another centre/unit might get ‘lost-to-follow-up’. To limit the number of patients lost-to-follow-up, their follow-up is continued within the same centre/different unit under the responsibility of the original investigator. All discontinuations will be documented along with the reason for withdrawal.
### 4.8. Missing data and patients lost to follow up

Patients are considered enrolled in the study after signing the Informed Consent form and after having received subsequently the Phagenyx catheter. Then the patients get randomised to one of both study groups. The patients enrolled in the study are patients on the Intensive Care Unit (ICU) who are weaned from the mechanical ventilation but who are still under daily high intensive care supervision given their ongoing tracheotomy and impossibility to take oral food. The primary end-point is assessed prior the patient leaves this high intensive care unit. Missing data are expected to be rare. These can be the result of a patient death, a patient withdrawing from the study, an incomplete/incorrect delivery of the pharyngeal electrical stimulation or an erroneous assessment of the decannulation of the tracheal tube not according to the protocol specifications. Missing or erroneous assessments are considered conservatively as “failed treatments”. Given the minimal amount of clinical procedures to apply after patient randomisation till primary end-point analysis, it is unlikely that study data will not be obtained. The statistical analysis of the primary end-point is done on an Intention-to-Treat basis.

Secondary end-points are to be assessed likely in a lower care unit within the same or another hospital/rehabilitation center. In case a patient is discharged to a lower care unit, first the name of a contact person of that unit is requested. If a patient gets lost to follow up, it is requested to make up to three attempts to contact the supervising physician. The loss of a patient in follow up is expected to have little or no impact on the assessment of the end-points, at most at those assessed at the 3 month follow up period, which is the mRS.

### 4.9. Appropriate training of investigational centre

Each clinical centre will be appropriately trained on study procedures prior to first patient enrolment. However, not all investigators have the same level of experience with the PES-treatment or the decannulation protocol. To avoid inter-observer bias ‘technical & medical training’ is provided to those centres/investigators prior the start of the study. If device labelling is appropriate according local language requirements, such training can be provided using CE marked commercially available products. If this is not the case, use of ‘For Clinical Investigation Use Only’ labelled products can be allowed in up to three ‘run-in patients’. Inclusion criteria are limited to ‘tracheotomised patients suffering from neurogenic dysphagia’ and clinical procedures are limited to the FEES decannulation assessment prior and after PES-treatment following the regular labelling of the product. These ‘run-in patients’ do not create any clinical data that are part of the clinical data analysis and do not contribute any information for any of the study end-points.
5. Study Design

The overall study design can be graphically represented as:

![Graphical representation of the total study design](image)

**Figure 14: Graphical representation of the total study design, from screening of patients until entry into the follow-up period.**

After randomisation, in the time period of 24-72 hrs after the FIRST decannulation attempt, the patient might appear in stable condition. In such a situation, the above schedule would apply. If however the condition of the patient would deteriorate, or on the contrary would improve (i.e. recannulation might have been necessary or decannulation might have been possible), this would constitute a novel situation with the following consequences:

- If the patient would deteriorate after a successful FIRST decannulation assessment and the patient must be re-intubated again (or tracheal tube cuff reinflated), then the patient would not be directed to the follow-up sessions, but rather be subjected to a subsequent PES-treatment;
- If the patient’s condition would improve after a failing FIRST decannulation assessment allowing the patient to be decannulated, then obviously the patient would not be exposed to a subsequent PES-treatment but he/she would be directed into the follow up-sessions.

The primary end-point remains assessed on the primary (FIRST) attempt to decannulate the patient, irrespective of the patient’s status at 48 hrs. The indicated subsequent PES treatment is to be delivered within 24 hrs after the second assessment of ventilation status at 48 hrs; in this case a novel Phagenyx nasogastric catheter must be placed. This can be depicted as:
Figure 15: Potential cross-over depending on stability of patient’s ventilation status over the initial 48 hrs after the first decannulation attempt.

During the follow up period, clinical data (including the decannulation status of the patient) will be collected at following time points:

- For a patient who was successfully decannulated and appeared stable in the subsequent 48 hrs, 48 hrs after the FIRST decannulation assessment;
- For a patient who was unsuccessfully decannulated and appeared stable in the subsequent 48 hrs, the time of the SECOND decannulation assessment;
- For a patient who was successfully decannulated but deteriorated and requiring re-intubation in the subsequent 48hrs, the time of the SECOND decannulation assessment;
- For a patient who was unsuccessfully decannulated but improved condition allowing decannulation in the subsequent 48 hrs, 48 hrs after the FIRST decannulation assessment.

Figure 16: Identification of time points to assess secondary end-points during the follow up period. NB NIHSS is not collected at 90 FU.

The ‘start of the follow up period’ starts at:

- For a patient who was successfully decannulated and appeared stable in the subsequent 48 hrs, 48 hrs after the FIRST decannulation assessment;
- For a patient who was unsuccessfully decannulated and appeared stable in the subsequent 48 hrs, the time of the SECOND decannulation assessment;
- For a patient who was successfully decannulated but deteriorated and requiring re-intubation in the subsequent 48hrs, the time of the SECOND decannulation assessment;
- For a patient who was unsuccessfully decannulated but improved condition allowing decannulation in the subsequent 48 hrs, 48 hrs after the FIRST decannulation assessment.
Finally, at a 3-month time point after the last PES treatment, the DSRS and mRS will be re-assessed by means of a telephone call to the patient by a medical staff member.

5.1. Investigational Sites

The centres can be identified and might be located in Europe, Middle-East, Africa and Canada (EMEAC-region). Centres can participate after an assessment of appropriate ability to contribute to the study. This assessment will be documented. A maximum of 15 centres will be invited to participate in the study. A list of participating study centres is kept current at the sponsor’s site.

5.2. Identification and Selection

A list of investigational sites is available at the sponsor’s site. The selection criteria are based on experience and a willingness to adequately support the study execution and its progress. Criteria include:

- Centres that have participated in the STEPS or PHADER study;
- Centres that provide evidence of experience by having used the Phagenyx devices as part of their standard/routine medical care (as demonstrated by using the products in at least three patients);
- Centres that provide confirmation that a minimum of five patients will be enrolled in the PHAST TRAC over a maximum period of 12 months;
- Centres that are willing to comply with the requirements of the CIP such as, but not limited to, accurate and complete data collection on applied standard clinical processes using investigational product, obtaining Ethics Committee approval for the study, signing a CDA and CA39, complying with the requirements for patient enrolment and follow-up, able to perform FEES guided decannulations, knowing and applying ISO 14155 requirements, complying with monitoring and auditing requirements etc.
- Centres having a ‘clinical study team’ available that is able to support the conduct of the study as confirmed upfront by the investigator.

5.3. Ethics Committee Approval

Each centre must obtain formal Ethics Committee approval prior to the start of the study and thus prior to enrolment of any patient. This approval must be forwarded to the sponsor who will provide at that time, access to the electronic data capture system. Submission documents from the sponsor are provided and additional support to apply for Ethics Committee approval can be provided upon request. The documents that are delivered to the investigator for this purpose are:

- Clinical Investigational Plan (CIP),
- Investigator Brochure (IB) – Amendment 5,
- Participant Information Sheet and Informed Consent Form provided in local language (see Appendix A.2. for an English template version),
- Clinical Agreement specifying the proposed compensation for study execution (see Appendix A.3. for an explanation on the standard template document – a template provided and accepted by the local investigation site might be added to the dossier for Ethics Committee submission, if available),
- Evidence of clinical investigation insurance (see Appendix A.4.),
- The structure of the database and data collection priority (see Appendix A.5.) and draft case report forms (CRF), i.e. indication of data collection blocks, to be used to document the clinical information (see Appendix A.6.),
- The SLT management plan questionnaire (see Appendix A.7)

5.4. Competent Authority Approval

The Phagenyx device will always be applied according to its current labelling and in compliance with the CE-label. However, in some patients the PES treatment will be offered a second time, i.e. in those patients randomised to the “EARLY TREATMENT” group who failed to be decannulated at the first attempt. The application of the therapy a second time in the same patient is currently not covered under the CE-label (see The CE label and the status of investigational device).

39 CDA and CA: Confidentiality Disclosure Agreement and Clinical Agreement.
Therefor the catheter products will be offered under the ‘FOR CLINICAL TRIAL USE ONLY’ label and the Phagenyx device becomes an investigational device for the purpose of the second treatment application as part of this study.

The use of investigational devices requires also oversight National Competent Authority approval prior to the start of the study. The sponsor will look after the communication with the Competent Authority and look for its approval. Receipt of approval is condition to allow start up of the study, aside from other local regulatory requirements such as EC approval and Investigator Agreement sign off.

5.5. Site Activation

A clinical investigation centre can only start enrolling patients in the study after having obtained the required approvals and after the study staff have been appropriately trained on the different aspects of the CIP by the sponsor. Training records will be appropriately maintained both at the sponsor’s and investigational site. For those centres not having adequate experience in either the PES treatment or the decannulation protocol, there is an additional requirement to build up this experience in up to three ‘run-in patients’. The training requirement will be identified, documented and implemented prior a first patient can be enrolled in the study. A formal approval for site activation is provided by the sponsor to the investigator after which access to the electronic data collection system will be granted.

5.6. Patient Discharge to Another Treatment Unit or to Home

Patient treatment and data collection do not pose a problem as long as a patient is treated within one care giving centre; transfer from one unit to another within the same hospital can be documented while the patient remains in the clinical study under supervision of the original investigator.

When a patient is discharged to another care giving centre at a time point earlier than one month (30 days) following the first successful or second decannulation attempt, this will be considered a ‘Hospital Discharge’, after which the patient exists from the study; yet, it is documented to which care giving centre the patient is discharged.

At the 3 month FU period DRSR and mRS will be attempted to be assessed by phone call to patients residing at home or at another care given centre.
6. **Investigation Procedures**

This prospective, single (assessor)-blinded randomised controlled interventional clinical study will be executed in compliance with the ISO 14155 (version 2011) and must be approved by the local Ethics Committee prior to commencement in the investigational centre. The voluntary participation of each patient, after being well informed, must be documented in writing.

The following table gives an overview of the investigation procedures applied in this study.

<table>
<thead>
<tr>
<th>Screening</th>
<th>Enrolment</th>
<th>Randomisation</th>
<th>Every PES Treatment</th>
<th>Each decannulation assessment</th>
<th>Initial Follow Up (every 48 hrs ≤ 10 days)</th>
<th>Extended Follow Up (every 5 days ≤ 30 days/HDI)</th>
<th>Last Follow Up (3 months)</th>
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* Additionally, NIHSS and MRS are performed at Follow up day 2 and at hospital discharge/Day 30 (whichever occurs first)

**Table 2: Overview of the study procedures.**

6.1. **Pre-screening of patients**

Post-stroke patients, residing on the ICU and requiring mechanical ventilation support, are 24 hrs a day under medical supervision. Over a time period of minimally 10 days the progress of healing is continuously assessed and offers a potential to evaluate – as part of routine care application - if the patient could meet the inclusion criteria with respect to transfer from the oral intubation to a tracheotomy, the weaning from mechanical ventilation support, and the use of sedatives. (see 4.1 Target Population).

The investigator is requested to maintain an overview of potential patients for study inclusion. Only those, who demonstrate to be willing to participate on a voluntary basis, can be further considered for study enrolment.

6.2. **Informed Consent**

Every patient who is considered for enrolment in the study must be informed appropriately about the study intentions and their rights prior any further study related activity can be executed. The procedures, study objectives and assessment tools/timing should be explained by the investigator in layman’s terms. The sponsor provides a (Patient) Participant Information Sheet providing all the relevant information (see Appendix A.2 for a template that can be used for local translation<sup>40</sup>). All questions from the patient in relation to the study should be appropriately addressed. After having sufficient time to decide whether they wish to participate, the formal Informed Consent Form (provided by the sponsor to the investigator in the local language and to be approved

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<sup>40</sup> Local Ethics Committee’s might want to impose specific forms or specifications into the Information Sheet. If so, this will be documented and implemented.
by the local Ethics Committee prior use by the investigator – see Appendix A.2) will be signed by the patient, a
close relative or by his/her legally authorised representative, e.g. in case of unconscious patients or less
conscious patients, as specified by local regulations and practice.

Only patients with an appropriately signed Informed Consent Form can be considered for further study
participation. Upon signing the Informed Consent Form, the patient will be issued a unique study participation
number.

The investigator will retain the original signed Informed Consent Form in the study site file.

**Vulnerable populations (ISO 14155 § 4.6 and §4.7.3.3).**
Some of the patients, potentially eligible for study enrolment, might be less conscious post-stroke (ref to the
RASS of “-1”, see Appendix B.5). Their recovery might allow them to understand the physician’s explanations
of the study and might allow them to decide themselves and independently from anyone else to voluntarily
participate in the study. If however, the level of consciousness would be inadequate, local EC procedures to
enrol such patients in a study will apply. These might encompass the involvement of other legal representatives,
witnesses and/or special documentation/approval aspects. These aspects will be followed and documented as
part of the clinical trial. No emergency treatments can be considered as part of the clinical trial.

‘Run-in patients’
In tracheotomised neurogenic dysphagia patients the FEES decannulation protocol can be applied to assess the
readiness of the patient to be decannulated. This protocol is a medical alternative method to the standard
clinical assessment applied in the hospital. In these but also in some other non-tracheotomised neurogenic
dysphagia patients the standard PES treatment will be applied according to the available CE-label specifications.
In countries, were the required local language CE-label specifications are not completely implemented, the PES-
treatment can only be applied with a dedicated “For Clinical Investigation Use Only” labelled Phagenyx device.
The treatment of the first patients (‘run-in patients’) can only occur after appropriate delivery by the sponsor
of the technical training to the appropriate people of the centre. These patients will be appropriately informed
about the procedure and are required to sign off a simplified Patient Informed Consent Form (see Appendix
A.2).

6.3. **Patient Eligibility**
All inclusion and none of the exclusion criteria must be fulfilled in order to assign a patient as eligible for study
inclusion, otherwise the patient will not advance any further into this clinical investigation and will exit the
study.

If the patient fulfils all of the inclusion and none of the exclusion criteria, he/she is invited to participate in the
study and to sign the Informed Consent form.

6.4. **Assessment and Randomisation Prior to Treatment**

6.4.1. **Screening of patients: stability of dysphagia**
When a patient is eligible for study inclusion, the stability of dysphagia is first assessed. The FEES
decannulation protocol is applied and the inability to decannulate the patient should be concluded twice
over a time period of 24-72 hrs. If this is demonstrated, the patient can proceed to the next step in the
study; if the patient can be decannulated at any of such time points, the patient is considered a screen
failure and the patient exits the study. Adverse events, occurring over a period of 30 days after the screen
failure has been concluded, are documented, reviewed and reported per the regulatory requirements.

6.4.2. **Randomisation**
Upon entry into the study, a nasogastric Phagenyx catheter will be positioned. When a nasogastric feeding
tube which is in use at this time point, it needs to be replaced by the Phagenyx catheter. Upon successful
positioning of the catheter, a randomised group assignment will be obtained for the patient via an
independent IWRS that is provided by the sponsor. This IWRS access is limited and restricted to the

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41 IWRS = Interactive Web Response System.
medical staff member applying the PES-treatments. No-one else of the medical staff nor the patient him/herself should be informed about the randomisation assignment: all should remain blinded.

6.4.3. Baseline assessment upon entry in the study.
At study entry, a series of clinical data will be recorded which – all together – completes the baseline assessment. Baseline assessment should be completed within 24 hrs after the randomisation time point. The following baseline data will be collected:

Demographic data
- Age,
- sex,
- distance from the entrance to the nostrils to the ear lobes and the distance from the ear lobe to the laryngeal prominence (Adam’s apple).

Dysphagia causal event documentation
Timing of stroke event, location in the brain, severity of event... will be retrospectively documented based upon the patient’s chart information. To estimate the severity of the stroke, the NIH SS (Appendix B.1) and ‘modified Rankin scale’ (Appendix B.2) are applied.

Dysphagia assessment
The level of severity of dysphagia will be assessed by means of:
- Dysphagia Severity Rating Scale (DSRS);

The applicable questionnaire for DSRS is listed respectively in Appendix B.3

Feeding status assessment
Feeding status should be assessed by means of the Functional Oral Intake Scale – FOIS (Crary, Carnaby-Mann, & Gorher, 2005). The applicable questionnaire is listed in Appendix B.4. In addition, the use of a nasogastric feeding tube, PEG, radiologically inserted gastrostomy (RIG) or potentially the execution of other surgical interventions (e.g. to avoid dehydration) should be documented. Consistency of fluids, types of diets, amounts of food intake, duration of feeding sessions and need for supervision during feeding should also be documented.

Initially all patients will be orally fed, however this condition might improve and should be documented.

Ventilation status assessment
Type, purpose and duration of artificial ventilation and/or tracheostomy should be documented retrospectively. Timing of and reason for removal of ventilation tube should also be recorded.

SLT management
The SLT management plan assessment is similar to the one applied in the STEPS and PHADER studies, sponsored by Phagenesis. As such results can be more easily compared.

The clinical assessment used to create the SLT management plan may be an SLT bedside swallow assessment, an objective (instrumental) swallow assessment such as a clinical FEES, or another local procedure that must be specified. However, the type of clinical assessment used to inform the SLT management plan must remain consistent at all time points for each patient throughout the study, i.e. should a patient swallow be assessed by SLT bedside assessment at baseline, usual SLT practice for conducting the assessment would be followed and this would also need to be the swallow assessment used to inform the remainder of the patient’s SLT management plan at the subsequent periods of this investigation (up to one month maximum). To clarify, the swallow assessment type may vary between two different patients in the same hospital, but should not vary at different time points for the same patient during the study.

For reasons of consistency of management, it is also important that where a clinical led FEES local protocol is not used as standard, that the same named SLT conducts the patient swallow assessments and
determines the management plan for a patient throughout the study. To clarify, more than one SLT may take part in this investigation but each SLT must be assigned consistently to a single patient throughout.

The SLT assessments and management plan should be carried out at baseline (retrospective documentation, current planning), and the actuals documented at the time of PES treatment and at distinct time points throughout the one-month follow-up period. The SLT plan will be recorded in the study files and provided case report forms.

The applicable questions are listed in Appendix A.7

6.5. **PES-Treatment Procedure**

Patients randomised to the ‘EARLY TREATMENT’ arm of the study will receive within 24 hrs after randomisation the first of the 3-day session of the PES-treatment. During the following 2 days the second and third session of 10 min of electrical stimulation is delivered, preferably at the same time point during the day.

The applied treatment is the standard PES treatment as described in the ‘Instructions For Use’ provided with the Phagenyx products. In brief:

- Optimisation of the treatment parameters is conducted; sensory threshold and maximum tolerable limits are assessed by using the Phagenyx Base Station by which the difference is calculated between the tolerable stimulation intensity and the lower threshold and where stimulation levels are set at 75% of this difference above the lower threshold;

- The standard treatment regime is delivered; this is fixed to three consecutive days of 10 minutes of PES at 5 Hz at the determined stimulation level.

Typically, upon diagnosis of dysphagia, the SLT will help determine the best therapy for a given patient to recover the swallowing functionality. This might take place early or later after the dysphagia causing event. As part of this investigation, it is important to document the planned and actual SLT treatments (see above) in addition to the planned and actual PES treatment.

Timing of PES treatment vis-à-vis the dysphagia causing event will be an important parameter to document alongside the treatment outcome as assessed by means of DSRS and FOIS.

The Phagenyx Catheter is intended to be for single patient use. It is possible that during use, the catheter is accidentally or intentionally removed. Repositioning, but eventually use of a new catheter, might be appropriate. The number of catheters used, the timing of placement and duration of use should be recorded as part of this study, in addition to the technical settings of stimulation levels and effective application of the PES treatment.

**Single blinded approach of the clinical trial**

Patients randomised to the “LATE TREATMENT” arm of the study will need to be kept blinded for the PES-procedure prior to the first decannulation attempt. For this reason all patients have a nasogastric catheter inserted prior to randomisation and training will be locally implemented to help assure that only the person who applies the treatment is unblinded. The medical staff member applying the treatment should execute the same handling as if the patient was going to receive a true PES treatment, this is achieved by the use of a test box unit (also known as a black box). The patient’s catheter cable is not connected to the Base Station and thus will not deliver any electrical stimulation to the patient. Optimal procedures will be worked out on an investigational site basis. Patients receiving the PES treatment do feel the stimulation as the level is set above threshold, therefore the study cannot be called “double blinded”. Yet, as all medical staff except the person delivering the treatment, remain blinded - including the assessor (person assessing the decannulation) - one can call the study a single-blinded trial.

6.6. **Decannulation Attempt**

A standard protocol (FEES decannulation protocol) is followed to assess the possibility to decannulate the patient. The assessor of the decannulation needs to remain blinded to randomisation of the patient to one of the treatment arms in the study. The applied steps are the first 3 steps of those mentioned in the article of (Warnecke, et al., 2013) and can be represented as follows:
Figure 17: Graphic representation of decision flow to support the decannulation protocol.

A dedicated training session is provided to the blinded assessor applying this protocol for decannulation to help assure consistent applications across study centres. It remains at all times the responsibility of the “assessor” of the decannulation to decide based on medical grounds if the patient can be decannulated or not. This is a safety decision. His/her decision will be implemented subsequently, irrespective of the assessment made by the Independent Review Board that runs in parallel. The FEES decannulation protocol is applied during the screening and assessment procedures.

Patients enrolled in the study and who are able to be successfully decannulated, will enter the follow up period immediately; those who fail to be decannulated, will receive a subsequent PES-treatment. Once the determination is made using the FEES protocol above, whether or not the patient is suitable for decannulation, it is left to the discretion of the physician (assessor) to leave the cannula for another 24-48 hrs but deflate the cuff to bridge a time period of weaning from the tracheal tube, which allows easy and fast switch to re-install the airway protection/ventilation if necessary. The timing of effective removal of the tracheal tube will be recorded. Patients who appear unstable during the initial 48 hrs after the first decannulation assessment might require medical intervention to adjust appropriately to the patient’s condition. In these patients the schedule outlined above is applied (see section 8).

6.7. LATE or Second PES-Treatment and Second Decannulation Attempt

In a time period between 48 to 72 hrs patients who failed to be decannulated (see above) will receive PES-treatment: this will be the first PES-treatment offered to patients who were assigned to the “LATE TREATMENT” group, but it will be the second PES-treatment for those patients randomised to the “EARLY TREATMENT” group. For those patients who will receive their second PES-treatment a new nasogastric Phagenyx catheter will need to be inserted. The model numbers will be documented.

Within a time period of minimally 24 to maximally 72 hrs after the 3rd session of this PES-treatment has been delivered, a second attempt to decannulate the patient will be executed. This process is similar to the one applied earlier. Also in this case, once the conclusion is reached that the patient can be decannulated, it is left to the discretion of the physician (assessor) to leave the cannula for another 24-48 hrs but deflate the cuff to bridge a time period of weaning from the tracheal tube, which allows easy and fast switch to re-install the airway protection/ventilation if necessary. After this, all patients will enter into the follow up period.
6.8. Follow-up Evaluations during Follow Up Period

The follow-up period will start as indicated above:
- For those patients who are successfully decannulated: at the time of decannulation;
- For all other patients: at the time of the second attempt to decannulate.

Follow-Up Assessments

A follow up scheme has been presented above (see 5. Study Design). It is the intention to observe and document the progression of healing with respect to severity of stroke and swallowing. For this, a continuous documentation of SLT-management is essential and during the first 10 days of the follow up period, this will be done every 48 hrs (+ 12 hrs), and during the subsequent 20 days every 5 days (+ 24 hrs). At day 30, or when the patient is discharged to home or to another rehabilitation centre/ward, an FU-session is scheduled. Finally, at 3-months post PES treatment (interval 60-120 days) medical staff will attempt to contact the patient via telephone to assess the DSRS and mRS at that time.

The severity of swallowing is assessed through the DSRS and FOIS scores; the severity of stroke is assessed through the NIH SS (Appendix B.1) and ‘modified Rankin scores’ (Appendix B.2).

Similarly to the situation where a patient withdraws from this study, patients will receive optimal standard medical care during the follow-up period of this study. After the follow-up period has ended the patient may remain at the hospital where the study took place or they may be discharged to another caregiving centre where they will continue to receive optimal standard care which includes all available standard treatment upon discretion of their physician. This excludes the PES treatment of this study, which is considered off-label as the treatment will have previously been given as part of the study.

6.9. Training prior study start.

In case the centre has no experience with the PES treatment by using the commercially available Phagenyx products, it is required to gain a minimum experience on PES treatment in neurogenic dysphagia patients. The sponsor offers this opportunity as part of this clinical trial if the local language labelling would prevent from acquiring such experience by using commercially available products. For these ‘run-in patients’, the following procedures apply:

1. Inclusion & exclusion criteria. These are identical to those prescribed in the labelling of the CE-approved Phagenyx device.
2. Informed Consent. Patient must agree to participate on a voluntary basis, must receive the information given on the Information Sheet and must document this by signing the Patient Informed Consent Form.
3. In neurogenic dysphagic patients, complying with the prescribed in/exclusion criteria, only the PES treatment will be applied. In tracheotomised neurogenic dysphagic patients, also the FEES decannulation procedure will be applied. Pseudo-anonymised video recordings of the FEES will be reviewed by the Independent Review Board to advice the centre on possible improvements of the clinical assessment.
4. No other than PES treatment or FEES assessments are to be performed, no other clinical procedures are to be applied and the patients are for sure not exposed to the randomisation process.
5. Up to three ‘run-in patients’ can be done prior study enrolment starts.
6. The sponsor will document the training requirements and its completion, and will give formal approval to start enrolling patients into the study thereafter; if training requirements are not completely met than a max of three more ‘run-in patients’ can be exceptionally allowed. If training remains inadequate, study closure at the site is considered.
7. No specific clinical data prior, during or after the PES/FEES procedures are documented.

7. Adverse Events (AEs)

This clinical investigation is executed in accordance with the ISO 14155 (2011). The definitions of AEs listed in this standard apply to the study (see Appendix A.1).

All adverse events shall be documented in a timely manner throughout the clinical investigation. Reporting requirements to EC and Competent Authorities are restricted to:
- All serious adverse device effects (SADEs) observed in a patient enrolled in the study;
- All unexpected adverse device effects (UADEs) observed in a patient enrolled in the study;
- All device deficiencies observed during the clinical trial period;
- Any patient death, whatever the cause might be.
- All serious adverse events whether or not related to the medical device.

For clarity, general non-serious non-device related AEs are documented in the study and will be reported as part of the study report. From the regulatory reportable AEs, sufficient information will be obtained so as to permit 1) an adequate determination of the outcome of the event (i.e. whether the effect should be classified as an SAE) and; 2) an assessment of the causal relationship between the AE and the Phagenyx devices. The following information will be collected for those AEs that require regulatory reporting:

- Title of Event
- Start date of event
- Intensity of event
- Frequency
- Outcome
- Relationship to Device/Procedure
- Seriousness Criteria
- Action Taken

Instructions will be given to the local study team with respect to the contact person at Phagenesis in case of observation of SAEs, SADEs and/or unanticipated AEs (see also Appendix A.1).

AEs occurring in any patient, who signed the informed consent form, will need to be documented during a subsequent period of one month as part of this study, and whether or not the patient was ultimately enrolled in the study (e.g. a patient who signed the informed consent, but decided not to participate prior the nasogastric catheter is positioned). If the patient was enrolled in the study, AE’s will be documented during a one-month follow-up period.

All SAE’s, SADE’s or unanticipated AE’s will be reviewed by the Chairman of the Scientific Committee, the Coordinating Investigator and a representative of the sponsor to decide on complete documentation, device relatedness and impact on risk assessment. Recommendations to reduce the risk will be made and documented. Appropriate measures will be implemented by the sponsor as based on the recommendations received.

8. Data Management

8.1. Electronic data collection system
A validated electronic data collection system will collect the clinical data. Access to the system will be granted to the investigation site by the sponsor after appropriate training of involved staff members and after the site has obtained and provided the sponsor with the proof of the local Ethics Committee approval and of the signed Investigator Agreement.

8.2. Data Collection
The investigator is responsible to ensure that data collection is timely, is accurate and is as complete as possible. In addition, section of the eCRF related to the randomisation and PES treatment will only be accessible by the person delivering the PES treatment, while other medical staff will have access to the other portions of the eCRF. This is to assure blinding of the clinical data.

During the FEES assessment of the decannulation activities, video recordings are performed. These are anonymized. The video-recordings will be used by a central, blinded, Independent Review Board to assess the appropriateness of the decannulation procedure at a given time. To keep the blinding a) recordings remain anonymized, and b) all patients receive the nasogastric catheter required to deliver the PES treatment and which is visible on the video-recordings.
The decision on appropriateness of decannulation will be used in parallel of the decision made by the local investigator but only for purposes of data analysis not for medical reasons and/or to manage the patient situation.

The outcome of video-assessments from the Independent Review Board will be compared by the assigned clinical research organisation (CRO) with the outcome of the investigator: encountered discrepancies will determine the need for additional training on the procedure but without an effect on the previously established end-points.

8.4. Monitoring, Auditing and Inspection

A clinical monitoring plan, based on risk assessments and focussed on the adverse device related events, on the primary and on the secondary objectives, is in place at the sponsor’s site. This will be executed during the conduct of the study. At regular time intervals, monitoring will be executed either via electronic review of data completion, via electronic automated or manual queries, or at the site via source document verification during personal site visits.

Site visits will be scheduled at the time of site initiation, in the time period between the first and fifth patient enrolment and at study closure. Additional site visits will be planned based upon a risk assessment approach. Monitoring will be done by qualified people as assigned by the sponsor.

The sponsor might plan to also execute a number of audits in selected centres to further help assure complete and accurate data collection, but also to help assure adherence to regulatory requirements.

Inspections can be executed unexpectedly by regulatory authorities at any of the participating study centres. In such an event, the investigator will explicitly allow these authorities to have access to the (patient) source data to allow review of the clinical study conduct per the current CIP. The patient Informed Consent Form will also refer to this access modality and the originals will be kept at hand during the total duration of the clinical trial.

8.5. Data Review, Cleaning and Queries

Data will be reviewed by either sponsor’s personnel or by assigned people from an appointed CRO. Based on the review of the mandatory clinical data, queries will be generated to further request any missing information. This will help to complete (clean) the database prior to any major analysis being performed.

Especially for the primary end-point and in view of the sequential analysis a fast transfer of minimal essential clinical data is required in order not to hamper swift statistical assessment of the level of significance of the difference in proportions of the populations that can be successfully decannulated between the ‘EARLY’ and ‘LATE TREATMENT’ groups.

To assure adequate data review, to control for appropriate delivery of PES treatment and to help assure complete data sets, the sponsor’s and the CRO’s personnel is blinded to the treatment data; only a dedicated ‘unblinded CRA’ has access to the eCRF with the ‘treatment data’.

8.6. Data Retention

Clinical data collected in this investigation are for the purpose to obtain regulatory approval to extend the labelling of the Phagenyx device towards allowing a second application of the standard PES treatment, not to bring the product to market as the device is granted already with CE-label to treat patients with neurogenic dysphagia.

In that perspective clinical data should be retained at the site and at the sponsor’s premises for a minimum of five (5) years after completion of the clinical study; prior this date, no study related clinical data may be destroyed without prior written approval from the sponsor. A formal indication of the study closure date will be provided by the sponsor at the end of the investigation. A reference is made to §7.4 of the ISO 14155, but also to Code of Federal Regulation, § 21CFR312.57 and 312.62 where a time period of 2 yrs after approval of the marketing application is specified. Retaining the study data for 5 yrs is deemed more than sufficient to comply with the regulatory requirements.
In case the investigator moves/retires, or otherwise leaves their post, they will provide Phagenesis with the name and address of the person assuming responsibility for records relating to this clinical investigation.

9. **Suspension, Termination and Close-out of Clinical Investigation**

Phagenesis may suspend or prematurely terminate either the clinical investigation in an individual investigation site or the entire clinical investigation for which the reasons will be documented. Reasons for suspension or premature termination at an investigation site may include incidences where monitoring or auditing identifies serious or repeated deviations from the protocol on the part of an investigator, but also unexpected low enrolment rates jeopardising the proper conduct of the study within the foreseen time windows. Phagenesis will ensure that the Ethics Committee (and if applicable, regulatory agency) is notified of any suspension or early termination of the clinical investigation, it will also notify all other principal investigators in the event that the suspension or termination was due to safety issues.

A principal investigator, Ethics Committee, or regulatory authority may suspend or prematurely terminate participation in the clinical investigation at the investigation sites for which they are responsible.

If suspicion of an unacceptable risk to patients arises during the clinical investigation, or when so instructed by the Ethics Committee or regulatory authorities, Phagenesis will suspend the clinical investigation while the associated risk is assessed. The sponsor will terminate the clinical investigation if an unacceptable risk is confirmed. Should the risk not be confirmed Phagenesis will, in accordance with regulations, supply relevant persons with justification and data supporting the decision to resume the clinical investigation.

Routine close-out procedures will be conducted ensuring that the Investigator’s records are complete, all documents needed for the sponsor files are retrieved, and previously identified issues have been resolved.

Enrolment of patients in the study might be suspended when the sequential data analysis demonstrates a statistical significant level of difference in proportions between study groups, or alternatively, when the analysis demonstrates that the difference is too small to reach ever a significant level. Such a decision is to made by the Scientific Committee.

Enrolment of patients (with a given indication) in a single centre might be suspended if the centre contributes 50% of the target patients in the study.

10. **Statistics and Data Analysis**

10.1. **Randomisation and stratification**

Patients will be randomised in blocks of 4 within centres. The statistical analysis will be stratified according to centre.

10.2. **Data Analysis and Presentation**

Clinical data from all, except the ‘run-in patients’, will be used for the data analysis and the reporting. Normally distributed continuous outcome variables will be summarized by their mean and s.d.; categorical variables will be summarized as proportions.

10.3. **Statistical Analysis of Primary End-point**

**Sequential monitoring: general aspects**

Interim analyses or group sequential monitoring of cumulative patient data will be performed on the primary outcome data. The main reason for interim analyses on efficacy is to determine whether EARLY PES treatment is significantly better than LATE treatment or whether there is no significant difference between the two. In both cases, when enough evidence has been gathered, the trial can be stopped early and patients can be offered the best treatment available (Whitehead, 1997 (rev 2nd Ed)).
Sequential analysis in PHAST TRAC and hypothesis testing.

For the control [LATE] treatment, the probability of successful decannulation is estimated as 20% [published data of Dr Dziewas, (Suntrup, et al., 2015)]. For the EARLY PES treatment, a probability of at least 45% is expected for successful decannulation: this is a 25% improvement over the control group. Based on these probabilities, a two-sided type I error of 0.05 and a power of 80%, monitoring boundaries for a triangular test can be specified (see Figure 9). Two test statistics, Z and V, are calculated after N= 50, 70 and $N_{\text{required}}$. Test statistic V stands for the cumulative amount of information and is a function of the number of patients; test statistic Z is equal to the difference between the observed and the expected (for a proportion successes of 0.20) number of successful decannulations for the EARLY treatment. When the (Z,V)-statistic based on the cumulative data crosses the upper red boundary, the null hypothesis of no difference will be rejected. When the lower dashed boundary is crossed, the null hypothesis will be accepted. PEST 4 software (PEST 4, 2000) will be used for implementation of the sequential analysis.

![Figure 18: Illustration of upper and lower boundaries of acceptance levels.](image)

10.4. Sample Size Determination and Study Stopping Rules

The fixed sample size to detect a difference of at least 25% is at least 102 patients, excl. drop-outs. With a sequential analysis, on average 71 to 73 patients will be needed to detect this or no difference, but depending on the true difference less or more observations will be required with a 90th percentile of 126 patients to be enrolled. The outlined interim analyses at N= 50, 70 and $N_{\text{required}}$ allow:

- To stop the study in case of futility (difference between groups very unlikely to be less than 25%);
- To stop the study in case of superiority of PES treatment (a significant difference between groups);
- To continue the study and enrol more patients until one of the decision boundaries is crossed after additional sequential analyses.

- During an interim analysis patient enrolment continues in the study; as a result e.g. more than 70 patients are likely to be enrolled by the time of completion of the second analysis. In the very unlikely event that no boundaries are crossed at $N_{\text{required}}$, additional analyses will be performed every 10th patient thereafter until either the upper or the lower boundary is crossed. As such there is no risk that the study remains indecisive due to a small sample size that is too small.

10.5. Implementation of sequential analysis in PHAST TRAC

Each time, the data of the primary end-point of a given group of patients has been obtained, the total cumulative data will be transferred by the CRO to the statistician for a next analysis. The statistician will advise the members of the Scientific Committee (see 11. Reports and Publications) in a blinded manner on continuing or stopping the study.

When the study is stopped, the estimates of the difference in proportion successful decannulation and of its 95%-confidence interval will be adjusted for the cumulative monitoring (PEST 4, 2000) (Whitehead, 1997 (rev 2nd Ed)). This way the true difference between group proportions is obtained to address the primary end-point of the study. The successful demonstration of the postulated hypothesis is based on the un-adjusted results.

$N_{\text{required}} = \text{estimated sample size based on extrapolation of results obtained at N50 and N70 to reach either the upper red or lower blue boundary.}$
The statistical analysis will take place conform the intention-to-treat principle.

A Statistical Analysis Plan is developed prior first data analysis. This plan will be executed subsequently. Study results will be all reported in the final study report.

11. Reports and Publications

Scientific Committee

A Scientific Committee is established, chaired by Professor P. Bath, University Nottingham, and assisted by the Coordinating Investigator, Prof. R. Dziewas, Münster. Other investigators might be appointed to participate in the Scientific Committee as needed and as appropriate. This committee will address the intended data collection as specified in this study. This group supervises the data analysis and primarily decides on the blinded outcome of interim data analyses to conclude patient enrolment. Data unblinding occurs after conclusion of patient enrolment. The members of the committee also agree on the publication policy and will inform other investigators accordingly. Dr. I. van der Tweel (UMC Utrecht, Department of Biostatistics & Research Support, Julius Centre, The Netherlands) is not a member but an advisor of the Scientific Committee and supervises the statistical analyses. She published on the nature of sequential analysis (van der Tweel & Roes, 2013).

A list of the other Scientific Committee members (investigators) is available at the sponsor’s site, no employee of the sponsor, nor one of the assigned CRO, is a member of the Scientific Committee to avoid any bias.

11.1. Interim Report

No formal interim reports are foreseen other than those describing the progress of the study (enrolment, data collection, monitoring etc.), unless identified ad-hoc by the Scientific Committee.

11.2. Final Report

A final report will be created per the ISO 14155 guidelines. This final report will be reviewed by the Scientific Committee-members and approved by all investigators.

11.3. Publications and Publication Policy

A publication policy will be created by the members of the Scientific Committee, defining the content and the timing of specific publications addressing the relevant symptoms, diagnosis, therapy and treatment outcome in the total patient population and in the ‘EARLY’ and ‘LATE TREATMENT’ subgroup of patients defined in this study. Authorship rules will also be defined in that policy and will consider the numerical and scientific contribution to the study (e.g. enrolment rates, timing of data collection, compliance to data collection requirements etc.). No publications other than those specified and approved by the members of the Scientific Committee are allowed to be published or presented in any kind during the conduct of the clinical study until the final report is approved and the investigation formally closed. Each investigator will be informed about the policy prior first enrolment of a patient in the study at the investigator’s site and agrees formally with this approach by signing the Investigator Agreement.

12. Ethical Considerations

12.1. Declaration of Helsinki

The study is executed in line with the relevant articles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in 1964 and as revised repeatedly and lately in Seoul (2008).

12.2. Ethics Committee Approval

At a minimum the local Ethics Committee must formally approve the conduct of the study in the investigator’s centre, unless local regulations dictate a different procedure. For this, the appropriate documents must be submitted and the investigator must provide the sponsor with a signed and dated letter granting approval from the local Ethic Committee.

12.3. Informed Consent and Patient Information

Each patient will be appropriately informed about the study purpose and their voluntary participation will be documented in writing by signing the provided Informed Consent Form (see Appendix A.2). This document also
states that all clinical data collected from a patient will be remain confidential, irrespective of the fact that the sponsor, delegates of the sponsor, and/or regulatory authority personnel can have direct access to the source data. It will also specify the duration of the clinical data retention, incl. the video-recordings.

12.4. **Patient compensation for study participation**
No compensation is provided to the patients for study participation. Travel costs, if any, are reimbursed via the investigator’s study centre upon provision of the receipts.

12.5. **Subject Insurance – Indemnity / Patient Pay-Outs**
The sponsor recognises its liability in law to compensate for any injury sustained by a patient participating in this clinical investigation when the injury directly evolves from the malfunctioning of the medical device (device deficiency) when correctly applied and used per the Instructions For Use or from the application of any study related procedure, more specifically from the application of the second PES-treatment in certain patients, which procedure establishes the only difference from the already CE-labeled application for which product liability coverage is offered. The insurance will comply with local and national guidelines.

13. **Good Clinical Practice (GCP) Compliance**

13.1. **Professional Conduct of the Clinical Study**
Only well identified study centres can participate in the study. The centre selection criteria are specified to assure that appropriate medical, technical and clinical investigator expertise is present prior approval of study participation. Prior the start of the study, the investigator will sign the CIP demonstrating the willingness to conduct the study according the specifications of the CIP.

13.2. **Training Provided by Sponsor**
Specific technical training to use the Phagenyx devices is not part of this study, given that the device is CE-marked and that availability of technical expertise is a requirement to participate in the study. Training is however provided by the sponsor to the investigator on the GCP aspects, on the CIP and as outlined in the ISO 14155.

13.3. **ISO 14155 (version 2011)**
The ISO 14155 describes the good clinical practices for conduct of clinical investigations in humans with medical devices. The study is set-up and is implemented according to these guidelines. Each centre will be trained on or should demonstrate acquaintance on the relevant elements of this standard prior first enrolment of a patient.

14. **References**


15. Appendices:
Series A appendices are study specific, Series B appendices are general/standard in nature and can be used for multiple studies.

**Series A: Study Specific Documents.**

A.1. Adverse event definition and handling
A.2. Patient Information Sheet and Informed Consent Form
A.3. Template Investigator Agreement
A.4. Insurance statement
A.5. Structure of database
A.6. Draft CRFs
A.7. Speech and Language Therapy management plan

**Series B: General Documents (Questionnaires).**

B.1 National Institute of Health Stroke Scale (NIHSS)
B.2 Modified Rankin Scale
B.3 Dysphagia Severity Ranking Scale (DSRS)
B.4 Functional Oral Intake Score (FOIS)
B.5 Richmond Agitation and Sedation Scale

If there are any non-substantial changes to any of these appendices or required changes by a local authority (e.g. Ethics Committee or Research Office), this would not require a revision of the CIP.
### A.1: Adverse Event (AE) definitions and handling

**Definitions**

<table>
<thead>
<tr>
<th>ADE</th>
<th>Adverse Device Effect: AE related to the use of an investigational medical device. This includes:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A. any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.</td>
</tr>
<tr>
<td></td>
<td>B. any event that is a result of a use error or intentional misuse.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE</th>
<th>Adverse Event: Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in patients, users or other persons whether or not related to the investigational medical device.</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>This includes:</td>
</tr>
<tr>
<td></td>
<td>A. events related to the investigational device or the comparator.</td>
</tr>
<tr>
<td></td>
<td>B. events related to the procedures involved (any procedure in the clinical investigation plan).</td>
</tr>
<tr>
<td></td>
<td>C. events related to the investigational medical device by users.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>SAE</th>
<th>Serious Adverse Event: AE that:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A. led to or may have led to a death (directly or indirectly),</td>
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<tr>
<td></td>
<td>B. led to a serious deterioration in health of the patient, user or any other person, whether or not related to the medical device, that either:</td>
</tr>
<tr>
<td></td>
<td>1. resulted in a life-threatening illness or injury, or</td>
</tr>
<tr>
<td></td>
<td>2. resulted in a permanent impairment of a body structure or a body function, or</td>
</tr>
<tr>
<td></td>
<td>3. required in-patient hospitalization or prolongation of existing hospitalization, or</td>
</tr>
<tr>
<td></td>
<td>4. resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.</td>
</tr>
</tbody>
</table>

| SADE | Serious Adverse Device Effect: ADE that has resulted in any of the consequences characteristic of a SAE. |

| USADE | Unanticipated serious adverse device effect: AE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. |

<table>
<thead>
<tr>
<th>Anticipated serious adverse device effects</th>
<th>An AE that is listed as a potential issue in the Risk Analysis of the company.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The identified anticipated SADES are listed in this Appendix.</td>
</tr>
</tbody>
</table>

| Device Deficiency | An inadequacy of the medical device with respect to its identity, quality, durability, reliability, safety or performance. This includes malfunctions, use errors, and inadequate labelling. Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence: |
a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate,
shall be reported to the Ethics Committee.

Handling
During the period of the investigation the handling of adverse events will occur per the guidelines given by the European Commission on clinical investigations\(^{43}\). As such new findings/updates in relation to already reported events are considered reportable events.

All relevant AE’s, SAEs, SADEs, unanticipated adverse effects, device deficiencies (previously called ‘incidents’) and new findings/updates in relation to already reported events must be reported to the sponsor. In case of death or SAE’s requiring urgent medical interventions: by telephone within 24 hours of the investigator becoming aware of the SAE.

The investigator should institute appropriate therapeutic and follow-up measures in accordance with good medical practice but should notify the monitor of such actions and record them in the patient’s case report form. Each telephone reported event must be documented in writing to Phagenesis Limited within three (3) working days of the event.

Safety reporting to Ethics Committees, responsibilities and timelines are detailed hereunder. Where national law differs from this CIP, the national law for that country will take precedence.

All SAEs, SADEs and/or UADEs will be followed-up until they are resolved or for 30 days after the patient’s participation in the clinical investigation ends.

<table>
<thead>
<tr>
<th>AE’s</th>
<th>Who</th>
<th>When</th>
<th>How</th>
<th>To Whom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator</td>
<td>As soon as possible</td>
<td>Respective CRF form</td>
<td>Sponsor</td>
<td></td>
</tr>
<tr>
<td>SAE</td>
<td>Investigator (where applicable)</td>
<td>Within 3 days of the investigator becoming aware of the event</td>
<td>AE report form</td>
<td>(Main) EC for the investigation</td>
</tr>
<tr>
<td></td>
<td>Sponsor</td>
<td>Within 2 days of sponsor becoming aware of the event</td>
<td></td>
<td>CA of country</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Within 30 days of sponsor becoming aware of the event.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device deficiency</td>
<td>Investigator</td>
<td>Without undue delay</td>
<td>AE report form</td>
<td>(Main) EC for the investigation</td>
</tr>
<tr>
<td></td>
<td>Sponsor</td>
<td>Within 7 days of sponsor becoming aware of the event</td>
<td></td>
<td>CA of country</td>
</tr>
<tr>
<td>Urgent safety measures</td>
<td>Investigator</td>
<td>(i) immediately (ii) within 3 days</td>
<td>(i) by telephone, followed in writing (ii) notice in writing setting out reasons for the urgent safety measures and the plan for further action</td>
<td>Sponsor</td>
</tr>
<tr>
<td></td>
<td>Sponsor</td>
<td>Within 2 days of sponsor becoming aware of the event</td>
<td></td>
<td>(Main) EC for the investigation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CA of country</td>
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</tbody>
</table>

\(^{43}\) [Link](http://ec.europa.eu/health/medical-devices/files/meddev/2_7_3_en.pdf)
New finding: update of already reported event

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Within 7 days of sponsor becoming aware of the event</th>
<th>AE report form</th>
<th>(Main) EC for the investigation</th>
</tr>
</thead>
</table>

### BfArM Reporting Requirements

<table>
<thead>
<tr>
<th>Condition for reporting to BfArM</th>
<th>Country of occurrence</th>
<th>Timeline for reporting to BfArM</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>A causal relationship between the SAE and the investigational medical device, a comparator device, diagnostic or therapeutic procedures performed as part of the clinical trial or other conditions of the trial conduct cannot be excluded</td>
<td>Germany</td>
<td>Immediately</td>
<td>German SAE Report Form for single reports</td>
</tr>
<tr>
<td>All other countries where the clinical trial is performed</td>
<td>Immediately</td>
<td>MEDDEV 2.7.3 Summary Table</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition for reporting to BfArM</th>
<th>Country of occurrence</th>
<th>Timeline for reporting to BfArM</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>A causal relationship between the SAE and the investigational medical device, a comparator device, diagnostic or therapeutic procedures performed as part of the clinical trial or other conditions of the trial conduct can be excluded</td>
<td>Germany</td>
<td>Quarterly</td>
<td>All SAEs that occurred outside of Germany and quarterly listings of SAEs that occurred in Germany respectively shall be documented using the same excel file in a cumulative manner using separate excel sheets</td>
</tr>
<tr>
<td>All other countries where the clinical trial is performed</td>
<td>Quarterly</td>
<td>All SAEs that occurred outside Germany to be documented on one sheet (sheet 1), irrespective of immediate or quarterly reports.</td>
<td></td>
</tr>
<tr>
<td>Quarterly listings of SAEs that occurred in Germany to be included on a separate sheet (sheet 2).</td>
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</table>

**NB** Independent of the criteria mentioned in the table, the sponsor must report all SAEs occurring in Germany to the competent authorities of other contractual states of the Agreement on the European Economic Area immediately if the clinical trial is also performed in those countries.
**Anticipated Adverse Device Effects**

Based on the Investigator Brochure, where the details of an extensive literature search are listed and based on the Instructions for Use, the following warnings and/or contra-indications are mentioned that potentially could lead to AEs which can be considered anticipated:

- difficulty or inability to position the Phagenyx Catheter in patients with anatomical abnormalities that preclude passage of the catheter (or any other feeding tube);

- as the use of the Phagenyx Catheter is contra-indicated to be used in patients with oral intubation\(^44\), history of oesophageal perforation, stricture or pouch, the use of the device is those patients can lead to complications;

- use of the Phagenyx Catheter should be avoided in patients with cardiac or respiratory condition that might render the insertion of a catheter into the throat unsafe;

- use of the Phagenyx device should be avoided in patients implanted with a pacemaker or a cardioverter defibrillator as interference between electrical stimulation and dysfunction of the device might result;

- when the patient is to receive an magnetic resonance imaging (MRI) scan, the Phagenyx Catheter should not be left in place to prevent generation of electrical current by the magnetic field in the metal leads;

- pharyngeal electrical stimulation should not be carried out in patients receiving oxygen therapy whilst the supply is in place or in operation and be in contact with the electrodes;

- pharyngeal electrical stimulation should not be carried out in female patients who are pregnant or who are nursing;

- when applying PES, distortions or anomalies in electrical encephalogram (EEG) or in electrocardiogram (ECG) recordings might occur when recorded in parallel to the PES by the applied current;  

- the Base Station should be used as indicated, no other devices should at any time be connected to the Base Station than Phagenesis approved USB sticks or catheters;

- damage to the packaging might lead to unsterile catheter products – in such a case the catheter should not be used;

- the catheter is indicated for single patient use – using the product in multiple patients is contraindicated and must be avoided;

- use of the catheter is indicated for a single patient for up to 30 days – thereafter it must be removed and disposed of in clinical waste;

- the electrodes of the catheter should never be handled/touched when the catheter is connected to Base Station – connection to the Base Station should only be done after the catheter has been inserted into the patient;

- the catheter should be checked before and after feeding to ensure there are no leaks;

- if changes in performance of the catheter are observed, it should not be used further;

- connection of the catheter to enteral feeding systems can occur but only via a stepped enteral connector and to enteral feeding sets and/or feeding pumps designed to deliver nutrition via an 8Fr feeding tube.

\(^{44}\) The wording “oral intubation” is intended to indicate those conditions where the presence of equipment for mechanical ventilation would prevent the use of Phagenyx Catheter and circumstances where electrical stimulation would occur in spaces with high oxygen concentration. Patients receiving continuous oxygen treatment that can have the oxygen treatment temporarily stopped and equipment removed during PES-treatment can still be included in the study. It is the treating physician’s responsibility to ensure that the continuous oxygen is stopped and equipment is removed prior to starting the PES-treatment.
No additional device related AEs were currently observed in the STEPS study.

In case of emergency, the following contact details should be used:

Name: Jaak Minten, CRO representative
Telephone number : +32 (0) 475-923-149

In addition, the study is executed under the supervision of a physician, who also co-reviews each SAE and ADE. The outcome of each review is documented in the files of the clinical study at Phagenesis.
A.2: Patient Information Sheet

Benefit of PHaryngeal electrical STimulation for early de-cannulation in TRACheotomised stroke patients with neurogenic dysphagia: a prospective randomised single-blinded interventional study (PHAST-TRAC study)

Why you have been chosen for this study

You have been diagnosed with or are suffering from ‘neurogenic dysphagia’ which makes your swallowing difficult. A variety of conditions such as Stroke, in combination with (artificial) mechanical ventilation or not, can lead to difficult swallowing. A common problem caused by difficult swallowing is that food or drinks may go down the wrong way and end up in your lungs. This can cause serious chest infections. All this might make your recovery more cumbersome and often alternative feeding methods are proposed as a therapy. Your oral ventilation tube has also been replaced with a direct access ventilation tube (known as a tracheotomy tube) to prevent complication linked with swallowing difficulties. To treat the symptoms of difficult swallowing, special training or swallowing techniques might have been explained to you by your care team. Unfortunately, current treatment methods are not always effective and some patients end up needing long-term feeding via a tube inserted in the nose or surgically placed in their stomach.

Description of the treatment device

There are alternative treatments. One of these is called ‘Pharyngeal Electrical Stimulation’ (PES), which is a simple and harmless technique for treating difficult swallowing. PES treatment is delivered by a medical device that is commercially available and that can be used by your care team on a routine basis at your bedside. The device is made up of a control unit and a small tube placed through your nose down your throat and into your stomach. It is very similar to the type of tube used to temporarily feed people with swallowing difficulty. It can also be used to give you medicine and liquids if you need them. The tube is this thick. (3mm) and is used to stimulate nerves in your throat (pharynx) for 10 minutes each day for 3 days in a row to improve your swallowing function. The intensity of the stimulation is adjusted on each day so that it is at the right level for you.

A minimum of 50 patients will take part in the study. Depending on the variability of observation made between different patients the maximum number of patients might vary; it is expected to be around 80, but might be as high 140 in case of (unexpected) very large variability and inconsistency. Your participation may last up to 6 weeks but every patient that takes part in the study will receive the same PES treatment. Some patients will receive the treatment sooner than others and some patients will receive the treatment twice. Apart from when you receive the PES treatment, you will otherwise be treated as recommended by your care team which is the standard practice when using this treatment.

Previous scientific research on this treatment

Scientific research on PES shows that it can help improve swallowing function. This previous research has mainly been performed in stroke patients. This study is designed to help understand the potential benefit (or lack of benefit) PES treatment can have in stroke patients who were mechanically ventilated and have a tracheotomy tube in place for swallowing difficulties. During previous studies, no new or unanticipated adverse events were observed; as such, the treatment can be described as safe.

Purpose of this clinical study

The purpose of this clinical study is to assess if the PES treatment can help stroke patients with a tracheotomy tube in place, have the tube removed earlier as compared to patients who do not receive the treatment at the same time point. The study will involve observing how the devices work and documenting the outcome of the treatment. Apart from the PES treatment, no additional specific medical interventions are required by this clinical study and you will continue to receive standard care as recommended by your care team.

As such, there is actually no “experimental” part of this study other than that some patients will receive the standard PES treatment two times. The intent is to collect clinical data related to the PES treatment and its effects on the ability to
remove your tracheotomy tube, but also on the improvement of your swallowing function and severity of stroke. Although the standard PES treatment is “safe”, it is not impossible that an unanticipated risk may occur during the clinical study, but the chances of this happening are small and we have taken steps to make sure it is as safe as possible for you to take part.

**What is involved?**

Before you participate in this study, your doctor will carefully check if you are able to take part and if you might benefit from the PES-treatment. For this you will be asked a series of questions and some medical checks will be made. There are certain conditions that make it unsafe for you to take part such as having a pacemaker, being pregnant or requiring continuous oxygen therapy. Your care team will check this and let you know if you can take part.

The ability to remove your tracheotomy tube will be assessed several times by your doctor using a standard tube removal camera test (endoscope). For the purposes of this study only, some extra documentation of video-recordings will be made during these camera tests. These recordings will be anonymised which means they will not contain any information that can personally identify you.

The severity of your swallowing difficulties will be measured by standard medical tests which would be routinely performed by your care team. They will explain these tests to you. Some of the tests will involve specific instruments, but the majority of observations will be made through the use of questionnaires completed either by you, the nurse or the doctor. This information or ‘data’ will be documented before, during and after the PES-treatment for up to a maximum time period of one month. These data can be collected while you are in the hospital or in a rehabilitation home. It is planned to publish the results of the study in scientific journals and to talk about it at scientific meetings. This will be done without affecting the confidential nature of your personal data, however it requires the storage of your clinical data (including the anonymised video-recordings) for up to a maximum period of 5 years after the end of the study.

**Assignment to the study groups.** Patients participating in this study, will be assigned (a process called ‘randomisation’) either to the “EARLY” or the “LATE” treatment group. The time difference between groups is 4-6 days only. You will have an equal chance of being assigned to either group, but all patients participating in the study will receive the same standard PES treatment. Once the standard PES treatments have finished, your doctor will attempt to remove the tracheotomy tube. If the tube cannot be removed successfully, you will given another standard period of PES treatment after which your doctor will retry to remove the tracheotomy tube a few days later.

**Blinding of study activities.** In order not to influence yourself nor the doctor who is going to perform the tube removal tests, you and all other members of the medical staff (except one person) will not be told about when the PES treatment is delivered to you. Only one person will know when and how the PES treatment was delivered. This standard study process is called “blinding”.

**Centre experience with PES treatments.** The Phagenyx products are commercially available, but it is possible that the center is not fully familiar with the technical or medical aspects of the product. As part of the study, adequate training is provided by the sponsor both on the technical and medical procedures. To avoid variation of clinical outcome, which might depend on the standardized execution of the treatment, the first patients enrolled in the study will not undergo randomization, but only participate in the initial screening, PES treatment and decannulation procedures. No clinical data will be collected in these patients, and no other study requirements apply.

**Your study participation**

Taking part in this study is completely voluntary and you will continue to receive the standard treatments for swallowing difficulty even if you do not participate. In the case that you decide not to take part you will still receive the best possible
treatment which might still include the same standard PES treatment. If you decide to participate, you will have to sign a ‘Patient Informed Consent Form’.

All the clinical data that is collected from you during the study will remain strictly confidential. In order to use and analyse your data, we will need to access your clinical records. Only people involved with the study, such as the clinical staff, those assigned by the study sponsor, and potentially some from government regulatory authorities (Europe, U.S.A., Asia) who collect information to check that the study is being run properly will have access to your data. The data collected will be maintained for a long time (maximally 5 years after study closure), but will remain strictly confidential and none of your personal data will be disclosed to inappropriate parties. By taking part in the study, and by signing the Informed Consent Form, you grant these persons/organisations access to your personal medical records and data. Please note that all your medical records are kept strictly confidential and that outside the hospital, only anonymised data is used and stored securely: this means your information will be labelled with a code/number and no information with your name or other identifiable information will leave the hospital.

You will be informed if any new information becomes available through the conduct of this study, or if the study concept changes by which your study participation could be jeopardised.

There are no expenses or compensation for taking part in this study. You will however be insured by the sponsor in the event of an injury arising from taking part in this clinical investigation. For any injury caused by taking part in this study, we will provide compensation in accordance with the local, national guidelines, e.g. those of the Association of the British Healthcare Industry (ABHI). We will pay compensation where the injury resulted from i) device being tested or administered as part of the research or ii) any test or procedure you received as part of the study.

Compensation will be paid regardless of whether you are able to prove that the company has been negligent or that the product is defective (please ask if you would like more information on this). We would not be bound by these guidelines to pay compensation where i) the injury resulted from a device or procedure outside the study protocol and/or ii) the protocol was not followed.

As your study participation is completely voluntary, you may withdraw from the study at any time without any consequence to your continued care. The same also applies if the sponsor decides to stop the clinical investigation early.

**Sponsor and contact details**

The study is set-up and sponsored by the manufacturer of the PES treatment, Phagenesis Limited, located in Manchester, United Kingdom. The sponsor’s representative in this hospital is:

_____________________________________________________________________(name of investigator, title)

_____________________________________________________________________(telephone number)

He/she is responsible for the correct conduct of the clinical study at this hospital. If you wish to take part or have any remaining questions about the study or about your rights, or in the case of an injury arising from taking part in this study, please contact this person. If you agree to take part in the study and if you wish, the investigator will inform your personal doctor (general practitioner) that you are taking part in this clinical study.
**PATIENT INFORMED CONSENT FORM**

**Study Title:** Benefit of PHaryngeal electrical STimulation for early de-cannulation in TRACheotomised stroke patients with neurogenic dysphagia: a prospective randomised single-blinded interventional study (PHAST TRAC study)

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### Name of Investigator: [input name of PI]  
Please Initial Box

1. I confirm that I have read and understand the information sheet dated 09 November 2015 (Version 2.1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from/on behalf of Phagenesis Limited, from regulatory authorities, the hospital, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records and data.

4. I agree that data collected from me in this study may be used as described in the information sheet, including transfer to countries outside the European Union submission to regulatory bodies (for example the Food and Drug Administration of America).

5. I agree to my GP and other relevant health professionals involved in my care being informed of my participation in the study and for them to be notified if changes in my care are deemed appropriate or any abnormal findings are detected during the assessments of this study.

6. I agree to take part in this study.

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### Name of Patient

<table>
<thead>
<tr>
<th>Date</th>
<th>Signature</th>
</tr>
</thead>
</table>

**OR**  

### Name of Legal Representative

<table>
<thead>
<tr>
<th>Date</th>
<th>Signature</th>
</tr>
</thead>
</table>

### Name of Person taking consent

<table>
<thead>
<tr>
<th>Date</th>
<th>Signature</th>
</tr>
</thead>
</table>

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**Complete:** 1 original wet-ink consent form. Original copy to be kept in study file, 1 copy in medical notes and give 1 copy to the patient.
A.3: Investigator Agreement: Standard Template
Phagenesis has a standard English version of the Investigator Agreement. Together with the CIP, the appropriate template translation or the English version of the agreement is added to the dossier.

The Investigator Agreement comprises two parts:
- One part specifies the duties of sponsor and investigator
- The second part specifies the compensation that is due for completion of clinical study activities.

On the contrary, if a local hospital investigator agreement template is available that can be approved by Phagenesis Limited’s legal department, then preferably that agreement will be used as part of the study.

A copy of the standard template can be obtained upon request.

A.4: Evidence of Clinical Investigation Insurance

Phagenesis Limited has brought the Phagenyx devices onto the market: these bear the CE mark and the company is liable for the product’s performance. The product is used as is, however in some patient a second application of the same standard PES treatment is applied. Based on this single element, the devices used in the clinical trial are assigned a “FOR CLINICAL INVESTIGATION ONLY” label.

Phagenesis agrees to abide by the local guidelines in a European country and to establish an appropriate patient insurance. A copy of the insurance policy can be obtained from the sponsor.

A.5: Structure of Data Forms/Database

An electronic data capture system is created and was validated. It will be made available to the investigators when the site is appropriately trained to use the database, when all required approvals for executing the study are obtained (ethics committee, national competent authority) and when the appropriate members of the medical staff (study team) are trained on the conduct of the clinical trial and on ISO 14155 / ICH GCP relevant aspects.

The database contains the questions as they appear on the Case Report Forms and collects the following main data sets:

CRF01: Patient Data: match with in/exclusion criteria
CRF02: Patient Baseline Data: assessment of dysphagia, stroke severity, ventilation status, feeding status
CRF03: PES treatment form
CRF04: Decannulation attempt outcome form
CRF05: Patient follow up form
CRF06: Lost-to-follow up, patient study exit form
In addition there is an Adverse Event form and a SLT-management form.

The electronic database is an interactive database that allows immediate feedback on the presence/absence and correctness of entered data. Appropriate training will be provided to the study team that supports the data collection.

The system will also allow for access to the IWRS system that provides immediate feedback to the certified requestor on the randomisation status of a certain patient. Only certified people will have access to this information, all others, including those performing data entry or monitoring the data will not have access to such information. This approach supports the maintenance of the blinding of patient and assessor of the decannulation process.

It will be requested to complete the information per patient as soon as it becomes available, especially the information on the outcome of the primary end-point. The relevant data are provided by the CRO to the Biostatistical department Utrecht, where the sequential analysis is executed under supervision of Dr I van der Tweel and where analysis reports will be generated after the primary end-point data are received and analysed.

This (blinded) report with the advice of the statistician to stop or continue patient enrolment will be discussed between the members of the Scientific Board, where the decision to (dis)continue the study enrolment will be made. A decision on discontinuation will be communicated within 5 working days to all investigators.

### A.6. Draft CRFs

Copies of the Case Report Forms (CRFs) are available and a set is provided to the investigator at the time of the protocol delivery. These dataforms serve as the backbone to construct the electronic data base system. Additional copies can be obtained upon request.

Appropriate training will be provided to the medical staff on the use of the eCRFs prior study start in the given centre.
A.7: Speech and Language Therapy Management

The following information will be recorded on the electronic data collection system. A paper copy will also be kept in the study files for source documentation verification.

Screening, Baseline, Follow up-Visit 1 (1-2 weeks), Follow up-Visit 2 (2 weeks-discharge) and Follow up-Visit 3 (8-16 weeks)

If the patient has had a further SLT assessment since that documented previously and there is new information to populate this pro-forma as a result of this, please complete the following information. N.B. If there has not been a further SLT assessment or any change in the information since the previous visits, please confirm this in the case report forms and in the source data.

3.B.8.1. Swallow assessment:
N.B: this assessment must be consistently done at all time points by the same person for this patient.

Patient’s Speech and Language Therapist’s Name:………………………………………………………………….

Date of swallow assessment: (dd/mmm/yyyy) ………………………………………… _ _ / _ _ _ / _ _ _ _

Indicate on the following scale the severity of swallowing as assessed by the SLT:
Where 1 = no problem at all to swallow fluids or any food; Where 7 = unable to swallow and requires instrumentation.

- Retrospective assessment at the time of start of SLT-management (this hospitalisation period):
   1 2 3 4 5 6 7 N/A
- Current assessment at the time of baseline:
   1 2 3 4 5 6 7 N/A

3.B.8.2. Further Assessments:

   1. Was an SLT management plan set-up since the dysphagia causing event? .......................................................... □ □ □
      If YES,
      a. When was it started up? (dd/mmm/yyyy) .....................
         .............................................................................. _ _ / _ _ _ / _ _ _ _

   2. Was the SLT management plan considered successful? .................... □ □ □
      If YES,
      a. Did swallowing ability improve considerably? ................. □ □ □
      b. Was diet adjusted towards a more normal diet? ............. □ □ □
      c. Was fluid intake adjusted towards a more regular pattern? .............................................................................. □ □ □

   3. Was the SLT management plan considered completed with no further follow-up treatments scheduled? .................................................. □ □ □
3.B.8.3. Current SLT Management

1. The current SLT Management plan is based on information from:
   a. SLT led bedside swallow assessment? ................................................................. ☐
   b. Clinical videofluoroscopy (i.e. local SLT practitioner protocol or radiology led; VFS)? ................................................................. ☐
   c. Fibreoptic Endoscopic Evaluation of Swallowing (FEES)? ......................... ☐
   d. Other (Please specify): .................................................................................. ☐

2. Diet recommendations (tick as appropriate):
   a. None? ........................................................................................................... ☐
   b. Normal? ....................................................................................................... ☐
   c. Normal avoiding challenging textures? ....................................................... ☐
   d. Soft? ............................................................................................................. ☐
   e. Soft-mashed? .............................................................................................. ☐
   f. Puree? .......................................................................................................... ☐
   g. Nil oral diet? ................................................................................................. ☐
   h. Other (e.g. puree trials, please specify): ....................................................... ☐

3. Current fluid recommendations (tick as appropriate):
   a. None? ........................................................................................................... ☐
   b. Normal? ....................................................................................................... ☐
   c. Syrup? .......................................................................................................... ☐
   d. Custard? ...................................................................................................... ☐
   e. Pudding? ...................................................................................................... ☐
   f. Nil oral fluids? ............................................................................................. ☐
   g. Other (Please specify): ................................................................................ ☐

4. Specific instrumentation that have currently been installed to manage the patients dysphagia: (tick as appropriate):
   a. None, no supplementary or alternative feeding is being given? ............. ☐
   b. PEG? .......................................................................................................... ☐
   c. Nasogastric (NG) tube? ............................................................................. ☐
   d. Other (Please specify): ................................................................................ ☐

5. Additional advice given to the patient in relation to feeding: (tick as appropriate):
   a. None? ........................................................................................................... ☐
   b. Assistance to feed? ..................................................................................... ☐
   c. Supervision & prompts re: bolus size or speed? ........................................... ☐
   d. Restrictions in quantity of oral intake per sitting? ................................... ☐
   e. Altered frequency of oral intake? .............................................................. ☐
   f. Specified body position during oral intake? ............................................. ☐
   g. Use of specialist equipment or utensils? .................................................... ☐
   h. Specified regime or oral hygiene? ............................................................. ☐
   i. Specified patient/care education? ............................................................... ☐
   j. Other (Please specify): ............................................................................. ☐
**B.1. National Institute of Health Stroke Scale (NIH SS)**

The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

<table>
<thead>
<tr>
<th>Score</th>
<th>Stroke Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Stroke Symptoms</td>
</tr>
<tr>
<td>1-4</td>
<td>Minor Stroke</td>
</tr>
<tr>
<td>5-15</td>
<td>Moderate Stroke</td>
</tr>
<tr>
<td>16-20</td>
<td>Moderate to Severe Stroke</td>
</tr>
<tr>
<td>21-42</td>
<td>Severe Stroke</td>
</tr>
</tbody>
</table>

**1. Level of Consciousness (LOC)**

Level of consciousness testing is divided into three sections. The first LOC items test for the patient's responsiveness. The second LOC item is based on the patient's ability to answer questions that are verbally presented by the examiner. The final LOC sub-section is based on the patient's ability to follow verbal commands to perform simple task. Although this item is broken into three parts, each sub-section is added to the final score as if it is its own item.

**A) LOC Responsiveness**

Scores for this item are assigned by a medical practitioner based on the stimuli required to arouse patient. The examiner should first assess if the patient is fully alert to his or her surroundings. If the patient is not completely alert, the examiner should attempt a verbal stimulus to arouse the patient. Failure of verbal stimuli indicates an attempt to arouse the patient via repeated physical stimuli. If none of these stimuli are successful in eliciting a response, the patient can be considered totally unresponsive.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Alert; Responsive</td>
</tr>
<tr>
<td>1</td>
<td>Not alert; Verbally arousable or aroused by minor stimulation to obey, answer, or respond.</td>
</tr>
<tr>
<td>2</td>
<td>Not alert; Only responsive to repeated or strong and painful stimuli</td>
</tr>
<tr>
<td>3</td>
<td>Totally unresponsive; Responds only with reflexes or is a-reflexic</td>
</tr>
</tbody>
</table>

**B) LOC Question**

Patient is verbally asked his or her age and for the name of the current month.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Correctly answers both questions</td>
</tr>
<tr>
<td>1</td>
<td>Correctly answers one question</td>
</tr>
<tr>
<td>2</td>
<td>Does not correctly answer either question</td>
</tr>
</tbody>
</table>
C) LOC Commands

The patient is instructed to first open and close his or her eyes and then grip and release his or her hand

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Correctly performs both tasks</td>
</tr>
<tr>
<td>1</td>
<td>Correctly performs 1 task</td>
</tr>
<tr>
<td>2</td>
<td>Does not correctly perform either task</td>
</tr>
</tbody>
</table>

2. Horizontal Eye Movement

Assesses ability for patient to track a pen or finger from side to side only using his or her eyes. This is designed to assess motor ability to gaze towards the hemisphere opposite of injury. This item is tested because **Conjugated eye deviation** is present in approximately 20% of stroke cases. CED is more common in right hemispheric strokes and typically in lesions effecting the **basal ganglia** and **temporoparietal cortex**. Damage to these areas can result in decreased spatial attention and reduced control of eye movements.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal; Able to follow pen or finger to both sides</td>
</tr>
<tr>
<td>1</td>
<td>Partial gaze palsy; gaze is abnormal in one or both eyes, but gaze is not totally paralyzed. Patient can gaze towards hemisphere of infarct, but can't go past midline</td>
</tr>
<tr>
<td>2</td>
<td>Total gaze paresis; gaze is fixed to one side</td>
</tr>
</tbody>
</table>

3. Visual field test

Assess the patient's vision in each visual fields. Each eye is tested individually, by covering one eye and then the other. Each upper and lower quadrant is tested by asking the patient to indicate how many fingers the investigator is presenting in each quadrant. The investigator should instruct the patient to maintain eye contact throughout this test, and not allow the patient to realign focus towards each stimulus. With the first eye covered, place a random number of fingers in each quadrant and ask the patient how many fingers are being presented. Repeat this testing for the opposite eye.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No vision loss</td>
</tr>
<tr>
<td>1</td>
<td>Partial hemianopia or complete quadrantanopia; patient recognizes no visual stimulus in one specific quadrant</td>
</tr>
<tr>
<td>2</td>
<td>Complete hemianopia; patient recognizes no visual stimulus in one half of the visual field</td>
</tr>
<tr>
<td>3</td>
<td>Bilateral Blindness, including blindness from any cause</td>
</tr>
</tbody>
</table>
4. Facial Palsy

Facial palsy is partial or complete paralysis of portions of the face. Typically this paralysis is most pronounced in the lower half of one facial side. However, depending on lesion location the paralysis may be present in other facial regions. While inspecting the symmetry of each facial expression the examiner should first instruct patient to show his or her teeth (or gums). Second, the patient should be asked to squeeze his or her eyes closed as hard as possible. After reopening his or her eyes, the patient is then instructed to raise his or her eyebrows.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal and symmetrical movement</td>
</tr>
<tr>
<td>1</td>
<td>Minor paralysis; function is less than clearly normal, such as flattened nasolabial fold or minor asymmetry in smile</td>
</tr>
<tr>
<td>2</td>
<td>Partial paralysis; particularly paralysis in lower face</td>
</tr>
<tr>
<td>3</td>
<td>Complete facial Hemiparesis, total paralysis in upper and lower portions of one face side</td>
</tr>
</tbody>
</table>

5. Motor Arm

With palm facing downwards, have the patient extend one arm 90 degrees out in front if the patient is sitting, and 45 degrees out in front if the patient is lying down. If necessary, help the patient get into the correct position. As soon as the patient’s arm is in position the investigator should begin verbally counting down from 10 while simultaneously counting down on his or her fingers in full view of the patient. Observe to detect any downward arm drift prior to the end of the 10 seconds. Downward movement that occurs directly after the investigator places the patient’s arm in position should not be considered downward drift. Repeat this test for the opposite arm. This item should be scored for the right and left arm individually, denoted as item 5a and 5b.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No arm drift; the arm remains in the initial position for the full 10 seconds</td>
</tr>
<tr>
<td>1</td>
<td>Drift; the arm drifts to an intermediate position prior to the end of the full 10 seconds, but not at any point relies on a support</td>
</tr>
<tr>
<td>2</td>
<td>Limited effort against gravity; the arm is able to obtain the starting position, but drifts down from the initial position to a physical support prior to the end of the 10 seconds</td>
</tr>
<tr>
<td>3</td>
<td>No effort against gravity; the arm falls immediately after being helped to the initial position, however the patient is able to move the arm in some form (e.g. shoulder shrug)</td>
</tr>
<tr>
<td>4</td>
<td>No movement; patient has no ability to enact voluntary movement in this arm</td>
</tr>
</tbody>
</table>
6. Motor Leg

With the patient in the supine position, one leg is placed 30 degrees above horizontal. As soon as the patient’s leg is in position the investigator should begin verbally counting down from 5 while simultaneously counting down on his or her fingers in full view of the patient. Observe any downward leg drift prior to the end of the 5 seconds. Downward movement that occurs directly after the investigator places the patient’s leg in position should not be considered downward drift. Repeat this test for the opposite leg. Scores for this section should be recorded separately as 6a and 6b for the left and right legs respectively.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No leg drift; the leg remains in the initial position for the full 5 seconds</td>
</tr>
<tr>
<td>1</td>
<td>Drift; the leg drifts to an intermediate position prior to the end of the full 5 seconds, but at no point touches the bed for support</td>
</tr>
<tr>
<td>2</td>
<td>Limited effort against gravity; the leg is able to obtain the starting position, but drifts down from the initial position to a physical support prior to the end of the 5 seconds</td>
</tr>
<tr>
<td>3</td>
<td>No effort against gravity; the leg falls immediately after being helped to the initial position, however the patient is able to move the leg in some form (e.g. hip flex)</td>
</tr>
<tr>
<td>4</td>
<td>No movement; patient has no ability to enact voluntary movement in this leg</td>
</tr>
</tbody>
</table>

7. Limb Ataxia

This test for the presence of a unilateral cerebellar lesion, and distinguishes a difference between general weakness and incoordination. The patient should be instructed to first touch his or her finger to the examiner’s finger then move that finger back to his or her nose, repeat this movement 3-4 times for each hand. Next the patient should be instructed to move his or her heel up and down the shin of his or her opposite leg. This test should be repeated for the other leg as well.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal coordination; smooth and accurate movement</td>
</tr>
<tr>
<td>1</td>
<td>Ataxia present in 1 limb; rigid and inaccurate movement in one limb</td>
</tr>
<tr>
<td>2</td>
<td>Ataxia present in 2 or more limbs: rigid and inaccurate movement in both limbs on one side</td>
</tr>
</tbody>
</table>

8. Sensory

Sensory testing is performed via pinpricks in the proximal portion of all four limbs. While applying pinpricks, the investigator should ask whether or not the patient feels the pricks, and if he or she feels the pricks differently on one side when compared to the other side.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No evidence of sensory loss</td>
</tr>
<tr>
<td>1</td>
<td>Mild-to-Moderate sensory loss; patient feels the pinprick, however he or she feels as if it is duller on one side</td>
</tr>
<tr>
<td>2</td>
<td>Severe to total sensory loss on one side; patient is not aware he or she is being touched in all unilateral extremities</td>
</tr>
</tbody>
</table>
9. Language

This item measures the patient's language skills. After completing items 1-8 it is likely the investigator has gained an approximation of the patient's language skills; however it is important to confirm this measurement at this time. The stroke scale includes a picture of a picture of a scenario, a list of simple sentences, a figure of assorted random objects, and a list of words. The patient should be asked to explain the scenario depicted in the first figure. Next, he or she should read the list of sentences and name each of the objects depicted in the next figure. The scoring for this item should be based on both the results from the test performed in this item in addition to the language skills demonstrated up to this point in the stroke scale.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal; no obvious speech deficit</td>
</tr>
<tr>
<td>1</td>
<td>Mild-to-moderate aphasia; detectable loss in fluency, however, the examiner should still be able to extract information from patient's speech</td>
</tr>
<tr>
<td>2</td>
<td>Severe aphasia; all speech is fragmented, and examiner is unable to extract the figure's content from the patient's speech</td>
</tr>
<tr>
<td>3</td>
<td>Unable to speak or understand speech</td>
</tr>
</tbody>
</table>

10. Speech

Dysarthria is the lack of motor skills required to produce understandable speech. Dysarthria is strictly a motor problem, and is not related to the patient's ability to comprehend speech. Strokes that cause dysarthria typically affect areas such as the anterior opercular, medial prefrontal and premotor, and anterior cingulate regions. These brain regions are vital in coordinating motor control of the tongue, throat, lips, and lungs. To perform this item the patient is be asked to read from the list of words provided with the stroke scale while the examiner observes the patients articulation and clarity of speech.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal; clear and smooth speech</td>
</tr>
<tr>
<td>1</td>
<td>Mild-to-moderate dysarthria; some slurring of speech, however the patient can be understood</td>
</tr>
<tr>
<td>2</td>
<td>Severe dysarthria; speech is so slurred that he or she cannot be understood, or patients that cannot produce any speech</td>
</tr>
</tbody>
</table>

11. Extinction and Inattention

Sufficient information regarding this item may have been obtained by the examiner in items 1-10 to properly score the patient. However, if any ambiguity exist the examiner should test this item via a technique referred to as "double simultaneous stimulation". This is performed by having the patient close his or her eyes and asking him or her to identify the side on which they are being touched by the examiner. During this time the examiner is alternating between touching the patient on the right and left side. Next, the examiner touches the patient on both sides at the same time. This should be repeated on the patients face, arms, and legs. To test extinction in vision, the examiner should hold up one finger in front of each of the patient's eyes and ask the patient to determine which finger is wiggling or if both are wiggling. The examiner should then alternate between wiggling each finger and wiggling both fingers at the same time.

<table>
<thead>
<tr>
<th>Score</th>
<th>Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal; patient correctly answers all questions</td>
</tr>
<tr>
<td>1</td>
<td>Inattention on one side in one modality; visual, tactile, auditory, or spatial</td>
</tr>
<tr>
<td>2</td>
<td>Hemi-inattention; does not recognize stimuli in more than one modality on the same side</td>
</tr>
</tbody>
</table>
**B.2. Modified Rankin Scale**  
(From Van Swieten et al. '1998')

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms: able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability: requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability: bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>
B.3. Dysphagia Severity Ranking Scale (DSRS)
A score from 0 to 4 is given for three different elements (fluids, diet, and supervision):

FLUIDS:

5. Normal fluids
6. Syrup consistency
7. Custard consistency
8. Pudding consistency
9. No oral fluids

DIET:

5. Normal
6. Selected textures
7. Soft, moist diet
8. Puree
9. Non-oral feeding

SUPERVISION

5. Eating orally completely independently
6. Eating with supervision
7. Feeding by third party (untrained)
8. Therapeutic feeding (SLT / trained staff)
9. No oral feeding

Note: A score of 4 or higher is considered unsafe; a score between 9 and 12 is considered severe.

B.4. Functional Oral Intake Scale (FOIS) 45

TUBE DEPENDENT (levels 1-3)

1. No oral intake
2. Tube dependent with minimal/inconsistent oral intake
3. Tube supplements with consistent oral intake

TOTAL ORAL INTAKE (levels 4-7)

4. Total oral intake of a single consistency
5. Total oral intake of multiple consistencies requiring special preparation
6. Total oral intake with no special preparation, but must avoid specific foods or liquid items
7. Total oral intake with no restrictions

B.5. Richmond Agitation Sedation Scale (RASS) 46

<table>
<thead>
<tr>
<th>Score Term Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4 Combative Overtly combative, violent, immediate danger to staff</td>
</tr>
<tr>
<td>+3 Very agitated Pulls or removes tube(s) or catheter(s); aggressive</td>
</tr>
<tr>
<td>+2 Agitated Frequent non-purposeful movement, fights ventilator</td>
</tr>
<tr>
<td>+1 Restless Anxious but movements not aggressive vigorous</td>
</tr>
<tr>
<td>0 Alert and calm</td>
</tr>
<tr>
<td>-1 Drowsy Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (&gt;10 seconds)</td>
</tr>
<tr>
<td>-2 Light sedation Briefly awakens with eye contact to voice (&lt;10 seconds)</td>
</tr>
<tr>
<td>-3 Moderate sedation Movement or eye opening to voice (but no eye contact)</td>
</tr>
<tr>
<td>-4 Deep sedation No response to voice, but movement or eye opening to physical stimulation</td>
</tr>
<tr>
<td>-5 Unarousable No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>

The scores -1 to -3 are observed under verbal stimulation, the scores -4 and -5 under physical stimulation.

**Procedure for RASS Assessment**

1. Observe patient
   a. Patient is alert, restless, or agitated. (score 0 to +4)

2. If not alert, state patient’s name and say to open eyes and look at speaker.
   b. Patient awakens with sustained eye opening and eye contact. (score –1)
   c. Patient awakens with eye opening and eye contact, but not sustained. (score –2)
   d. Patient has any movement in response to voice but no eye contact. (score –3)

3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.
   e. Patient has any movement to physical stimulation. (score –4)
   f. Patient has no response to any stimulation. (score –5)

---


### Summary of changes in the protocol

<table>
<thead>
<tr>
<th>Design</th>
<th>Original Protocol</th>
<th>Summary of changes in Final Protocol compared to Original Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>International multi-site prospective randomised controlled trial.</td>
<td>No changes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Main hypothesis (null)</th>
<th>Original Protocol</th>
<th>Summary of changes in Final Protocol compared to Original Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“At least 25% more tracheotomised patients after supratentorial stroke can be decannulated after a first period of pharyngeal electrical stimulation (PES) treatment and following a standardised assessment scheme executed by the local blinded assessor/investigator at 24-72 hrs after the PES-treatment has been completed as compared to control patients who only get standard therapy over the same time period.”</td>
<td>Wording changed from “At least 25% more” to “A significantly larger proportion”.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Randomisation</th>
<th>Original Protocol</th>
<th>Summary of changes in Final Protocol compared to Original Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(‘Early’ versus ‘late’ PES). The ‘late’ treatment group initially acts as the control group for the ‘early’ treatment group but receives PES treatment during open label period if still tracheotomised due to their dysphagia severity.</td>
<td>No changes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allocation</th>
<th>Original Protocol</th>
<th>Summary of changes in Final Protocol compared to Original Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blocks of 4 per site allocated by an Interactive Web Response System.</td>
<td>No changes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blinding</th>
<th>Original Protocol</th>
<th>Summary of changes in Final Protocol compared to Original Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-blind (blinded outcome assessor)</td>
<td>No changes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Original Protocol</th>
<th>Summary of changes in Final Protocol compared to Original Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active: PES for 10 minutes a day for 3 consecutive days using the Phagenyx™ system. Sham: Phagenyx™ catheter in place but no electrical stimulation delivered.</td>
<td>No changes</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary objectives</th>
<th>Original Protocol</th>
<th>Summary of changes in Final Protocol compared to Original Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Measure the severity of dysphagia at the time of decannulation, and during the follow up period in terms of standard assessment scores; - Assess the proportion of patients who benefit from a first PES treatment but at a later time period of standard therapy in the ‘LATE TREATMENT’ (control) group, i.e. 170-288 hrs after the initial randomisation; - Assess the proportion of patients who benefit from a second PES treatment after failing a first attempt to decannulate the patient in the EARLY treatment arm; - Assess the severity level of stroke at different time points after PES treatment up to three months; - Measure the number of days a patient stays on a given ward/ICU; - Assess the amount of recannulations over a time period of 30 days (or until hospital discharge) after the preceding decannulation; - Assess the occurrence of severe adverse events during the observation period up to 30 days (or hospital discharge) after decannulation or a second failure to decannulate; - Assess the optimal treatment parameters (threshold, tolerance, intensity of stimulation);</td>
<td>No changes</td>
<td></td>
</tr>
</tbody>
</table>
### Predictors
- The proportion of patients that can be decannulated after a (second) PES-treatment in the time period between 170-288 hrs after the randomisation time point: the PES-treatment will be the first one to apply in the ‘LATE TREATMENT’ group, but it will be the second application in those patients of the ‘EARLY TREATMENT’ group that failed to be decannulation at the first attempt (i.e. 24-72 hrs after the end of the first PES treatment);
- Severity of dysphagia over a time period of 30 days (or until hospital discharge) after decannulation by means of relevant standard assessment scales (Dysphagia Severity Rating Scale and Functional Oral Intake Scale); every 48 hrs during the first 10 days and every 5 days thereafter until hospital discharge or maximum 30 days, the severity of dysphagia is measured and compared with the patient’s own condition at the time of baseline and of decannulation attempts;
- the treatment optimisation parameters (threshold, tolerance and intensity of the electrical stimulation);
- Severity of level of stroke at baseline, at 72-144 hrs after randomisation, at hospital discharge and at 3 months post-PES treatment by means of standard scoring scales (National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS));
- Demographics, symptoms and description of underlying dysphagia causes;
- Speech and Language Therapist-management plan and execution during the identified distinct time points of the clinical study;
- Adverse Events and device deficiencies;
- Health economics: duration of ICU-stay/hospitalisation/ stay at different care giving units until 30 days FU or until hospital discharge, whatever comes first.

### Adverse events (AEs)
All AEs were recorded in the study via the electronic data capture system from the point the Declaration of Consent Form.

All Serious AEs were assessed by the Coordinating Investigator for relationship to treatment and device.

SAE review process was changed from review by the Coordinating Investigator for relationship to treatment and device to review by an independent Data Safety Monitoring Board (IDSMB). The IDSMB was established to review all Serious AEs for relationship to treatment and device.

### Statistical analysis – predictors
Interim analyses or group sequential monitoring of cumulative patient data will be performed on the primary outcome data in successive groups of 10 patients.

Descriptive statistics of all other study data.

Removal of wording “in successive groups of 10 patients” and implementation of interim analysis with stopping rules as follows:
- The outlined interim analyses at N= 50, 70 and N_required allow:
<table>
<thead>
<tr>
<th>Eligibility criteria</th>
<th><strong>Inclusion criteria:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Experienced a haemorrhagic or ischemic stroke; AND</td>
</tr>
<tr>
<td></td>
<td>- Experienced a supratentorial stroke; AND</td>
</tr>
<tr>
<td></td>
<td>- Were mechanically ventilated for a minimum of 48 hrs after the stroke event; AND</td>
</tr>
<tr>
<td></td>
<td>- Were subsequently tracheotomised for any reason; AND</td>
</tr>
<tr>
<td></td>
<td>- Were weaned from mechanical ventilation – thus being able to sustain own respiration; AND</td>
</tr>
<tr>
<td></td>
<td>- Are free from sedatives for a minimum of 3 days prior the first decannulation attempt; AND</td>
</tr>
<tr>
<td></td>
<td>- Were found ineligible for decannulation minimally 10 days after the stroke event; AND</td>
</tr>
<tr>
<td></td>
<td>- Were found ineligible for decannulation minimally 24 and maximally 72 hrs after the first decannulation attempt; AND</td>
</tr>
<tr>
<td></td>
<td>- Cannot receive oral food (thus DSRS=12 and/or FOIS = 1);</td>
</tr>
<tr>
<td></td>
<td>- Have a score of ≥ 1 on the Richmond Agitation and Sedation Scale (RASS); AND</td>
</tr>
<tr>
<td></td>
<td>- Are over 18 years old; AND</td>
</tr>
<tr>
<td></td>
<td>- Give themselves (or have legal relatives/authorities representing themselves per the local practice to give) voluntary written informed consent;</td>
</tr>
</tbody>
</table>

**Exclusion criteria:**

- Have an undefined date of stroke causing the dysphagia (but not excluding stroke occurring

- To stop the study in case of futility (difference between groups very unlikely to be less that 25%);
- To stop the study in case of superiority of PES treatment (a significant difference between groups);
- To continue the study and enrol more patients until one of the decision boundaries is crossed after additional sequential analyses.

- During an interim analysis patient enrolment continues in the study; as a result e.g. more than 70 patients are likely to be enrolled by the time of completion of the second analysis. In the very unlikely event that no boundaries are crossed at $N_{required}$, additional analyses will be performed every 10th patient thereafter until either the upper or the lower boundary is crossed. As such there is no risk that the study remains indecisive due to a small sample size that is too small.

No changes to inclusion criteria.

Change to some exclusion criteria wording as follows:

- Have a pacemaker or an implantable defibrillator; or
- Have a nasal anatomical deformity, nasal airway obstruction, have had oesophageal surgery or any other circumstance where placement of a standard NG feeding tube would be deemed unsafe; or
- Have a cardiac or respiratory condition that might render the insertion of the catheter into the throat unsafe; or
- Receive oxygen therapy whilst the oxygen supply is in place or in operation.

Addition of the FEES decannulation protocol to demonstrate dysphagia stability and the inability to decannulate the patient as part of the post-consent screening activity.
during the night, for which the date will be the morning the stroke was observed); or
- Have a infratentorial stroke; or
- Suffer from pre-existing neurogenic dysphagia or a disease linked to that symptom (for example Parkinson Disorder); or
- Suffer from non-neurogenic dysphagia (e.g. cancer); or
- Suffer from neuromuscular disorders (e.g. myasthenia gravis, motor neuron disease); or
- Participate in any other study potentially influencing the outcome of PES, both medicinal or medical device product related and for which the patient signed a consent form for his/her study participation; or
- Receive or have received within one month prior to the intended PES treatment any other type of standard cranial or percutaneous electrical stimulation therapy to treat dysphagia; or
- Have a cardiac pacemaker or a cardioverter defibrillator implanted unless the device can be switched off completely at the time of treatment delivery; or
- Have experienced an oesophageal perforation, or have an oesophageal stricture or pouch; or
- Have an unstable cardiopulmonary status; or
- Have severe pneumonia that cannot be stabilized by medication and prevents the patient to be decannulated; or
- Receive continuous oxygen treatment or have the equipment for such treatment permanently in place preventing the positioning of the Phagenyx Catheter (this does not exclude patients that can have the oxygen treatment temporarily stopped and equipment removed during PES-treatment); or
- Are pregnant or nursing women; or
- Require emergency treatment, preventing appropriate conduct of the subject informed consent process; or
- Have a life expectancy less than the duration of the patient’s follow up period, i.e. less than three months.

Outcomes

**Primary outcome:**

- Proportion of patients in the ‘EARLY TREATMENT’ arm of the study that can be decannulated after a first exposure to the standard PES treatment as delivered by the Phagenyx device and the proportion of patients in the ‘LATE TREATMENT’ arm that can be decannulated at a comparable time point but without exposure to the standard PES treatment.

**Secondary outcomes:**

- To determine the severity of dysphagia at regular time intervals during the study until hospital discharge or until 30 days after the last

**Primary outcome:**

Addition of the following wording for clarification purposes

- "In this study, the readiness for decannulation of the patient is used as the primary end-point. Based on this assessment, the ability to remove the tracheal tube, either executed by the effective removal of the tracheal tube or by deflation of the tube-cuff, is used as the surrogate measure for the improved swallowing function of the patient. The timing of this assessment is referred to as time 0. Additional
decannulation attempt, by means of relevant standard assessment scales (DSRS and FOIS) and to compare this with the patient’s baseline condition;
- To determine the success rates of decannulation in the ‘LATE TREATMENT’ arm of the study after exposure to the standard PES treatment as delivered by the Phagenyx device;
- To measure the success rates of decannulation in the ‘EARLY TREATMENT’ arm of the study after a second exposure to the standard PES treatment as delivered by the Phagenyx device;
- To measure the treatment optimisation parameters (threshold, tolerance and intensity of the electrical stimulation),
- To measure the severity of the stroke by using the standard NIHSS and mRS at different time points after PES treatment during the 30 day follow up period and – for mRS – at the 3-month time point.

**Additional outcomes will document:**
- Demographics, symptoms and description of underlying dysphagia causes;
- SLT-management plan and execution during the identified distinct time points of the clinical study;
- AEs and device deficiencies
- Health economics: duration of ICU-stay/hospitalisation/ stay at different care giving units until 30 days FU or until hospital discharge, whatever comes first.

**Secondary outcomes:**
Clarification to time points of when severity of level of stroke is captured:
- “baseline, at follow up Day2, at hospital discharge/day 30 (whichever occurs first) by means of standard scoring scales (NIHSS and mRS), and at 3 months post-PES treatment by using the mRS.”

**Additional outcomes:**
- No changes
1. Study design:

1.1. Hypothesis
The hypothesis of the study is formulated as:
“A significantly larger proportion of tracheotomised patients after supratentorial stroke can be decannulated after a first period of pharyngeal electrical stimulation (PES) treatment and following a standardised assessment scheme executed by the local blinded assessor/investigator at 24-72 hrs after the PES-treatment has been completed as compared to control patients who only get standard therapy over the same time period.”

The hypothesis is based on former scientific work done by Prof Dr R Dziewas and colleagues (Suntrup S., et al., 2015) where he demonstrated in a single centre randomized trial in a comparable patient population that the difference between control and treatment group was 55 %.

1.2. Primary Objective
The primary objective is to assess the proportion of tracheotomised patients after supratentorial stroke that benefit from and have an earlier removal of the tracheal tube at the first attempt between 24 and 72 hrs after completion of the PES treatment as compared to the proportion of patients who only get standard therapy.

1.3. Secondary Objectives
Secondary objectives are to:
- Measure the severity of dysphagia at the time of decannulation, and during the follow up period in terms of standard assessment scores;
- Assess the proportion of patients who benefit from a first PES treatment but at a later time period of standard therapy in the ‘LATE TREATMENT’ (control) group, i.e. 170-288 hrs after the initial randomisation;
- Assess the proportion of patients who benefit from a second PES treatment after failing a first attempt to decannulate the patient in the EARLY treatment arm;
- Assess the severity level of stroke at different time points after PES treatment up to three months;
- Measure the number of days a patient stays on a given ward/ICU;
- Assess the amount of recannulation attempts over a time period of 30 days (or until hospital discharge) after the preceding decannulation;
- Assess the occurrence of serious adverse events during the observation period up to 30 days (or hospital discharge) after decannulation or a second failure to decannulate;
- Assess the optimal treatment parameters (threshold, tolerance, intensity of stimulation);
- Document the SLT management plan and its execution.

A total of 15 centers (located mainly in Germany, Austria and possibly in other European countries) will participate in the study and will enrol each a targeted minimum of 4 patients. One site cannot enrol more than 50 % of the target sample size of the study.

1.4. Subsequent clinical procedures
After the primary end-point assessment, patients are observed for 48 hrs and patient’s status re-assessed. The status of 48 hrs is determinant if a patient can enter the follow up period (if decannulated) or will be subjected to a next or second PES treatment. Patients who are successfully decannulated at that time will enter into the ‘follow up period’; those who are still intubated will enter into an “electrical stimulation period”.
Follow up of patients
The follow up visits are defined by the following sequence:

At every indicated time point clinical data are collected to allow documentation of the progression of the swallowing function (DSRS, FOIS, feeding status, SLT management) as well as respiratory function (ventilation status).

Electrical stimulation period
Patients failing to be decannulated and who are intubated at 48 hrs after the primary decannulation assessment will be treated subsequently with a normal PES treatment (3 consecutive days with 10 min of stimulation): for those patients from the control group, this will be their first PES treatment; for those patients from the treatment group, this will be their second PES treatment. After the 3rd day of PES, a (second) decannulation attempt will be applied in these patients, similar to the process applied at the time of the first assessment. Irrespective of the outcome of this second assessment, the patients will enter subsequently into the follow up period.

2. Statistics and Data Analysis: per the protocol specifications.

2.1. Randomisation and stratification
Patients will be randomised in blocks of 4 within centres. The statistical analysis will be stratified according to centre.

Deviations from the protocol considered for the analysis: none

Extra information on top of protocol specifications:
The 1:1 randomization tables are available for first 15 centres and lists in blocks of 4 patients, those patients who are assigned to the group A (control, LATE Rx) or to the group B (treatment, EARLY Rx). Randomization scheme is established for first 20 patients of each one of a total of 15 centres — thus the randomization of 300 pts is fixed. After a center has enrolled 75% of the randomization plan, the scheme will be extended for that center by reversed order of group assignments for the next 20 patients.
As an example (only showing first block of 4 pts for each of the sites listed):

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<thead>
<tr>
<th>Center XX</th>
<th>Center YY</th>
<th>Center ZZ</th>
<th>....</th>
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</table>

Randomization schemes remain blinded for all, except for the database builder (required for assigning the randomization via the IWRS\textsuperscript{47}, one person at the CRO (required to help assure appropriate therapy delivery and appropriate consistency between decannulation outcomes as assessed by investigators and Independent Review Board), and the statistician (required to apply the PEST 4 sequential data analysis plan). After completion of enrolment, per direction of the Scientific Committee, the randomization schemes can be disclosed but will be part of the final study report.

2.2. Data Analysis and Presentation

Normally distributed continuous outcome variables will be summarized by their mean and s.d.; categorical variables will be summarized as proportions.

**Deviations from the protocol considered for the analysis:** none

**Extra information on top of protocol specifications:**

The primary endpoint analyses will be conducted based on the outcome of decannulation as documented by investigator, irrespective of the status of monitoring. The interim analyses will be done on non-monitored data; however, once enrolment is completed, the next following and final analysis will only be done on monitored data and using a cleaned and closed database.

Secondary endpoint analyses will only be conducted on the cleaned and closed database, thus after completion of the monitoring activities as planned in the data monitoring plan.

Exceptions to this approach might apply depending on special requests made by the Scientific Committee, depending on the outcome of the primary end-point analysis (see Scientific Committee Charter). The Scientific Committee might also determine and request additional data analyses for its purposes of publications in medical journals. This is beyond the scope of this SAP.

2.3. 6.3 Sample Size Determination

Based on assumptions from the study results from Dr Dziewas’ publication (Suntrup S., et al., 2015) a minimum difference of 25% of decannulation success between groups was considered a priori to assess the sample size. “25%” is considered a reasonable, feasible, justifiable and clinical very relevant difference between study groups in a multi-centre trial in view of the single centre observed difference of 55%.

On top of the expected 25% difference between groups, it is assumed that the proportion of patients recovering their swallowing function on their own after the point of randomization and not receiving PES will be equal or less than what was observed in the control group of Dr Dziewas’ study, i.e. 20%. The two study groups are:

- **Group ‘LATE Rx’** (Late Treatment, control group, group A) will comprise half of the randomised patients who will each receive during the first 3-6 consecutive days after randomisation only standard therapy, but on the 4\textsuperscript{th} – 9\textsuperscript{th} day will start the 3 days of PES Treatment;
- **Group ‘EARLY Rx’** (Early Treatment, group B) will comprise half of the randomised patients who will each receive 3 days of PES treatment starting within 24 hrs after randomisation.

Upon receipt of primary endpoint data from pre-determined numbers of patients, interim analyses will be performed to assess the level of significance of the difference in proportions of patients that can be decannulated in both study arms.

\textsuperscript{47}IWRS: Interactive web-based randomisation scheme
The fixed sample size to detect a difference of at least 25% under given assumptions using standard statistics is at least 102 patients, excl. drop-outs. With a sequential analysis, on average 71 to 73 patients will be needed to detect this or no difference. The larger the true difference between groups, the smaller the sample size needs to be to demonstrate statistical significance. With a group difference less than 25% the total sample size could be as high as 126 (i.e. the 90th-percentage of the required number of patients).

Patient enrolment will cease once futility is statistically demonstrated or once superiority of the PES treatment is demonstrated significantly. If none of both can be demonstrated, patient recruitment will continue until a decision boundary is crossed.

**Deviations from the protocol considered for the analysis:** none

### 2.4. Different patient populations

1. Target population: neurogenic dysphagia patient fulfilling all the inclusion and none of the exclusion criteria.
2. Intention to treat population is defined as those patients that were randomized in the study after having received the nasogastric Phagenyx catheter.
3. Safety population is defined as any patient who received at least one administration of either control or PES treatment.
4. Per protocol population is defined as any patient who received the complete initial course of treatment and underwent the appropriate complete/correct decannulation assessment following the last electrical stimulation sequence of the initial course of treatment.

These different populations, except the ‘safety population’, are used to conduct data analysis of the primary endpoint only. Occurrence of SAE’s are analysed also in the ‘safety population’.

### 2.5. Statistical Analysis of Primary Endpoint

**Primary endpoint**

The primary endpoint is defined based on the assessment of the investigator (decannulator) who performs the assessment at the time point indicated by the protocol. The aim is to compare the proportions of patients with a successful decanulation in the control and treatment groups:
The decannulation assessment is done following the standard approach:

Decannulation protocol

Subsequent to each decannulation, the following questions are to be answered in the eCRF:

These questions reflect the arguments to support the decision on decannulation, which is posed by:

Question number 4.4.1 is the fundamental question addressing the outcome of the primary end-point as assessed by the investigator (decannulator). An answer YES on question 4.4.1, followed by answers NO to question 4.4.2 and 4.4.2b. would result in an ‘inconsistent’ data entry that would trigger popping up an ‘error message’ requiring the physician to reconsider and correct the data entry or to add a justification.

A deflation of the cuff is considered equivalent to the removal of the tracheal tube as the trachea and lungs are no longer protected against aspiration and the swallowing function is considered improved sufficiently to assure saliva is removed via the regular physiological processes.
The proportions of patients successfully decannulated (YES on question 4.4.1) per the applicable decannulation protocol (NO on each question of 4.3. step 1, 2 and 3) are calculated and compared between the control (LATE Rx)-group and the treatment (EARLY Rx)-group.

The analysis of the patient outcomes at this specific time point is applied to demonstrate whether or not the null hypothesis (no difference between groups) can be rejected.

Missing or erroneous assessments are considered conservatively as “failed treatments”

Sequential monitoring: general aspects

Interim analyses or group sequential monitoring of cumulative patient data will be performed on the primary outcome data from fixed pre-determined numbers of patients.

Deviations from the protocol (version 4.0) considered for the analysis: none

Initial foreseen frequency of interim analyses was set to every 10th patient (CIP, version 3.0). This frequency is replaced by a fixed number of interim analyses at N=50, 70 and \( N_{\text{required}} \). \( N_{\text{required}} \) is estimated based on previous observations and should reflect the sample size where either the upper or lower decision boundary is crossed. In the unlikely event that at \( N_{\text{required}} \) neither the upper nor the lower boundary is crossed additional analyses will be performed after every 10 new patients until either of both boundaries is crossed. This way it is avoided that the study would remain undecisive.

Extra information on top of protocol descriptions:

The statistical group under the leadership of Dr I van der Tweel at the UMC Utrecht, Department of Biostatistics & Research Support, Julius Centre, The Netherlands, executes the statistical analysis on the primary endpoint applying the sequential analysis on the ‘intention-to-treat’ patient population. A trigger to the interim analyses is given by the CRO based on the availability of data in the database from a fixed, pre-determined group of patients on the clinical assessment of the decannulation as a primary endpoint and appropriate data are transferred. Other non-primary endpoint related analyses referred to in the SAP are executed by a statistician under leadership of the CRO after closing and cleaning of the database.

The outcome of the interim analyses is communicated to the members of the Scientific Committee according to the specifications defined in the Scientific Committee Charter.

The main reason for interim analyses on efficacy is to determine whether the outcome of primary decannulation assessment in the EARLY PES treatment is significantly better than in the LATE treatment group or whether there is no significant difference between the two. In both cases, when enough evidence has been gathered, the trial can be stopped early and patients can be offered the best treatment available (Whitehead, 1997 (rev 2nd Ed)).

Initial approach of sequential analysis in PHAST TRAC and hypothesis testing

For the control [LATE] treatment, the probability of successful decannulation is estimated as 20% [published data of Dr Dziewas]. For the EARLY PES treatment, a probability of at least 45% is expected for successful decannulation: this is a 25 % improvement over the control group. The ultimate sample size depends on the chosen expected difference: the larger the true difference the smaller the required number of observations. Between investigators, it was agreed to target a difference of 25 % in the multi-centre trial. This was the basis for the hypothesis posed in version 1-3 of the CIP and maintained in version 4.0 as the basis for the sample size calculation.

The sequential tests require critical boundaries to be specified in advance. These boundaries depend on the expected treatment effect (25% improvement in successful decannulation), the type I error (\( \alpha = 0.05 \)) and the type II error (B, or the statistical power 1- B (80%) ). Since the boundaries depend on these three parameters, the overall power and type I error rate are guaranteed at each interim analysis, irrespective of the amount of information (as measured by the statistic V) that is obtained up till that point. The actual determination of the

48 More info on Sequential Analysis as executed per PEST 4.4 program is found on http://www.mps-research.com/PEST.
49 Note: the early results have been published meanwhile by Dr Dziewas and were presented on international congresses (Suntrup S. , et al., 2015).
50 Investigator meeting Frankfurt 9th January 2015.
boundaries require numerical solutions of mathematical equations which take all three parameters into account. Since this is mathematically intensive, a computer program like PEST is required to obtain them. The resulting boundaries can be represented as in the figure below.

Two test statistics, $Z$ and $V$, are calculated after each new group of 10 patient outcomes. $V$ and $Z$ can be calculated by:

$$Z = \frac{n_c S_c - n_e S_e}{n}$$

and

$$V = \frac{n_n n_c S_c}{n^2}$$

Where $n$ is the total number of responses (at time of the interim analysis), $n_c$ is the number of responses in the control group, $n_e$ is the number of responses in the experimental (treatment) group, $S_c$ is the number of successes in the experimental group, $S_c$ is the number of successes in the control group, $S$ is the total number of successes and $F$ is the total number of failures.

A point will be placed in the figure at this $Z,V$ combination.

Test statistic $V$ stands for the cumulative amount of information and is a function of the number of patients; test statistic $Z$ is equal to the difference between the observed and the expected (for a proportion successes of 0.20) number of successful decannulations for the EARLY treatment.

When the $(Z,V)$-statistic based on the cumulative data crosses the lower dashed boundary, the null hypothesis will be accepted; when it crossed the upper red boundary, the null hypothesis of no difference will be rejected.

![Figure 1: Illustration of upper and lower boundaries of acceptance levels.](image)

Adjustment for multiple analyses

By performing interim analyses, multiple looks are taken at the same, accumulating data set. In other words, multiple tests are performed on the cumulative data. By performing multiple tests, the type I error rate is increased which needs to be corrected. This can be considered as a penalty in comparison to a standard, fixed sample design where the data are analysed only at the end of the trial. However, the sequential analysis approach has some very nice properties, such as being able to stop the trial as soon as enough evidence for a significant treatment effect is available which could occur (but not necessarily occurs) at a lower sample size than was estimated beforehand.

From the above, it appears that a conclusion on appropriate rejection of the null-hypothesis can be made when the $(Z,V)$-statistics result in a point that is located outside the upper red or the lower dashed lines (see figure). Once this occurs, the estimate of the difference in proportion successful decannulation (and 95% confidence interval) will be calculated with an adjustment for the fact that the cumulative data were tested multiple times. That is, when a sequential design is used, the usual maximum likelihood estimate of the treatment difference will be biased (will be too large), so a bias-adjusted maximum likelihood estimate is needed instead. This adjustment is built into the program PEST. An explanation on why a smaller observed treatment difference than anticipated beforehand may lead to a statistically significant result, is beyond the scope of this SAP (reference to Whitehead). Yet this might lead to confusion when the adjusted value of the true group difference appears less than 25% or the p-value ends up larger than 0.05. Simulations demonstrated that such an outcome is
extreme rare but could lead to the precarious situation where an earlier analysis indicates that the upper red boundary was crossed (successful demonstration of hypothesis) while – after adjustment – the absolute difference appears to be less than what was hypothesized, potentially with a p-value (a little) larger than 0.05.

**Final approach on sequential analysis in the PHAST TRAC study**

To avoid confusion, the newly postulated hypothesis does no longer refer to a specific minimum proportional group difference (although the expected difference remains at 25%), and the frequency of the sequential analysis approach has been adjusted towards:

- A futility analysis at N = 50;
- An analysis at N=70 to determine if the upper red or lower blue boundary is crossed or – if not – to estimate the remaining number of required observations \( N_{\text{required}} \) to make a solid conclusive decision on the group difference;
- A final assessment at \( N_{\text{required}} \): after very likely a boundary has been crossed.

The extremely small likelihood of getting any meaningful conclusion before a sample size of 50 is reached makes early interim analyses irrelevant to draw conclusions. Therefore, a first interim analysis is done at N = 50 but only for reasons of futility. A subsequent interim analysis at N =70 is done primarily to estimate the sample size that is likely needed to draw a meaningful conclusion. However, if the true group difference is indeed much larger than 25% then the null hypothesis might be rejected at that time point.

**Stopping rules for the PHAST TRAC study and impact on sample size**

Strict stopping rules are delineated from the above.

- Study stops at N= 50 if futility is concluded;
- Study stops when evidence is available to accept or reject the null hypothesis.

Given the delay between time of collection, transfer and analysis of data, it is likely that a number of additional patients will have been enrolled. It was defined upfront, that a minimum of 80 must and an appropriate number of patients should be enrolled in the study and included in the final study result analysis to reach a definite conclusion, unless the study was stopped for reasons of futility after N=50. This means that, in the unlikely event of not crossing any decision boundary at \( N_{\text{required}} \), additional patients are enrolled and additional sequential analyses will be conducted every 10th patient until either the upper or the lower decision boundary is crossed. This prevents the study enrolment to be concluded while no conclusion can be drawn on the primary end-point.

2.6. **Implementation of sequential analysis in PHAST TRAC**

Each time, the data of the primary endpoint of a given group of patients has been obtained (availability of answers on question 4.6.3 in the data base), the total cumulative data will be transferred by the CRO to the statistician for a next analysis. The statistician will advise the members of the Scientific Committee on continuing or stopping the study.

When the study is stopped, the estimates of the difference in proportion successful decannulation and of its 95%-confidence interval will be adjusted for the cumulative monitoring (PEST 4, 2000) (Whitehead, 1997 (rev 2nd Ed)).

Every interim analysis to test the study hypothesis will take place conform the intention-to-treat principle.

**Deviation from the protocol considered for the analysis:** none

**Additional information on top of the protocol specifications:**
**Target patient populations**

The analyses of the primary endpoint will be executed on a number of different populations to ensure robustness in the results, yet the ultimate conclusion will be based on the Intention-to-treat (ITT) analysis. The endpoint is also assessed at the end of the study according to different other patient population specifications:

A. All randomised patients (intention to treat – ITT population);
B. All patients receiving any treatment session (control or treatment) (safety population);
C. All patients receiving all three treatment sessions prior the first decannulation assessment;
D. All patients undergoing a correct/complete FEES assessment during the first decannulation assessment receiving previously any PES treatment session;
E. All patients undergoing correct/complete FEES assessment during the first decannulation assessment and receiving previously all three 10 min PES treatment sessions at appropriate stimulation levels (per protocol population) and who are treated per the appropriate randomization assignment.

**Analysis of decannulation status during follow up period.**

During the subsequent follow up period the situation of tracheal intubation might be reconfirmed or be changed depending on the condition of the patient. Different scenario’s might apply, especially during the initial 48 hrs after the determination of the primary endpoint. These can be graphically represented as:

![Diagram of decannulation status during follow up period]

It is not expected that during the first 48 hrs a change in ‘decannulation assessment outcome’ will occur. This will lead to an automatic start-up of the follow up sessions for those patients who were successfully decannulated (+ in the graph) at that very same time. Those patients who failed to be decannulated and remain cannulated at the 48 hrs time point (- in the graph) will be scheduled to receive subsequently PES treatment, as regularly foreseen by the study protocol. First of three PES applications will start within 24 hrs after the reconfirmation of the decannulation status.

The outcome of decannulation status at 48 hrs after the first decannulation assessment will be used to re-assess the primary endpoint. The outcome proportions at this time point (48 hrs) will be compared with the ones obtained at time 0 (initial decannulation assessment).

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51 Correct and complete FEES assessment during first decannulation assessment: “NO” on the three questions of the 3-step decannulation protocol (see questions of eCRF indicated by 4.3.2, 4.3.3 and 4.3.4) and “YES” on 4.3.5. indicating that the appropriate FEES-video recording is available and accessible for re-assessment by the Independent Review Board.

52 PES = pharyngeal electrical stimulation
This re-assessment will only be done as a double check for the initial primary end-point assessment and will only be done at the end of study enrolment, not at interim time points. The outcome will be considered informative as compared to the initial primary endpoint analysis.

The re-assessment of the primary endpoint will also be done using the outcome analysis done by the Independent Review Board using the FEES video’s obtained during the primary decannulation assessment. The statistical analysis using these data will also be done only at the end of study enrolment. The outcome will be considered informative as compared to the initial primary endpoint analysis.

In addition, the status of tracheotomy is followed up for every patient and the proportions of patients being decannulated or remaining cannulated during the follow up period will be calculated at every indicated follow-up session.

The re-analysis of the primary endpoint is done on the ITT-population only and at the conclusion of the study only.

### 2.7. Statistical Analysis of Secondary End-points

**Swallowing function and severity of stroke**

No interim analysis are planned to analyse the secondary endpoints: only at the conclusion of enrolment the data will be cleaned and analysed using a ‘closed and cleaned database’. Exceptions to this might be caused by a special and unique/exceptional request at appropriate time by the Scientific Committee (see Scientific Committee Charter), knowing that analysis will be based on incompletely monitored, ‘non-cleaned’ data from the database.

Parameters of secondary endpoints are documented at baseline, at the time of the primary decannulation assessment, at the time of the second decannulation assessment (if applicable) and at repeated time points during the follow up period (2, 4, 6, 8, 10, 15, 20, 25, 30 and 90 days after the start of the follow up period). Follow up visits might be skipped if the patient was discharged from the hospital to home; discharge to another rehabilitation centre will be considered as an ‘in hospital situation’. The 90-day follow up visit is done via telephone if the patient is discharged to home at that time. All secondary endpoints are exploratory and therefore no adjustment for multiple testing will be applied.

The following parameters will be represented as mean ± SD at these time points (assuming they follow a Normal distribution):

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<tr>
<th>Parameter</th>
<th>Base</th>
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<th>2&lt;sup&gt;nd&lt;/sup&gt; DC</th>
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<th>15d</th>
<th>20d</th>
<th>25d</th>
<th>30d</th>
<th>PHD</th>
<th>90d</th>
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<tr>
<td>DSRS&lt;sup&gt;53&lt;/sup&gt; score</td>
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<td>FOIS&lt;sup&gt;54&lt;/sup&gt; score</td>
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<td>NIH SS&lt;sup&gt;55&lt;/sup&gt;</td>
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<td>mRS&lt;sup&gt;56&lt;/sup&gt;</td>
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DC: de-cannulation assessment; PHD = pre-hospital discharge

The outcome of each of these measures is analysed using linear mixed model comparing the control (LATE Rx) with the treatment (EARLY Rx) groups. Each variable will be graphically represented to demonstrate its average change over time. Significant differences from the baseline condition will be identified. In addition, the difference at a given time point between groups will be compared, especially but not only the parameters measured at the time of the first decannulation assessment are compared to the values measured at baseline. This is done using contrasts in the linear mixed model analysis. In all statistical analyses, a 2-sided significance level of 5% (p-value < 0.05) will be used to declare a result as statistically significant.

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<sup>53</sup> DSRS = Dysphagia Severity Rating Scale  
<sup>54</sup> FOIS = Functional Oral Intake Scale  
<sup>55</sup> NIHSS= National Institute of Health Stroke Scale  
<sup>56</sup> mRS= modified Ranking Scale
Safety analysis

The numbers and percentages of patients experiencing any adverse event (AE), any adverse device effect (ADE), any serious adverse event (SAE), any serious adverse device effect (SADE), and any unanticipated serious adverse device effect (USADE) will be summarized per treatment group. The numbers and percentages of patients experiencing any adverse events will also be summarized by maximum severity and relatedness to study treatment per treatment group.

AEs will be summarized by preferred term, by relatedness to study treatment and by severity, per treatment group. ADEs will be summarized by preferred term and severity per treatment group. All AEs, ADEs, SAEs and SADEs and USADEs for each patient will also be listed.

Survival analysis will be performed for the following endpoints:
- Time from randomization to death (days)
- Time from randomization to removal of nasogastric tube or PEG (days) for all patients who received PES treatment (safety population);
- Time from randomization to discharge from hospital (days).

Kaplan-Meyer plots for each survival analysis will be produced showing the survival functions of the two treatment groups. Incidence percentage, percentage censored, median survival time and hazard ratios (and their 95% confidence intervals) will be calculated for the two treatment groups. A Log-Rank test will be used to determine if the difference in survival between the two treatment groups is statistically significant. The analysis is applied to the observations made between randomization and the 90 day follow up period. Censoring will occur if a patient withdrew from the study before experiencing the endpoint in question.

Concomitant medications taken by more than 2% of the total population will be summarized by treatment group. The 2% is chosen in order to limit the total variability of meaningful data.

Additional secondary end-point analyses

The collected clinical data allows:
- to determine the success rates (proportions) of decannulation in the ‘LATE TREATMENT’ arm of the study after exposure to their first standard PES treatment as delivered by the Phagenyx device;
- to measure the success rates (proportions) of decannulation in the ‘EARLY TREATMENT’ arm of the study after a second exposure to the standard PES treatment as delivered by the Phagenyx device;
- to measure the treatment optimisation parameters (threshold, tolerance and intensity of the electrical stimulation) as mean and SD for the ‘EARLY Treatment’ and the ‘LATE treatment’ groups.

If statistical comparison between treatment groups or comparison between two time intervals is meaningful depends on the available number of observations that can be made in the time period after the primary end-point assessment. Obviously, this depends on the number of patients that are effectively decannulated at that time point. Further analyses will be decided on at the moment that such crucial information becomes available. In addition, following parameters will be described as appropriate (typically proportions of occurrence in the specific study groups):

- Demographics, symptoms and description of underlying dysphagia causes;
- SLT\(^{37}\)-management plan and execution;

The health economic outcome parameters will be measured as median number of days and its interquartile range for:
- duration of ICU-stay;
- total duration of hospitalisation;
- duration of stay at different care giving units until discharge to home

\(^{37}\) SLT = Speech and Language Therapist
Median, minimum, maximum and interquartile range will be presented when appropriate as well as the number of participants in each study group.

Missing data will be excluded from the analyses and the number of patients with missing results will be summarized.

3. Reports and Publications

Scientific Committee

A Scientific Committee is established and a charter created. This charter specifies the responsibilities and working guidelines of the SC. It also specifies the communication plan for the statistician to the SC-members and for the SC-members to the sponsor. The members of the SC are identified in the charter and its updates. Per the protocol, specifications following reports and publications are planned to be produced:

3.1. Interim Report

No formal interim reports are foreseen other than those describing the progress of the study (enrolment, data collection, monitoring etc.

3.2. 7.2 Final Report

A final report will be created per the ISO 14155 guidelines. This final report will be reviewed by the Scientific Committee-members and approved by all investigators. It will include all the clinical data obtained from all (anonymized) patients, as well as the outcome of all the statistical analyses.

3.3. Publications and Publication Policy

A publication policy will be created by the members of the Scientific Committee, defining the content and the timing of specific publications addressing the relevant symptoms, diagnosis, therapy and treatment outcome in the total patient population and in the ‘EARLY’ and ‘LATE TREATMENT’ subgroup of patients defined in this study.

Trial results will be published irrespective of the outcome of the comparison of the primary endpoint between study groups.

Authorship rules will also be defined in that policy and will consider the numerical and scientific contribution to the study (e.g. enrolment rates, timing of data collection, compliance to data collection requirements etc.).

No publications other than those specified and approved by the members of the Scientific Committee are allowed to be published or presented in any kind during the conduct of the clinical study until the final report is approved and the investigation formally closed. Each investigator will be informed about the policy prior first enrolment of a patient in the study at the investigator’s site and agrees formally with this approach by signing the Investigator Agreement.

4. References


Final Statistical Analysis Plan (v3.0, 22Apr2016)

1. Study design:

1.1. Hypothesis

The hypothesis of the study is formulated as:

“A significantly larger proportion of tracheotomised patients after supratentorial stroke can be decannulated\(^{18}\) after a first period of pharyngeal electrical stimulation (PES) treatment and following a standardised assessment scheme executed by the local blinded assessor/investigator at 24-72 hrs after the PES-treatment has been completed as compared to control patients who only get standard therapy over the same time period.”

The hypothesis is based on former scientific work done by Prof Dr R Dziewas and colleagues (Suntrup S., et al., 2015) where he demonstrated in a single centre randomized trial in a comparable patient population that the difference between control and treatment group was 55%.

1.2. Primary Objective

The primary objective is to assess the proportion of tracheotomised patients after supratentorial stroke that benefit from and have an earlier removal of the tracheal tube at the first attempt between 24 and 72 hrs after completion of the PES treatment as compared to the proportion of patients who only get standard therapy.

1.3. Secondary Objectives

Secondary objectives are to:

- Measure the severity of dysphagia at the time of decannulation, and during the follow up period in terms of standard assessment scores;
- Assess the proportion of patients who benefit from a first PES treatment but at a later time period of standard therapy in the ‘LATE TREATMENT’ (control) group, i.e. 170-288 hrs after the initial randomisation;
- Assess the proportion of patients who benefit from a second PES treatment after failing a first attempt to decannulate the patient in the EARLY treatment arm;
- Assess the severity level of stroke at different time points after PES treatment up to three months;
- Measure the number of days a patient stays on a given ward/ICU;
- Assess the amount of recannulation attempts over a time period of 30 days (or until hospital discharge) after the preceding decannulation;
- Assess the occurrence of serious adverse events during the observation period up to 30 days (or hospital discharge) after decannulation or a second failure to decannulate;
- Assess the optimal treatment parameters (threshold, tolerance, intensity of stimulation);
- Document the SLT management plan and its execution.

A total of 15 centers (located mainly in Germany, Austria and possibly in other European countries) will participate in the study and will enrol each a targeted minimum of 4 patients. One site cannot enrol more than 50% of the target sample size of the study.

1.4. Subsequent clinical procedures

After the primary end-point assessment, patients are observed for 48 hrs and patient’s status re-assessed. The status of 48 hrs is determinant if a patient can enter the follow up period (if decannulated) or will be subjected to a next or second PES treatment. Patients who are successfully decannulated at that time will enter into the ‘follow up period’; those who are still intubated will enter into an “electrical stimulation period”.

\(^{18}\) The word “decannulation” refers to the ability of the patient to be decannulated based on a decision making process that is directed through the “decannulation protocol” developed by the research group of Dr Dziewas.
**Follow up of patients**

The follow up visits are defined by the following sequence:

At every indicated time point clinical data are collected to allow documentation of the progression of the swallowing function (DSRS, FOIS, feeding status, SLT management) as well as respiratory function (ventilation status).

**Electrical stimulation period**

Patients failing to be decannulated and who are intubated at 48 hrs after the primary decannulation assessment will be treated subsequently with a normal PES treatment (3 consecutive days with 10 min of stimulation): for those patients from the control group, this will be their first PES treatment; for those patients from the treatment group, this will be their second PES treatment. After the 3rd day of PES, a (second) decannulation attempt will be applied in these patients, similar to the process applied at the time of the first assessment. Irrespective of the outcome of this second assessment, the patients will enter subsequently into the follow up period.

2. **Statistics and Data Analysis: per the protocol specifications.**
   
   2.1. **Randomisation and stratification**

   Patients will be randomised in blocks of 4 within centres. The statistical analysis will be stratified according to centre.

   **Deviations from the protocol considered for the analysis:**  none

   **Extra information on top of protocol specifications:**

   The 1:1 randomization tables are available for first 15 centres and lists in blocks of 4 patients, those patients who are assigned to the group A (control, LATE Rx) or to the group B (treatment, EARLY Rx). Randomization scheme is established for first 20 patients of each one of a total of 15 centres – thus the randomization of 300 pts is fixed. After a center has enrolled 75% of the randomization plan, the scheme will be extended for that center by reversed order of group assignments for the next 20 patients.
As an example (only showing first block of 4 pts for each of the sites listed):

<table>
<thead>
<tr>
<th>Center XX</th>
<th>Center YY</th>
<th>Center ZZ</th>
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Randomization schemes remain blinded for all, except for the database builder (required for assigning the randomization via the IWRS\(^{59}\), one person at the CRO (required to help assure appropriate therapy delivery and appropriate consistency between decannulation outcomes as assessed by investigators and Independent Review Board), and the statistician (required to apply the PEST 4 sequential data analysis plan). After completion of enrolment, per direction of the Scientific Committee, the randomization schemes can be disclosed but will be part of the final study report.

Exception: the center(s) in Italy could not obtain PES-experience using the commercially available PHagenyx device. A protocol deviation was implemented exclusively for Italian centers where first 3 patients are to be treated outside of the randomisation scheme prior patients are enrolled contributing to the statistical analyses. The first 3 patients are considered ‘run-in patients’ and do not contribute to the primary end-point assessment.

2.2. Data Analysis and Presentation

Normally distributed continuous outcome variables will be summarized by their mean and s.d.; categorical variables will be summarized as proportions.

Extra information on top of protocol specifications:

The primary endpoint analyses will be conducted based on the outcome of decannulation as documented by investigator, irrespective of the status of monitoring. The interim analyses will be done on non-monitored data; however, once enrolment is completed, the next following and final analysis will only be done on monitored data and using a cleaned and closed database.

Secondary endpoint analyses will only be conducted on the cleaned and closed database, thus after completion of the monitoring activities as planned in the data monitoring plan.

Exceptions to this approach might apply depending on special requests made by the Data Safety Monitoring Board, depending on the outcome of the primary end-point analysis (see Charter of Data Safety Monitoring Board). The Scientific Committee might also determine and request additional data analyses for its purposes of publications in medical journals. This is beyond the scope of this SAP.

2.3. Sample Size Determination

Based on assumptions from the study results from Dr Dziewas’ publication (Suntrup S., et al., 2015) a minimum difference of 25% of decannulation success between groups was considered a priori to assess the sample size. “25%” is considered a reasonable, feasible, justifiable and clinical very relevant difference between study groups in a multi-centre trial in view of the single centre observed difference of 55%.

On top of the expected 25% difference between groups, it is assumed that the proportion of patients recovering their swallowing function on their own after the point of randomization and not receiving PES will be equal or less than what was observed in the control group of Dr Dziewas’ study, i.e. 20%. The two study groups are:

- Group ‘LATE Rx’ (Late Treatment, control group, group A) will comprise half of the randomised patients who will each receive during the first 3-6 consecutive days after randomisation only standard therapy, but on the 4\(^{th}\) – 9\(^{th}\) day will start the 3 days of PES Treatment;

- Group ‘EARLY Rx’ (Early Treatment, group B) will comprise half of the randomised patients who will each receive 3 days of PES treatment starting within 24 hrs after randomisation.

\(^{59}\) IWRS: Interactive web-based randomisation scheme
Upon receipt of primary endpoint data from pre-determined numbers of patients, interim analyses will be performed to assess the level of significance of the difference in proportions of patients that can be decannulated⁶⁰ in both study arms.

The fixed sample size to detect a difference of at least 25% under given assumptions using standard statistics is at least 102 patients, excl. drop-outs. With a sequential analysis, on average 71 to 73 patients will be needed to detect this or no difference. The larger the true difference between groups, the smaller the sample size needs to be to demonstrate statistical significance. With a group difference less than 25% the total sample size could be as high as 126 (i.e. the 90⁰- percentile of the required number of patients).

Patient enrolment will cease once futility is statistically demonstrated or once superiority of the PES treatment is demonstrated significantly. If none of both can be demonstrated, patient recruitment will continue until a decision boundary is crossed.

**Deviations from the protocol considered for the analysis:** none

### 2.4. Different patient populations

1. **Target population:** neurogenic dysphagia patient fulfilling all the inclusion and none of the exclusion criteria.
2. **Intention to treat population** is defined as those patients that were randomized in the study after having received the nasogastric Phagenyx catheter.
3. **Safety population** is defined as any patient who received at least one administration of either control or PES treatment.
4. **Per protocol population** is defined as any patient who received the complete initial course of treatment and underwent the appropriate complete/correct decannulation assessment following the last electrical stimulation sequence of the initial course of treatment.

These different populations, except the ‘safety population’, are used to conduct data analysis of the primary endpoint only. Occurrence of SAE’s are analysed also in the ‘safety population’.

### 2.5. Statistical Analysis of Primary Endpoint

**Primary endpoint**

The primary endpoint is defined based on the assessment of the investigator (decannulator) who performs the assessment at the time point indicated by the protocol. The aim is to compare the proportions of patients with a successful decannulation in the control and treatment groups:

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⁶⁰ See footnote on meaning of “decannulation”.

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The decannulation assessment is done following the standard approach:

**Decannulation protocol**

Subsequent to each decannulation, the following questions are to be answered in the eCRF:

These questions reflect the arguments to support the decision on decannulation, which is posed by:

Question number 4.4.1 is the fundamental question addressing the outcome of the primary end-point as assessed by the investigator (decannulator). An answer YES on question 4.4.1, followed by answers NO to question 4.4.2 and 4.4.2b, would result in an ‘inconsistent’ data entry that would trigger popping up an ‘error message’ requiring the physician to reconsider and correct the data entry or to add a justification.

A deflation of the cuff is considered equivalent to the removal of the tracheal tube as the trachea and lungs are no longer protected against aspiration and the swallowing function is considered improved sufficiently to assure saliva is removed via the regular physiological processes.
The proportions of patients successfully decannulated (YES on question 4.4.1) per the applicable decannulation protocol (NO on each question of 4.3. step 1, 2 and 3) are calculated and compared between the control (LATE Rx)-group and the treatment (EARLY RX)-group\(^1\).

The analysis of the patient outcomes at this specific time point is applied to demonstrate whether or not the null hypothesis (no difference between groups) can be rejected.

Missing or erroneous assessments are considered conservatively as “failed treatments”

**Sequential monitoring: general aspects\(^2\)**

Interim analyses or group sequential monitoring of cumulative patient data will be performed on the primary outcome data from fixed pre-determined numbers of patients.

**Deviations from the protocol (version 4.0) considered for the analysis: none**

Initial foreseen frequency of interim analyses was set to every 10\(^{th}\) patient (CIP, version 3.0). This frequency is replaced by a fixed number of interim analyses at N=50, 70 and \(N_{\text{required}}\). \(N_{\text{required}}\) is estimated based on previous observations and should reflect the sample size where either the upper or lower decision boundary is crossed. In the unlikely event that at \(N_{\text{required}}\) neither the upper nor the lower boundary is crossed additional analyses will be performed after every 10 new patients until either of both boundaries is crossed. This way it is avoided that the study would remain undecisive.

**Extra information on top of protocol descriptions:**

The statistical group under the leadership of R Stellato at the UMC Utrecht, Department of Biostatistics & Research Support, Julius Centre, The Netherlands, executes the statistical analysis on the primary endpoint applying the sequential analysis on the ‘intention-to-treat’ patient population. A trigger to the interim analyses is given by the CRO based on the availability of data in the database from a fixed, pre-determined group of patients on the clinical assessment of the decannulation as a primary endpoint and appropriate data are transferred. Other non-primary endpoint related analyses referred to in the SAP are executed by a statistician under leadership of the CRO after closing and cleaning of the database.

The outcome of the interim analyses is communicated to the members of the Scientific Committee according to the specifications defined in the Scientific Committee Charter.

The main reason for interim analyses on efficacy is to determine whether the outcome of primary decannulation assessment in the EARLY PES treatment is significantly better than in the LATE treatment group or whether there is no significant difference between the two. In both cases, when enough evidence has been gathered, the trial can be stopped early and patients can be offered the best treatment available (Whitehead, 1997 (rev 2nd Ed)).

**Initial approach of sequential analysis in PHAST TRAC and hypothesis testing**

For the control [LATE] treatment, the probability of successful decannulation is estimated as 20% [published data of Dr Dziewas]\(^3\). For the EARLY PES treatment, a probability of at least 45% is expected for successful decannulation: this is a 25 % improvement over the control group. The ultimate sample size depends on the chosen expected difference: the larger the true difference the smaller the required number of observations. Between investigators\(^4\), it was agreed to target a difference of 25 % in the multi-centre trial. This was the basis for the hypothesis posed in version 1-3 of the CIP and maintained in version 4.0 as the basis for the sample size calculation.

The sequential tests require critical boundaries to be specified in advance. These boundaries depend on the expected treatment effect (25% improvement in successful decannulation), the type I error \((\alpha = 0.05)\) and the

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\(^1\) The “ability to be decannulated” as assessed by the question 4.4.1. is completed with additional information on the effective removal of the tracheal tube (or deflation of the cuff) by question 4.4.2. The action of removing the tube is tracked but is different from the decision taken in Q4.4.1. on the ability to decannulate the patient.

\(^2\) More info on Sequential Analysis as executed per PEST 4.4 program is found on [http://www.mps-research.com/PEST](http://www.mps-research.com/PEST).

\(^3\) Note: the early results have been published meanwhile by Dr Dziewas and were presented on international congresses (Suntrup S., et al., 2015).

\(^4\) Investigator meeting Frankfurt 9\(^{th}\) January 2015.
type II error (B, or the statistical power 1- B (80%)). Since the boundaries depend on these three parameters, the overall power and type I error rate are guaranteed at each interim analysis, irrespective of the amount of information (as measured by the statistic V) that is obtained up till that point. The actual determination of the boundaries require numerical solutions of mathematical equations which take all three parameters into account. Since this is mathematically intensive, a computer program like PEST is required to obtain them. The resulting boundaries can be represented as in the figure below.

Two test statistics, Z and V, are calculated after each new group of 10 patient outcomes. V and Z can be calculated by:

\[ Z = \frac{n_{c}S_{e} - n_{e}S_{c}}{n} \] \[ V = \frac{n_{e}n_{c}SP}{n^3} \]

Where \( n \) is the total number of responses (at time of the interim analysis), \( n_{c} \) is the number of responses in the control group, \( n_{e} \) is the number of responses in the experimental (treatment) group, \( S_{e} \) is the number of successes in the experimental group, \( S_{c} \) is the number of successes in the control group, \( S \) is the total number of successes and \( F \) is the total number of failures.

A point will be placed in the figure at this Z,V combination.

Test statistic V stands for the cumulative amount of information and is a function of the number of patients; test statistic Z is equal to the difference between the observed and the expected (for a proportion successes of 0.20) number of successful decannulations for the EARLY treatment. When the (Z,V)-statistic based on the cumulative data crosses the lower dashed boundary, the null hypothesis will be accepted; when it crossed the upper red boundary, the null hypothesis of no difference will be rejected.

Figure 1: Illustration of upper and lower boundaries of acceptance levels.

Adjustment for multiple analyses

By performing interim analyses, multiple looks are taken at the same, accumulating data set. In other words, multiple tests are performed on the cumulative data. By performing multiple tests, the type I error rate is increased which needs to be corrected. This can be considered as a penalty in comparison to a standard, fixed sample design where the data are analysed only once at the end of the trial. However, the sequential analysis approach has some very nice properties, such as being able to stop the trial as soon as enough evidence for a significant treatment effect is available which could occur (but not necessarily occurs) at a lower sample size than was estimated beforehand.

From the above, it appears that a conclusion on appropriate rejection of the null-hypothesis can be made when the (Z,V)-statistics result in a point that is located outside the upper red or the lower dashed lines (see figure). Once this occurs, the estimate of the difference in proportion successful decannulation (and 95% confidence interval) will be calculated with an adjustment for the fact that the cumulative data were tested multiple times. That is, when a sequential design is used, the usual maximum likelihood estimate of the treatment difference will be biased (will be too large), so a bias-adjusted maximum likelihood estimate is needed instead. This adjustment is built into the program PEST. An explanation on why a smaller observed treatment difference than anticipated beforehand may lead to a statistically significant result, is beyond the scope of this SAP (reference
to Whitehead). Yet this might lead to confusion when the adjusted value of the true group difference appears less than 25% or the p-value ends up larger than 0.05. Simulations demonstrated that such an outcome is extreme rare but could lead to the precarious situation where an earlier analysis indicates that the upper red boundary was crossed (successful demonstration of hypothesis) while – after adjustment – the absolute difference appears to be less than what was hypothesized, potentially with a p-value (a little) larger than 0.05.

**Final approach on sequential analysis in the PHAST TRAC study**

To avoid confusion, the newly postulated hypothesis does no longer refer to a specific minimum proportional group difference (although the expected difference remains at 25%), and the frequency of the sequential analysis approach has been adjusted towards:

- A futility analysis at N = 50;
- An analysis at N = 70 to determine if the upper red or lower blue boundary is crossed or – if not – to estimate the remaining number of required observations ($N_{\text{required}}$) to make a solid conclusive decision on the group difference;
- A final assessment at $N_{\text{required}}$ after very likely a boundary has been crossed.

The extremely small likelihood of getting any meaningful conclusion before a sample size of 50 is reached makes early interim analyses irrelevant to draw conclusions. Therefore, a first interim analysis is done at N = 50 but only for reasons of futility. A subsequent interim analysis at N = 70 is done primarily to estimate the sample size that is likely needed to draw a meaningful conclusion. However, if the true group difference is indeed much larger than 25% then the null hypothesis might be rejected at that time point.

**Stopping rules for the PHAST TRAC study and impact on sample size**

Strict stopping rules are delineated from the above.

- Study stops at N = 50 if futility is concluded;
- Study stops when evidence is available to accept or reject the null hypothesis at an N of 70 or higher.

Given the delay between time of collection, transfer and analysis of data, it is likely that a number of additional patients will have been enrolled. It was defined upfront that a minimum of 80 must, and an appropriate number of patients should, be enrolled in the study and included in the final study result analysis to reach a definite conclusion, unless the study was stopped for reasons of futility after N = 50. This means that, in the unlikely event of not crossing any decision boundary at $N_{\text{required}}$, additional patients are enrolled and additional sequential analyses will be conducted every 10th patient until either the upper or the lower decision boundary is crossed. This prevents the study enrolment to be concluded while no conclusion can be drawn on the primary end-point.

**Simulations of primary end-point analysis applying different assumptions**

The sample size of the study population was calculated based upon the assumptions that we would observe a 20% responder rate for readiness for decannulation in the control group and a minimum difference of 25% for readiness for decannulation responder rate between treatment group and control group (45% responder rate in the treatment group, 25% effect size).

A first simulation was done where these outcomes were randomly varied around these basic assumptions (20% responder rate in the control group, 25% effect size) with 1000 simulations with variations in effect sizes between – 48.5% (worst case) to 83.3% (best case). The level of significance was determined in all cases and the % of significant p-values ($p<0.05$) was determined for different levels of effect sizes. The outcome was:

- For effect sizes < 15% we will not find a statistically significant, positive outcome
- For effect sizes < 20% we will find a statistically significant, positive outcome in an estimated 1.1% of cases (11 cases) with N within the max number of 140 patients
- For effect sizes < 25% we will find a statistically significant, positive outcome in an estimated 18.4% of cases (184 cases) with N between 80 and 130

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65 140 patients has been referenced in the CIP v 4.0 as the maximum number of patients to be included in the study. This was indicated to be equivalent to the 90th percentile of 126 pts, whereby the latter is the correct driving figure.
- For effect sizes > 25% we will find a statistically significant, positive outcome in all cases (577 cases) with N between 50 and 120

A second similar simulation was done but using different upfront assumptions, i.e. that the responder rate in the control group is lower and around 10 %, with again 1000 cases with variations in effect sizes between -25% (worst case) and 80% (best case) – then the outcome was:
- For effect sizes < 15% we will find a statistically significant, positive outcome in 0.2% of cases (2 cases) with N within the max number of 140 patients
- For effect sizes <20% we will find a statistically significant, positive outcome in 9.6% of cases (96 cases) with N within the max number of 140 patients
- For effect sizes <25% we will find a statistically significant, positive outcome for 25.1% of cases (251 cases) with N between 60 and 140
- For effect sizes > 25% we will find a statistically significant, positive outcome for all cases (573 cases) with N between 50 and 100

These simulations were done as it can be expected that the success rate in the control might be less than 20% due to the inclusion criteria that every patient must demonstrate the presence of a stable dysphagia by twice failing a decannulation attempt prior to randomization. This requirement was different in the feasibility study of Dr Dziewas, where only 1 decannulation failure was sufficient to allow enrollment of the study in his study. The effect of the extended inclusion criteria on the lowering of the % success rate in the control is unknown, but – as the simulations demonstrate – for the same effect size, lower response rates in both groups have a positive impact on the significance level.

2.6. Implementation of sequential analysis in PHAST TRAC

Each time, the data of the primary endpoint of a given group of patients has been obtained (availability of answers on question 4.6.3 in the data base), the total cumulative data will be transferred by the CRO to the statistician for a next analysis. The statistician will advise the members of the Scientific Committee on continuing or stopping the study.

When the study is stopped, the estimates of the difference in proportion successful decannulation and of its 95%-confidence interval will be adjusted for the cumulative monitoring (PEST 4, 2000) (Whitehead, 1997 (rev 2nd Ed)).

Every interim analysis to test the study hypothesis will take place conform the intention-to-treat principle.

Deviations from the protocol considered for the analysis: none

Additional information on top of the protocol specifications:

Target patient populations

The analyses of the primary endpoint will be executed on a number of different populations to ensure robustness in the results, yet the ultimate conclusion will be based on the Intention-to-treat (ITT) analysis. The endpoint is also assessed at the end of the study according to different other patient population specifications:

A. All randomised patients (intention to treat – ITT- population);
B. All patients receiving any treatment session (control or treatment) (safety population);
C. All patients receiving all three treatment sessions prior the first decannulation assessment;
D. All patients undergoing a correct/complete FEES assessment66 during the first decannulation assessment receiving previously any PES67 treatment session;
E. All patients undergoing correct/complete FEES assessment during the first decannulation assessment and receiving previously all three 10 min PES treatment sessions at appropriate stimulation levels (per protocol population) and who are treated per the appropriate randomization assignment.

66 Correct and complete FEES assessment during first decannulation assessment: “NO” on the three questions of the 3-step decannulation protocol (see questions of eCRF indicated by 4.3.2, 4.3.3 and 4.3.4) and “YES” on 4.3.5. indicating that the appropriate FEES-video recording is available and accessible for re-assessment by the Independent Review Board.
67 PES = pharyngeal electrical stimulation
**Analysis of decannulation status during follow up period**

During the subsequent follow up period the situation of tracheal intubation might be reconfirmed or be changed depending on the condition of the patient. Different scenario’s might apply, especially during the initial 48 hrs after the determination of the primary endpoint. These can be graphically represented as:

It is not expected that during the first 48 hrs a change in ‘decannulation assessment outcome’ will occur. This will lead to an automatic start-up of the follow up sessions for those patients who were successfully decannulated (+ in the graph) at that very same time. Those patients who failed to be decannulated and remain cannulated at the 48 hrs time point (- in the graph) will be scheduled to receive subsequently PES treatment, as regularly foreseen by the study protocol. First of three PES applications will start within 24 hrs after the reconfirmation of the decannulation status.

The outcome of decannulation status at 48 hrs after the first decannulation assessment will be used to re-assess the primary endpoint. The outcome proportions at this time point (48 hrs) will be compared with the ones obtained at time 0 (initial decannulation assessment).

This re-assessment will only be done as a double check for the initial primary end-point assessment and will only be done at the end of study enrolment, not at interim time points. The outcome will be considered informative as compared to the initial primary endpoint analysis.

The re-assessment of the primary endpoint will also be done using the outcome analysis done by the Independent Review Board using the FEES video’s obtained during the primary decannulation assessment. The statistical analysis using these data will also be done only at the end of study enrolment. The outcome will be considered informative as compared to the initial primary endpoint analysis.

In addition, the status of tracheotomy is followed up for every patient and the proportions of patients being decannulated or remaining cannulated during the follow up period will be calculated at every indicated follow-up session.

The re-analysis of the primary endpoint is done on the ITT-population only and at the conclusion of the study only.
2.7. **Statistical Analysis of Secondary End-points**

*Swallowing function and severity of stroke*

No interim analysis are planned to analyse the secondary endpoints: only at the conclusion of enrolment the data will be cleaned and analysed using a ‘closed and cleaned database’. Exceptions to this might be caused by a special and unique/exceptional request at appropriate time by the Scientific Committee (see Scientific Committee Charter), knowing that analysis will be based on incompletely monitored, ‘non-cleaned’ data from the database.

Parameters of secondary endpoints are documented at baseline, at the time of the primary decannulation assessment, at the time of the second decannulation assessment (if applicable) and at repeated time points during the follow up period (2, 4, 6, 8, 10, 15, 20, 25, 30 and 90 days after the start of the follow up period). Follow up visits might be skipped if the patient was discharged from the hospital to home; discharge to another rehabilitation centre will be considered as an ‘in hospital situation’. The 90-day follow up visit is done via telephone if the patient is discharged to home at that time. All secondary endpoints are exploratory and therefore no adjustment for multiple testing will be applied.

The following parameters will be represented as mean ± SD at these time points (assuming they follow a Normal distribution):

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<th>Parameter</th>
<th>Base</th>
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<td>DSRS$^{68}$ score</td>
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DC: de-cannulation assessment; PHD = pre-hospital discharge

The outcome of each of these measures is analysed using linear mixed model comparing the control (LATE Rx) with the treatment (EARLY Rx) groups. Each variable will be graphically represented to demonstrate its average change over time. Significant differences from the baseline condition will be identified. In addition, the difference at a given time point between groups will be compared, especially but not only the parameters measured at the time of the first decannulation assessment are compared to the values measured at baseline. This is done using contrasts in the linear mixed model analysis. In all statistical analyses, a 2-sided significance level of 5% (p-value < 0.05) will be used to declare a result as statistically significant.

**Safety analysis**

The numbers and percentages of patients experiencing any adverse event (AE), any adverse device effect (ADE), any serious adverse event (SAE), any serious adverse device effect (SADE), and any unanticipated serious adverse device effect (USADE) will be summarized per treatment group. The numbers and percentages of patients experiencing any adverse events will also be summarized by maximum severity and relatedness to study treatment per treatment group.

AEs will be summarized by preferred term, by relatedness to study treatment and by severity, per treatment group. ADEs will be summarized by preferred term and severity per treatment group. All AEs, ADEs, SAEs and SADEs and USADEs for each patient will also be listed.

Survival analysis will be performed for the following endpoints:

- Time from randomization to death (days)
- Time from randomization to removal of nasogastric tube or PEG (days) for all patients who received PES treatment (safety population);
- Time from randomization to discharge from hospital (days).

$^{68}$ DSRS = Dysphagia Severity Rating Scale
$^{69}$ FOIS = Functional Oral Intake Scale
$^{70}$ NIHSS = National Institute of Health Stroke Scale
$^{71}$ mRS = modified Ranking Scale
Kaplan-Meyer plots for each survival analysis will be produced showing the survival functions of the two treatment groups. Incidence percentage, percentage censored, median survival time and hazard ratios (and their 95% confidence intervals) will be calculated for the two treatment groups. A Log-Rank test will be used to determine if the difference in survival between the two treatment groups is statistically significant. The analysis is applied to the observations made between randomization and the 90 day follow up period. Censoring will occur if a patient withdrew from the study before experiencing the endpoint in question.

Concomitant medications taken by more than 2% of the total population will be summarized by treatment group. The 2% is chosen in order to limit the total variability of meaningful data.

**Additional secondary end-point analyses**

The collected clinical data allows
- to determine the success rates (proportions) of decannulation in the ‘LATE TREATMENT’ arm of the study after exposure to their first standard PES treatment as delivered by the Phagenyx device;
- to measure the success rates (proportions) of decannulation in the ‘EARLY TREATMENT’ arm of the study after a second exposure to the standard PES treatment as delivered by the Phagenyx device;
- to measure the treatment optimisation parameters (threshold, tolerance and intensity of the electrical stimulation) as mean and SD for the ‘EARLY Treatment’ and the ‘LATE treatment’ groups.

If statistical comparison between treatment groups or comparison between two time intervals is meaningful depends on the available number of observations that can be made in the time period after the primary endpoint assessment. Obviously, this depends on the number of patients that are effectively decannulated at that time point. Further analyses will be decided on at the moment that such crucial information becomes available. In addition, following parameters will be described as appropriate (typically proportions of occurrence in the specific study groups):
- Demographics, symptoms and description of underlying dysphagia causes;
- SLT\textsuperscript{72}-management plan and execution;

The health economic outcome parameters will be measured as median number of days and its interquartile range for:
- duration of ICU-stay;
- total duration of hospitalisation;
- duration of stay at different care giving units until discharge to home

Median, minimum, maximum and interquartile range will be presented when appropriate as well as the number of participants in each study group.

Missing data will be excluded from the analyses and the number of patients with missing results will be summarized.

### 3. Reports and Publications

**Data Safety Monitoring Board\textsuperscript{73}**

It was decided to establish a DSMB, a charter was established outlining the following roles:
- Reviewing, implementing and approving the DSMB charter
- Assessing the safety and effectiveness data of the study at the planned interim analyses
- Advising/Suggesting the Sponsor regarding the continuation or change of design of the trial based on the reviewed safety and effectiveness data.

The outcome of the interim analyses will be communicated in a blinded way to the members of the DSMB by the statistician (R Stellato) during ‘closed sessions’ (not attended by sponsor). Based on the interim analysis the DSMB will advise the sponsor to:

\textsuperscript{72} SLT = Speech and Language Therapist

\textsuperscript{73} Extracts out of the charter of the DSMB.
1. Stop enrollment in the study: if at any interim analyses it appears not feasible to demonstrate a significant difference between treatment groups under the given assumptions of expected spontaneous success rate in control and treatment group (N=50 or above), or, alternatively, that statistical evidence is available that there is a statistically significant difference between groups;

2. Continue enrollment: if none of the upper or lower decision boundaries has been crossed (maximum sample size is determined as 140 pts).

3. Modify study design – if it appears that:
   a) Sample size calculation assumptions were incorrect;
   b) Apparent study design aspects will lead to incorrect study conclusions;
   c) Specific clinical procedures jeopardizes the safe execution of the study.

The role of the DSMB ceases at the conclusion of the study. The role of the Scientific Committee has changed towards a focus on publishing the study results.

**Scientific Committee**

A Scientific Committee is established and a charter created. This charter specifies the responsibilities and working guidelines of the SC. It also specifies the communication plan for the statistician to the SC-members and for the SC-members to the sponsor. The members of the SC are identified in the charter and its updates. Per the protocol, specifications following reports and publications are planned to be produced:

**3.1. Interim Report**

No formal interim reports are foreseen other than those describing the progress of the study (enrolment, data collection, monitoring etc.

**3.2. Final Report**

A final report will be created per the ISO 14155 guidelines. This final report will be reviewed by the DSMB and Scientific Committee-members and approved by all investigators. It will include all the clinical data obtained from all (anonymized) patients, as well as the outcome of all the statistical analyses.

**3.3. Publications and Publication Policy**

A publication policy will be created by the members of the Scientific Committee, defining the content and the timing of specific publications addressing the relevant symptoms, diagnosis, therapy and treatment outcome in the total patient population and in the ‘EARLY’ and ‘LATE TREATMENT’ subgroup of patients defined in this study.

Trial results will be published irrespective of the outcome of the comparison of the primary endpoint between study groups.

Authorship rules will also be defined in that policy and will consider the numerical and scientific contribution to the study (e.g. enrolment rates, timing of data collection, compliance to data collection requirements etc.). No publications other than those specified and approved by the members of the Scientific Committee are allowed to be published or presented in any kind during the conduct of the clinical study until the final report is approved and the investigation formally closed. Each investigator will be informed about the policy prior first enrolment of a patient in the study at the investigator’s site and agrees formally with this approach by signing the Investigator Agreement.

**4. References**


### Summary of changes in Statistical Analysis Plan

<table>
<thead>
<tr>
<th></th>
<th>Original SAP (v2.0, 09Nov2015) <em>(Please note, v1.0 was never approved and thus never enacted)</em></th>
<th>Changes in Final SAP (v3.0, 22Apr2016) compared to Original SAP (v2.0)</th>
<th>Additional analysis conducted for present report</th>
</tr>
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<tbody>
<tr>
<td><strong>Main hypothesis (null)</strong></td>
<td>A significantly larger proportion of tracheotomised patients after supratentorial stroke can be decannulated after a first period of pharyngeal electrical stimulation(^a) (PES) treatment and following a standardised assessment scheme executed by the local blinded assessor/investigator at 24-72 hrs after the treatment has completed as compared to control patients who only get standard therapy over the same time period.</td>
<td>No changes.</td>
<td>No changes.</td>
</tr>
<tr>
<td><strong>Sample size calculation</strong></td>
<td>The fixed sample size to detect a difference of at least 25% under given assumptions using standard statistics is at least 102 patients, excl. drop-outs. With a sequential analysis, on average 71 to 73 patients will be needed to detect this or no difference. The larger the true difference between groups, the smaller the sample size needs to be to demonstrate statistical significance. With a group difference less than 25% the total sample size could be as high as 126 (i.e. the 90th-percentile of the required number of patients). Patient enrolment will cease once futility is statistically demonstrated or once superiority of the PES treatment is demonstrated significantly. If none of both can be demonstrated, patient recruitment will continue until a decision boundary is crossed.</td>
<td>No changes.</td>
<td>No changes for the sequential analysis. Description of sample size calculation within the present report amended for conciseness as follows: “To detect a significant difference of 25% between the two groups using sequential analysis, a sample size of 72 patients was needed assuming a spontaneous recovery rate in the control group of 20%, a type I error equal to 0.05 and a power of 0.80. Interim analyses were to be performed after primary outcome data were available for 50 (futility) and 70 (decision boundary crossed) patients.”.</td>
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<td><strong>Statistical Analysis – Main outcome</strong></td>
<td>To test the primary hypothesis, a group sequential analysis was employed.</td>
<td>No changes.</td>
<td>No changes.</td>
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<td><strong>Frequency of Group Sequential Analysis</strong></td>
<td>The newly postulated hypothesis does no longer refer to a specific minimum proportional group difference (although the expected difference remains at 25%), and the frequency of the sequential analysis</td>
<td>No changes.</td>
<td>No changes.</td>
</tr>
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\(^a\) PES: electrical stimulation of the pharynx at a predetermined patient-dependent level during 10 minutes and during 3 consecutive days.
analysis approach has been adjusted towards:
- A futility analysis at N = 50;
- An analysis at N=70 to determine if the upper red or lower blue boundary is crossed or – if not – to estimate the remaining number of required observations (N_{required}) to make a solid conclusive decision on the group difference;
- A final assessment at N_{required} after very likely a boundary has been crossed.

The extremely small likelihood of getting any meaningful conclusion before a sample size of 50 is reached makes early interim analyses irrelevant to draw conclusions. Therefore, a first interim analysis is done at N = 50 but only for reasons of futility. A subsequent interim analysis at N =70 is done primarily to estimate the sample size that is likely needed to draw a meaningful conclusion. However, if the true group difference is indeed much larger than 25% then the null hypothesis might be rejected at that time point.

In the unlikely event of not crossing any decision boundary at N_{required}, additional patients are enrolled and additional sequential analyses will be conducted every 10th patient until either the upper or the lower decision boundary is crossed. This prevents the study enrolment to be concluded while no conclusion can be drawn on the primary end-point.

When the study is stopped, the estimates of the difference in proportion successful decannulation and of its 95%-confidence interval will be adjusted for the cumulative monitoring (PEST 4, 2000) (Whitehead, 1997 (rev 2nd Ed)).
<table>
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<th>Section</th>
<th>Description</th>
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<th>Details</th>
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| Standard statistics for primary end-point assessment. | The analyses of the primary endpoint will be executed on a number of different populations to ensure robustness in the results, yet the ultimate conclusion will be based on the Intention-to-treat (ITT) analysis. The endpoint is also assessed at the end of the study according to different other patient population specifications:  
A. All randomised patients (intention to treat – ITT-population);  
B. All patients receiving any treatment session (control or treatment) (safety population);  
C. All patients receiving all three treatment sessions prior the first decannulation assessment;  
D. All patients undergoing a correct/complete FEES assessment\(^{75}\) during the first decannulation assessment receiving previously any PES\(^{76}\) treatment session;  
E. All patients undergoing correct/complete FEES assessment during the first decannulation assessment and receiving previously all three 10 min PES treatment sessions at appropriate stimulation levels (per protocol population) and who are treated per the appropriate randomization assignment. | No changes. | No changes.  
After group sequential analysis, the primary efficacy outcome was further analysed using Fisher’s exact test. For sensitivity purposes, heterogeneity was assessed in pre-specified subgroups (age, sex, stroke type, time from onset to randomisation, duration of mechanical ventilation, baseline stroke severity (NIHSS), and stimulation intensity) by adding an interaction term in an unadjusted ordinal logistic regression model. |
| Statistical Analysis – Secondary outcomes | The outcome of DSRS, FOIS, NIHSS, mRS is analysed using linear mixed model comparing the control (LATE Rx) with the treatment (EARLY Rx) groups. Each variable will be graphically represented to | No changes. | Specifications clarified for statistics applied to secondary outcomes in present report. Outcomes were analysed using Fisher’s exact test for... |

\(^{75}\) Correct and complete FEES assessment during first decannulation assessment: “NO” on the three questions of the 3-step decannulation protocol (see questions of eCRF indicated by 4.3.2, 4.3.3 and 4.3.4) and “YES” on 4.3.5. indicating that the appropriate FEES-video recording is available and accessible for re-assessment by the Independent Review Board.  
\(^{76}\) PES = pharyngeal electrical stimulation
demonstrate its average change over time. Significant differences from the baseline condition will be identified. In addition, the difference at a given time point between groups will be compared, especially but not only the parameters measured at the time of the first decannulation assessment are compared to the values measured at baseline. This is done using contrasts in the linear mixed model analysis. In all statistical analyses, a 2-sided significance level of 5% (p-value < 0.05) will be used to declare a result as statistically significant.

The collected clinical data allows:
- to determine the success rates (proportions) of decannulation in the ‘LATE TREATMENT’ arm of the study after exposure to their first standard PES treatment as delivered by the Phagenyx device;
- to measure the success rates (proportions) of decannulation in the ‘EARLY TREATMENT’ arm of the study after a second exposure to the standard PES treatment as delivered by the Phagenyx device;
- to measure the treatment optimisation parameters (threshold, tolerance and intensity of the electrical stimulation) as mean and SD for the ‘EARLY Treatment’ and the ‘LATE treatment’ groups.

If statistical comparison between treatment groups or comparison between two time intervals is meaningful depends on the available number of observations that can be made in the time period after the primary end-point assessment. Obviously, this depends on the number of patients that are effectively decannulated at that time point. Further analyses will be decided on at the moment that such crucial information becomes available.

| binary data; Mann-Whitney U test for ordinal data, and Student’s t test (pooled) for continuous data. |
| Regression analyses were performed using binary logistic regression, Cox regression and multiple linear regression with no adjustments for multiplicity of testing and all analyses were by intention to treat. |
Descriptive statistics is applied for all other parameters.

| Safety Analysis | The numbers and percentages of patients experiencing any adverse event (AE), any adverse device effect (ADE), any serious adverse event (SAE), any serious adverse device effect (SADE), and any unanticipated serious adverse device effect (USADE) will be summarised per treatment group. The numbers and percentages of patients experiencing any AEs will also be summarised by maximum severity and relatedness to study treatment per treatment group. AEs will be summarised by preferred term, by relatedness to study treatment and by severity, per treatment group. ADEs will be summarised by preferred term and severity per treatment group. | No changes. | Outcomes were analysed using Mann-Whitney U test for ordinal data. |

| Survival analysis | Survival analysis will be performed for the following endpoints:  
- Time from randomisation to death (days)  
- Time from randomisation to removal of nasogastric tube or PEG (days) for all patients who received PES treatment (safety population);  
- Time from randomisation to discharge from hospital (days). | No changes. | Outcomes were analysed as intended using Kaplan-Meier survival curves. |