Pharyngeal Electrical stimulation for Acute Stroke dysphagia Trial (PhEAST)

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SYNOPSIS

Title	Pharyngeal Electrical Stimulation for Acute Stroke dysphagia Trial
Acronym	PhEAST
Short title	Pharyngeal Electrical Stimulation for Post Stroke dysphagia
Chief Investigator	Professor Philip M Bath
Objectives	**Overall** To assess whether Pharyngeal Electrical Stimulation (PES) is safe and effective at improving post-stroke dysphagia (PSD). **Primary** • Does 6 days of PES accelerate return to oral intake of food and drink as assessed using the dysphagia severity rating scale and blinded to treatment? **Secondary** • Does PES improve swallowing and reduce pneumonia, antibiotic exposure, hospital length of stay and disability? • Does PES increase quality-of-life? • Is PES cost effective as compared to usual care? • What subgroups predict response to PES?
Trial Configuration	International prospective randomised open-label blinded-endpoint (PROBE) parallel group superiority phase IV effectiveness trial
Setting	Secondary care: acute stroke services
Sample size estimate	The null hypothesis is that PES does not alter DSRS at day 14 post recruitment in participants with PSD. The primary outcome, DSRS (dysphagia severity rating scale) will be compared between PES and no PES using multiple linear regression with adjustment for stratification and minimisation variables. Assuming alpha 5%, power 90%; DSRS difference 1.2, standard deviation 5.0; losses 3%, crossovers 3%; sample rounded up, a sample size of N=800 is needed (PES n=400, control n=400) (assumptions based on pilot trials and STEPS trial).
Number of participants	800
Eligibility criteria	***Inclusion***: 800 hospitalised adults (age >=18) with recent (4-31 days) ischaemic or haemorrhagic anterior or posterior circulation stroke (as diagnosed clinico-radiologically) at a stroke centre, and clinical dysphagia

	defined as a functional oral intake scale (FOIS) score of 1 (nothing by mouth, feeding by naso-gastric tube [NGT]/percutaneous endoscopic gastrostomy [PEG] tube) or 2 (tube dependent with minimal attempts of food or liquids). ***Excluded***: Non-stroke dysphagia, e.g., due to traumatic brain haemorrhage, subarachnoid haemorrhage, brain tumour, Parkinson's disease, multiple sclerosis, severe dementia, head or neck cancer. Pre-stroke dysphagia or dependency (modified Rankin scale, mRS 4/5). Ongoing or anticipated ventilation/intubation/tracheostomy or use of electrical or magnetic stimulation. Malignant middle cerebral artery syndrome. Pregnant. Pacemaker. Need for >2 litres of oxygen. Two or more NGT pulled out unless nasal bridle in place. Investigator feels patient will not tolerate PES catheter.
Description of interventions	***Intervention arm*** PES on top of guideline-based standard-of-care. PES will be administered on days 1-6 using a commercial catheter with integral feeding tube. PES involves six daily 10 minute treatments at 5 Hz; threshold and tolerability currents will be assessed and the treatment current set at threshold + 0.75 x (tolerability - threshold) with current generated by a base-station. Dosing levels will be monitored, and sites informed if the stimulation current is too low, i.e. <20 mA; sites will be re-trained on the importance of delivering adequate current, if necessary. The catheter will be replaced once only if pulled out before 3 treatments have been administered. Treatment will be administered by PES-trained research coordinators, nurses or SLTs who are not involved in outcome data collection. ***Comparator arm*** No PES catheter/stimulation on top of best guideline-based standard-of-care dysphagia management. A standard NGT will be used for feeding as necessary.
Duration of study	From randomisation: treatment for 6 days, primary outcome at day 14, final follow-up at day 90. Trial and funding 3.25 years. Secondary endpoint at Day 365 (all cause mortality).
Randomisation and blinding	Randomised 1:1 with stratification on country and minimisation on age, sex, dysphagia severity rating scale (DSRS), impairment (National Institutes of Health stroke scale [NIHSS]), stroke type (ischaemic/haemorrhagic), circulation (anterior/posterior), time to randomisation; with 10% simple randomisation. Treatment will be delivered by a dedicated member of staff not otherwise involved in the trial. Outcomes will be assessed by other staff blinded to randomised treatment.
Outcome measures	**Primary at day 14±1** Dysphagia assessed using DSRS, based on bedside clinical assessment/management conducted at days 14±1. Outcome assessment will be assessed by DSRS/FOIS-trained research coordinators, nurses or SLTs who are not involved in treatment. ***Secondary at day 7±1***

	PES threshold, tolerability and stimulation currents; number of catheters used. ***Secondary at day 14±1*** DSRS >3, FOIS, EAT-10 and feeding status score (FSS); NGT/PEG in situ; pneumonia; antibiotic use; weight; EQ5D-5L, EQ-VAS (source recorded - patient or proxy). *Note 1*: We have included several measures of dysphagia and feeding: DSRS, FOIS, EAT-10 and FSS to triangulate the presence and magnitude of dysphagia and effects on feeding. These will be analysed together using the Wei-Lachin test.[1] ***Secondary at discharge/death by hospital assessor blinded to treatment***: Length of stay; antibiotic use; swallowing therapy contact time; time to removal of NGT/PEG; admitted to ICU; discharged with PEG; disposition (home, residential home, nursing home, hospital, death). ***Secondary at day 90±7 by central telephone assessor blinded to baseline, treatment and in-hospital data (or by post)***: DSRS, FOIS, EAT-10, FSS; home time; dependency (modified Rankin Scale [2]), disability (Barthel Index), quality of life (EQ-5D5L/EQ-VAS.), cognition (TICS [3]), mood (Zung [4]);[2,5-9] disposition. *Note 1*: These outcomes are all sensitive to therapeutic change. ***Secondary at day 365*** – all cause mortality. ***Safety***: PES has an excellent safety record in previous trials. Participants with PSD, who usually have severe stroke, will have multiple adverse events and SAEs. Hence, we will limit recording to: SAEs over 0-7 days, procedure/device-related (S)AEs over days 0-14; fatal SAEs over days 8-90 days; and all-cause mortality to day 365. **Costs** Health care resource use at discharge and day 90.
Statistical methods	The primary outcome, DSRS, will be compared between PES and no PES using multiple linear regression with adjustment for stratification and minimisation variables. The null hypothesis is that PES does not alter DSRS at day 14 in participants with PSD. Assuming alpha 5%, power 90%; DSRS difference 1.2, standard deviation 5.0; losses 3%, crossovers 3%; sample rounded up, a sample size of N=800 is needed (PES n=400, control n=400).

ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CF	Informed Consent Form
CI	Chief Investigator overall
CRF	Case Report Form
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
DSRS	Dysphagia severity rating scale
eCRF	Electronic case record form
EOT	End of Trial
EQ-VAS	EuroQuality of Life-visual analogue scale
EQ-5D-5l	EurolQol-ƒƒfive dimensions-5 levels
FOIS	Functional oral intake scale
FSS	Feeding status score
GCP	Good Clinical Practice
mA	Milliampere
MHRA	Medicines and Healthcare products Regulatory Agency
mRS	Modified Rankin scale
NGT	Naso-gastric tube
NHS	National Health Service
NIHSS	National Institutes of Health stroke scale
NMES	Neuro-muscular electrical stimulation
PEG	Percutaneous endoscopic gastrostomy
PES	Pharyngeal electrical stimulation
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
PLR	Personal legal representative (health)
PSD	Post stroke dysphagia
REC	Research Ethics Committee
R&D	Research and Development department
rTMS	Repetitive transcranial magnetic stimulation
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SUADE	Serious unexpected adverse device event
TMG	Trial Management Group
TSC	Trial Steering Committee

UADE	Unexpected adverse device event
VFS	Videofluoroscopy

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Stroke and dysphagia
Acute stroke is common (UK 140K pa) and complicated by dysphagia (swallowing problems) in >50% of patients, many of whom remain dysphagic a year later.[10,11] Post stroke dysphagia (PSD) is an independent predictor of poor outcome with aspiration of material into the lungs, pneumonia, malnutrition and death.[11,12] Patients often need feeding through a nasogastric tube (NGT) or percutaneous endoscopically-introduced gastrostomy tube (PEG), have prolonged hospital stay, and end up in long-term institutional care.[11,13] Hence, PSD negatively impacts on quality of life and its care is expensive and may be a tipping point for admission to residential care.

Treatment of PSD
Although PSD may be treated using a number of physical and behavioural techniques, the evidence base is controversial, and there are no definitive treatments.[11,14] Besides behavioural approaches as used routinely by Speech & Language Therapists (SLT), a number of stimulation techniques - physical stimulation, transcranial direct current stimulation and transcranial magnetic stimulation - have been tested in small randomised trials; although several of these have mechanistic information, they remain research techniques with a limited evidence base and lack defined administration and dosing details. Thirty-two Chinese trials of acupuncture have been reported and show reduced dysphagia; however they are mostly small (total of 2982 participants, mean size 93, range 48-200), lack a consistent approach to treatment (and so do not have a well described mechanistic basis) and are generally of low quality [14]. Thirteen trials of neuromuscular electrical stimulation (NMES) have been published and although they suggest that NMES improves swallow scores, there are a number of concerns. First, the trials are small (total of 559 participants, mean size 46, range 20-72) and tend to be of low quality (ongoing update of [14]). Second, there are little mechanistic data to support how NMES works although a key aim is to reduce muscle atrophy rather than address stroke-induced damage to CNS swallow centres. Third, patients have to be awake and able to generate a swallow (to command or reflexively) and follow instructions. Fourth, NMES requires several weeks of treatment and so is expensive to deliver and more suited to outpatient treatment. Last, NMES is largely used in private practice (including in the UK) with practitioners having to pay individually for training from the manufacturer, a model that is not practical at the NHS scale.

Pharyngeal electrical stimulation (PES)
In contrast to the earlier listed stimulation techniques, PES has a robust theoretical base and a well-defined treatment paradigm, including requiring only 3-6 days of treatment. Prof Shaheen Hamdy (University of Manchester) has demonstrated that human swallowing has bilateral representation in the brain with a 'dominant' cortex (unrelated to handedness).[15] Dysphagia often follows a stroke affecting the dominant swallowing cortex, and is exacerbated in recurrent strokes. Swallowing is dependent on afferent feedback via bulbar cranial nerves innervating the pharynx. Increased sensory input from the pharynx, delivered as PES, has been shown to drive long-term beneficial changes in the cortical control of swallowing [16] with reorganisation of the swallowing cortex.[16-18]

PES has been developed academically by Prof Shaheen Hamdy and then commercially by a University of Manchester spin-out company, Phagenesis Ltd (***Table 1***).

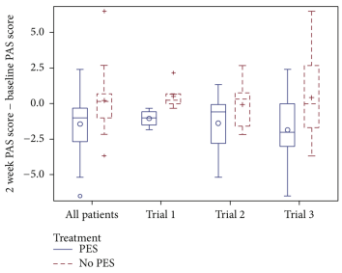
Table 1. Summary of previous PES stroke studies and planned trial

	Pilot trials [19-21]	STEPS [22]	PHAST-TRAC [23]	PHADER [24]	PhEED [25]	PhEAST Planned
Design	PROBE	Sham BE	Adaptive PROBE	Single arm BE	Adaptive PROBE	PROBE
Stroke N	73	162	69	85 of 245	3	800
Inclusion	PAS ≥4	PAS ≥3	Tracheotomy	DSRS ≥6	PAS ≥4	FOIS ≤2
VFS/FEES	VFS	VFS	FEES	No	VFS	No

OTR days	≤32	≤42	Subacute	Subacute	7-28	4-31
PES dose	x3	x3	x3/6	x3	x3	x6
Stimulation	/	14.8±7.9	33.6±8.3 mA	28.5±10.1 mA	27.6±6.6 mA	≥20 mA?
1ry @ day	PAS/DSRS	PAS @14	Decannulation @2	DSRS @90	PAS @02	DSRS @14
2ry @ day	/	DSRS @14	/	PAS @90	DSRS @07	FOIS @14
Effect, PAS	Improved	Neutral	/	Positive	N/A	/
Effect, DSRS	Improved	Neutral	/	Positive	N/A	/

BE: blinded-outcome; DSRS: dysphagia severity rating scale; FEES: flexible endoscopic evaluation of swallowing; FOIS: functional oral intake scale; N/A: not applicable; OTR: onset to randomisation; PAS: penetration aspiration scale; VFS: videofluoroscopy

- A phase I study [26] suggested that PES should be delivered at 5 Hz for 10 minutes, a paradigm maximising the effect on brain excitability.[26,27] In a randomised dose-comparison trial in patients with subacute stroke, PES reduced radiological aspiration (lower penetration aspiration score, PAS) on VFS.[19] PES also reduced clinical dysphagia (assessed as the dysphagia severity rating scale, DSRS) and length of stay in hospital in patients with PSD in a sham-controlled parallel group phase II trial.[19] In a NIHR RfPB-funded multicentre phase II randomised sham-controlled trial, the study was feasible in respect of recruitment, compliance and retention; PES non-significantly reduced clinical dysphagia and length of stay in hospital.[20]
- An individual patient data meta-analysis of these three small phase II trials (n=73) found that PES significantly reduced aspiration (PAS, ***Figure 1***) and dysphagia (DSRS, ***Figure 2***), and was safe and well tolerated.[21] PES has also shown promise in phase II trials in accelerating decannulation of intubated stroke patients post-ventilation, and improving dysphagia in multiple sclerosis.[28,29]



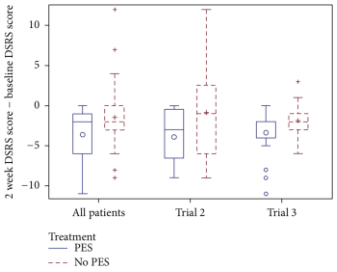


Figure 1: Effect of PES on PAS (3 pilot trials). Figure 2: Effect of PES on DSRS (2 pilot trials)

- STEPS (PB=CI; RD/HI=PIs):[22] International randomised single-blind phase III trial in 162 patients with a recent ischaemic or haemorrhagic stroke and radiological aspiration (PAS>=3). The study was feasible (recruitment, compliance and retention) and PES was safe but did not reduce aspiration (PAS) or dysphagia (DSRS) relative to sham. A meta-analysis of STEPS and the earlier pilot trials continued to show a reduction in DSRS with PES (***Figure 3***).[22]

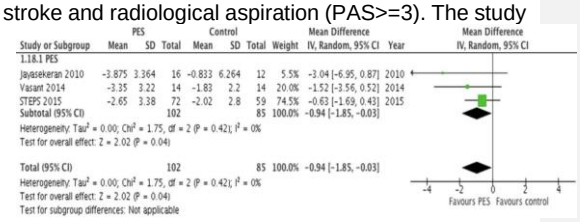


Figure 3: Effect of PES on DSRS at 2 weeks in 2 pilot trials and STEPS

- PHAST-TRAC (RD=CI; PB=TSC Chair. http://www.isrctn.com/ISRCTN1813720):[23,30] International randomised single-blind phase III with adaptive group sequential design in patients

with a recent stroke requiring ventilation and who could not be decannulated due to dysphagia. PES was superior to sham at 69 patients and stopped early.

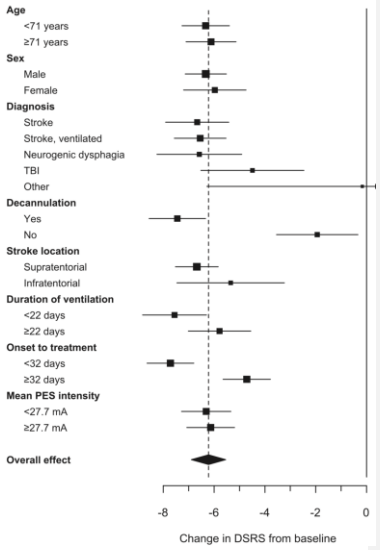
- PHADER (SH=CI; PB/RD=Co-CIs. http://www.isrctn.com/ISRCTN87110165);[24] International single arm study in 245 patients with unventilated stroke, ventilated stroke and other causes of neurogenic dysphagia. PES was associated with improved DSRS and PAS, both overall and in each diagnostic group including in both non-ventilated and ventilated stroke (***Table 1***).
- PhEED (PB=deputy CI. https://clinicaltrials.gov/ct2/show/NCT03358810):[25] International randomised single-blind phase III trial with adaptive group sequential design. The trial was stopped early due to low recruitment in the USA, explained by the: (i) need for VFS at baseline and outcome (primary outcome), and (ii) presence of clinical dysphagia but only mild radiological aspiration in many of those screened; of a target of 120 participants, 50 were consented for screening with VFS but only 17 treated vs 3.
- PhINEST (https://clinicaltrials.gov/ct2/show/NCT03840395): Ongoing randomised post-extubation trial in intensive care units in patients with neurogenic dysphagia.

In spite of this accumulation of clinical trial data, efficacy in PHAST-TRAC and PHADER, and having a CE mark and FDA breakthrough designation, PES lacks an adequate evidence base from large pragmatic trials and information on health economics, and so is not used widely nor has it been assessed by NICE for adoption in the NHS.

Our trial design builds on learning points from the three pilot trials and the STEPS, PHAST-TRAC, PHADER and PhEED studies of PES for PSD, and meta-analyses of these.[19,21-25,31] As such, it will be deliverable, relevant and able to change practice:

- Treat within 1 month after stroke onset;[23,24] PES may be less effective if given later as in PHAST-TRAC and PHADER (***Figure 4***).

Figure 4: Interaction between PES and time in PHADER [24]



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- Recruit only severe dysphagia (DSRS>7 [21]), a group who are more likely to need tube feeding and have extended hospital stay; PES is less effective in mild dysphagia (STEPS [22]).

Recruit both anterior and posterior circulation stroke.[24]

- Ensure investigators are adequately trained and regularly retrained to ensure fidelity.[22]
- Treat with sufficient stimulation current (>20 mA); high current was effective in PHAST-TRAC (mean 33.6±8.3 mA) [23] and PHADER (28.5±10.1 mA) [24] whereas low current was ineffective in STEPS (14.8±7.9 mA).[22]
- Deliver calculated, not less (PhEED [25]), current = threshold + 0.75 x (tolerability - threshold).
- Avoid any stimulation in control group (as was given in STEPS [22]).
- Use back-to-back 3-day treatment cycles of PES (i.e. 6 treatment days in total), as in PHAST-TRAC.[23] Notes: PES has CE mark for 2 cycles of treatment, and has been used for up to 15 treatments across 5 days.[19]
- On average, 1.1 PES catheters are needed per patient to allow for some being pulled out by confused patients.[24] Allowing for 1.4 catheters per patient will provide a sufficient buffer to prevent undertreatment due to insufficient catheters.
- The clinical DSRS score (which is relevant to patients and can be assessed in all) should be used as the primary outcome; it is validated [32] and is improved by PES.[19,21,22,31]
- DSRS is not sensitive to treatment immediately after the end of treatment.[24] Measurement at 14 days, i.e. 8 days after end of PES, allows the treatment effect to develop and be assessed.

- Avoid outcomes based on instrumental testing with VFS or FEES due to restricted availability so making recruitment more difficult, as in PHADER, PhEED and STEPS [22,24,25] (and compounded by the pandemic since VFS is considered an aerosol generating procedure by The Royal College of Speech and Language Therapists, who provide clinical guidelines and the policy for administering VFS).
- Consider using a group sequential design, as in PHAST-TRAC [23] (***Figure 5***).

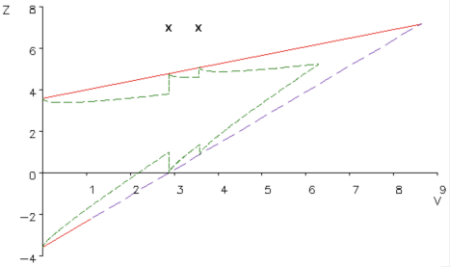


Figure 5: Sequential analysis showing interim analyses - left x at top: trial positive so excluding futility; right x: superiority so stop (both as per protocol) ➔

- Use an ordinal/continuous, not binary, outcome/analysis to both reduce sensitivity to baseline severity and to maximise statistical power.[21]

Why 6 days of treatment?

The first study of PES for PSD assessed a variety of treatment paradigms in a small dose-response study comprising control, PES once a day for 3 days, PES once a day for 5 days, PES three times a day for 3 days, and PES three times a day for 5 days. PAS scores were lower (i.e. improved/less aspiration) with treatment vs control and once vs three times per day; there was no difference between 3 and 5 days of treatment.[19] More recently, the larger PHAST-TRAC trial showed that an additional 3 days of treatment converted 4 non-responders after 3 days to responders after 6 days.[23] So, whilst PES was originally tested then marketed for 3 days of treatment, this has been extended to 6 days. The CE mark has been updated to reflect these research findings and now covers treatment for 6 days. There are minimal negative aspects to the trial on extending PES from 3 to 6 days of treatment since patients with PSD are often in hospital for longer to receive other rehabilitation treatment. However, there are no data reflecting a further lengthening of treatment to, say, 9 days. Hence, we recommend the evidence-based treatment of 6 days of once-daily treatment.

Why this research is needed now?

PSD is common, associated with poor outcomes and quality of life, and there are no recognised treatments. As a result, PSD is:

- Unpleasant: Although NGT feeding prevents dehydration and malnutrition, it: is disliked by patients and family (distress during tube insertion and irritation when in place); has huge socio-cognitive implications, removing the pleasure of drinking/eating; reduces oral health; is complicated by premature NGT removal by confused patients, this needing further NGT(s) (with more chest x-rays, CXR); and often needs replacement with a long-term PEG tube; there is no evidence that the risk is reduced.
- Hazardous: PSD is complicated by aspiration, pneumonia and malnutrition, these leading to dependency, disability and death. PSD, with age and stroke severity, is a key determinant of outcome; tube insertion and feeding come with complications.[11]
- Logistically challenging and expensive for healthcare: Bed-occupancy due to extended hospital stay; staff - nursing management of NGT/drugs/feed; speech & language therapy (SLT), dietician management of tube feeding, gastroenterologist insertion of percutaneous endoscopic gastrostomy tubes; drugs – antibiotics for pneumonia so potentially increasing resistance and hospital acquired infections; investigations – videofluoroscopy (VFS), fibreoptic endoscopic evaluation of swallowing (FEES), CXR; devices – NGT/PEG, bridles. Importantly, nursing homes rarely take NGT-fed patients so availability and training for PEG determine when and where patients can be discharged.
- There are no ongoing trials of PES in non-ventilated stroke patients. The WHO ICTRP

(https://apps.who.int/trialsearch/) reports ongoing trials of PES for extubation of ventilated stroke patients (NCT04010617), ICU-related dysphagia (PhINEST, NCT03840395) and amyotrophic lateral sclerosis (NCT03481348). None of these are large.

If PES is effective at reducing dysphagia and returning patients to oral feeding, and so reduces length of stay in hospital, then it is likely to be cost effective as compared to usual care. PES has a European Conformité Européene (CE) mark and is available in the UK and across Europe but lacks an adequate evidence base, hence the need for this large trial. Public-patient involvement (PPI) representatives confirm the importance of PSD and finding effective treatments.

DETAILS OF DEVICE

Description

PES on top of guideline-based standard-of-care. PES will be administered on days 1-6 using a commercial catheter (Phagenyx®, Phagenesis Ltd, Manchester UK) with integral feeding tube. PES involves six daily 10 minute treatments at 5 Hz; threshold and tolerability currents will be assessed and the treatment current set at threshold + 0.75 x (tolerability - threshold) with current generated by a base-station.[19-25] Dosing levels will be monitored and sites informed if the stimulation current is too low, i.e. <20 mA; sites will be re-trained on the importance of delivering adequate current, if necessary. The catheter will be replaced once only if pulled out before 3 treatments have been administered. Treatment will be administered by PES-trained research coordinators, nurses or SLTs who are not involved in outcome data collection. Treatment will be stopped if there is no further need for tube feeding. See below for Training.

The PES System is indicated for the treatment of post-stroke neurogenic oropharyngeal dysphagia and is a two-part neurostimulation system composed of a durable component, the Base Station, and a single-use sterile disposable catheter. The Base Station acts as the user interface and provides the means to generate, optimize and monitor the delivery of electrical stimulation. The catheter design is based on that of an NGT but incorporates electrodes with appropriate wiring and insulation for delivery of electrical stimulation to the pharyngeal mucosa. The catheter has been designed to also deliver enteral nutrition to the patient as needed. Phagenyx received CE Mark in 2012. As Phagenyx® is CE marked and used within its intended purposes a letter of no objection from the competent authority for that usage is not required.

The Base Station has the following functions:

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

Figure 6 provides the front and back appearances of the Base Station with key features labelled. The design of the Base Station and associated software complies with medical device electrical and software standards. Moreover, appropriate hardware risk control measures have been taken so that a software failure is not associated with risk of serious injury. Hence, the overall safety of the Phagenyx System is Class A.

Figure 6: Phagenyx Base Station with labelled components:

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

The catheter is a two-part construction. The inner core is in the form of a nasogastric (NG) feeding tube with a guidewire. The outer part is in the form of a thin-walled Sleeve that incorporates two ring electrodes, insulated wires located in the walls of the Sleeve to deliver the current, and a connector (the S-connector) (***Figure 7***). The Sleeve is designed to be positioned on the NG tube and to be capable of freely moving up and down along its length. The catheter is available in one size only. The NG tube has an outer diameter (OD) of 8F (2.75 mm) and is 123 cm long to provide sufficient length to access the stomach for feeding purposes. The outer catheter sleeve has an OD of 11.5F (3.85 mm) and is approximately 70 cm long.

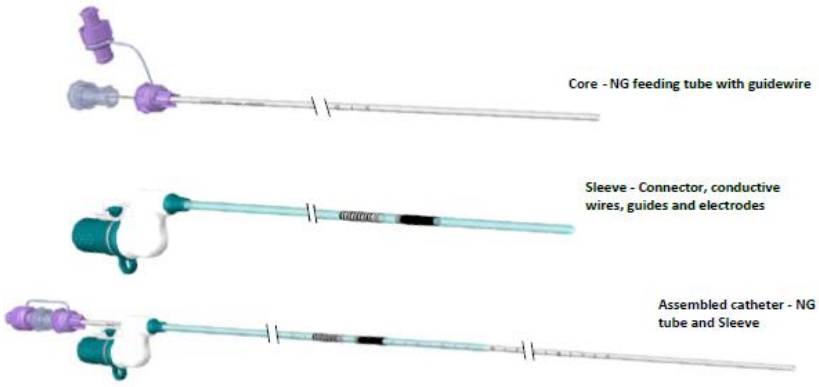


Figure 7: Phagenyx Catheter

Manufacture

The Phagenyx® system is manufactured by Phagenesis Ltd (Manchester UK. It has an EU CE Mark and FDA breakthrough device designation. There is no control device. Phagenesis will provide devices (catheters, base stations) and training in their use without charge.

Packaging and labelling

The catheter is supplied by Phagenesis Ltd as a single-use sterile product. The catheter and accessories are supplied in a formed tray (***Figure 8***). The tray and contents are terminally sterilized using ethylene oxide.

There are two accessories parts supplied with the catheter:

1. A Garment Clip to secure the external parts of the catheter to alleviate weight
2. A Transition Adaptor to enable standard connections for feeding delivery

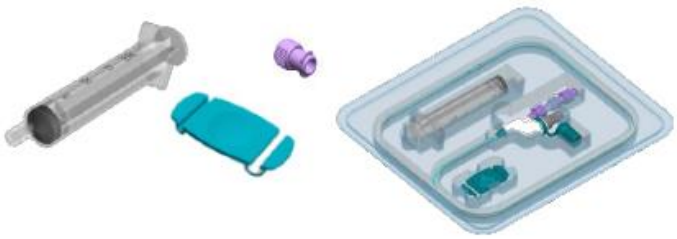


Figure 8: Phagenyx Catheter packaging with accessories

Storage, dispensing and return

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

The device is CE-marked and will not be labelled as investigational. Sites will be provided a Base Station for the trial (which will be additional to any base station that they already have for routine clinical use).

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

Placebo/Sham

There is no placebo/sham. Participants randomised to control will receive no PES catheter/stimulation on top of best guideline-based dysphagia management. A standard NGT will be used for feeding as necessary.

Known Side Effects

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

The Phagenyx® System is a non-significant risk (NSR) device and its safety profile is well characterized by evidence accumulated from multiple phase II, III and IV clinical studies over a period of 15 years. There are no characteristic device or treatment specific effects that are considered to be serious adverse events - please see section on Serious Adverse Device Events. The additional risks associated with the clinical study design are all well understood and can be easily mitigated. None of the protocol-specific assessments are expected to add significant risk over those risks inherent in the care of patients suffering dysphagia in the subacute stroke setting.

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

PES should not be used in the presence of any active implanted electrical device, e.g., cochlear implant, implantable cardioverter-defibrillator (ICD), permanent pacemaker.

Reference Safety Information:
Since the Phagenyx® system has a CE Mark and is already marked in the enrolling countries, and there is no placebo/sham control, no investigator brochure is needed.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

To assess whether PES is safe and effective at improving post-stroke dysphagia.

PRIMARY OBJECTIVE

To assess whether 6 days of PES accelerates return to oral intake of food and drink as assessed using the dysphagia severity rating scale and blinded to treatment.

SECONDARY OBJECTIVES

To assess whether:
- PES improves swallowing and reduces pneumonia, antibiotic exposure, hospital length of stay, and disability.
- PES increases quality-of-life.
- PES is cost effective as compared to usual care.
- Participant subgroups predict response to PES.

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

International prospective randomised open-label blinded-endpoint (PROBE) parallel group superiority phase IV effectiveness trial of PES vs no PES in hospitalised patients with subacute stroke and dysphagia.

Primary endpoint

Dysphagia assessed using DSRS (***Table 2***), based on bedside clinical assessment/management conducted at days 14±1 post randomisation. Outcome assessment will be assessed by DSRS/FOIS-trained research coordinators, nurses or SLTs who are not involved in treatment.

Table 2: DSRS and subscales giving old consistencies and new IDDSI levels.[32]
(*SALT = speech and language therapist****)***

Score	Fluids	Score	Diet	Score	Supervision
4	No oral fluids	4	Non oral feeding	4	No oral feeding
3	IDDSI level 4 – extremely thick	3	IDDSI level 4 - pureed diet or level 5 – minced & moist	3	Therapeutic feeding (SALT/trained staff)
2	IDDSI level 3 – moderately thick	2	IDDSI level 6 – soft & bite sized	2	Feeding by third party (untrained)
1	IDDSI level 1 – slightly thick or level 2 mildly thick	1	IDDSI level 7 - easy to chew	1	Eating with supervision
0	IDDSI level 0 - thin	0	IDDSI level 7- regular	0	Eating independently

DSRS supervision score 3 is always chosen when a patient is on limited or consistent oral trials and still requires NG/ PEG tube.
Oral trials are scored from the fluid and diet subscales (i.e. 3 onwards) and can be either trials of food *or* fluid or trials of food *and* fluids.

Secondary endpoint

Day 7±1 (end-of-treatment) by hospital treating staff blinded to baseline: PES threshold, tolerability and stimulation currents; number of catheters used.
Day 14±1 by hospital (or telephone) assessor blinded to treatment:[11] DSRS >3,[21] FOIS, EAT-10 [33] and feeding status score (FSS);[34] NGT/PEG in situ; pneumonia; antibiotic use; weight; EQ5D5lEQ-VAS (patient/proxy).
Note 1: We have included several measures of dysphagia and feeding: DSRS, FOIS, EAT-10 and FSS to triangulate the presence and magnitude of dysphagia and effects on feeding. These will be analysed together using the Wei-Lachin test.[1]
Discharge/death by hospital assessor blinded to treatment: Length of stay; pneumonia/use of antibiotics; swallowing therapy contact time; time to removal of NGT/PEG; admitted to ICU; discharged with PEG; disposition (home, residential home, nursing home, hospital, death).
Day 90±7 by central telephone assessor blinded to baseline, treatment and in-hospital data (or by post): DSRS, FOIS, EAT-10, FSS; home time;[35] dependency (modified Rankin Scale [2]), disability (Barthel Index), quality of life (EQ-5D5L/EQ-VAS.), cognition (TICS [3]), mood (Zung [4]);[2,5-9] disposition.
Day 365: All-cause mortality (from Office of National Statistics).
Cost
Health service resource use at discharge
Resource Use at day 90

Safety endpoints

PES has an excellent safety record in previous trials whilst participants with PSD, who usually have severe stroke, will have multiple adverse events and SAEs. Hence, we will limit recording to:

- SAEs over 0-7 days.
- Procedure/device-related (S)AEs over days 0-14.
- Discontinuations due to (S)AEs.
- Fatal SAEs over days 8-90 days.

Events will be adjudicated blinded to participant information and treatment assignment.

Stopping rules and discontinuation

By data monitoring committee
The stopping rules for effectiveness are based on the combination of presence of 'proof beyond a reasonable doubt' and the likelihood that the results would change clinical practice. The possible DMC recommendations at any assessment are:

1. *Stop enrolment if the study is negative, i.e., treatment is hazardous*: statistical evidence that DSRS or fatal SAE rates are significantly higher in the PES than sham group (p<0.01);
2. *Stop enrolment if the study is positive, i.e., treatment is beneficial:* the combination of statistical evidence that DSRS is significantly lower in the PES than sham group "beyond reasonable doubt" (i.e. Haybittle-Peto boundary rule, p<0.001 [36]) and the overall trial results will lead to a change in clinical practice, e.g. by taking account of delta DSRS and evidence that at least some secondary outcomes are also being benefitted (some of, e.g. FOIS, length of hospital stay, pneumonia, antibiotic use).
3. *Continue enrolment if the study is neutral:* or if conditions 1 and 2 are not present.
4. *Modify study design* – if it appears that:
    i. Sample size calculation assumptions were incorrect, e.g., if standard deviation exceeds 6.0;
    ii. Apparent study design aspects will lead to incorrect study conclusions;
    iii. Specific clinical procedures jeopardise the safe execution of the study.

Formal statistical analyses will be used as "stopping guidelines" rather than absolute rules. In the light of interim data, and other evidence from relevant studies (including updated overviews of relevant randomised controlled trials), the DMC will inform the TSC, if in their view there is proof beyond reasonable doubt that the data indicate that the intervention is either clearly indicated or contra-indicated, either for all or for a particular subgroup of study participants. A decision to inform the TSC will in part be based on statistical considerations. Appropriate criteria for proof beyond reasonable doubt are not specified precisely. A difference of at least 3 standard errors in the primary endpoint may be needed to justify halting, or modifying, the study prematurely. This approach has the practical advantage that the exact number of analyses are of little importance, and so no fixed schedule is proposed. The DMC may also consider supporting evidence from secondary outcomes in their decision making, but the overall guidance remains that the results should be sufficiently convincing to change practice.

Participants may stop treatment if they, their family (if they lack capacity) or their clinical team wish for this.

By funder

There will be two trial phases separated by a stop- go decision (***Table 3***):

Internal pilot phase (vanguard phase): Recruitment of 150 participants from 15 sites by month 15 (0.84 ppm) (***Figure 9***). These sites will necessarily include those of the applicants and some larger hospitals with existing PES experience. Progression criteria from pilot to main phase and necessary actions are shown in ***Table 3***.

Table 3: Trial progression criteria - target recruitment rate 0.83/site/month

	N	Black	Red	Amber	Green
% threshold		<35%	35-69%	70-99%	>=100%
Participants recruited	150	<53	53-104	105-149	>=150
Sites opened	15	<5	5-10	11-14	>=15
Actions		Stop trial	Actions 2	Actions 1	Continue trial

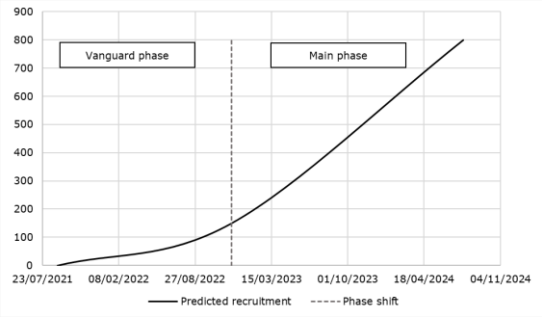
Amber actions 1: Increase recruitment - protocol review, identify/remove barriers, re-train sites, increase recruitment at active sites/close inactive sites, increase number of sites.

Red actions 2: as for amber + acceleration plan as per HTA.

We will review recruitment of sites and participants monthly and commence mitigation measures if it becomes clear that the study is behind schedule.

There will be no break in recruitment between phases unless recommended by the DMC.

Figure 9: Planned recruitment rate showing stop-go decision point ➔



Main phase: Recruitment of 650 participants over 18 months from an additional 35 sites, so 50 sites in total (0.73 ppm) (***Figure 9***). The expected recruitment rate is slightly lower than in the pilot phase since there will be a higher proportion of lower volume stroke sites. The reason for this difference is to ensure the main protocol works in experienced sites before expanding out to sites where PES-training will be key.

RANDOMISATION AND BLINDING

Efficacy/futility/safety stopping rules

Randomisation

Adaptive randomisation PES:control 1:1 will use stratification on country and minimisation on age (<75/75+), sex, DSRS (<12/12), impairment (NIHSS <15/15+), stroke type (ischaemic/haemorrhagic), circulation (anterior/posterior), time to randomisation (<15/15+ days); 10% simple randomisation. This randomisation approach increases statistical power.[37] The randomisation-stratification-minimisation system is that used in prior trials (ENOS, TARDIS, PODCAST, TICH-2, RIGHT-2) [7-9,38,39].

Whilst investigators, participants and their family will be unblinded, outcome assessors will be blinded to treatment. Nevertheless, although PES will not be masked, many participants will have severe stroke and will have a nasogastric tube inserted and so they may be unaware of treatment assignment.

Investigators (medics, research nurses/healthcare professionals, speech therapists) many enrol participants. Randomised treatment assignment will occur when essential baseline data are entered into the trial computer system by investigators. As such, allocation is concealed from investigators up to the time that they have screened, consented and collected and entered baseline data into the trial database.

Maintenance of randomisation codes and procedures for breaking code

Adaptive randomisation will use minimisation so there will be no treatment code lists. The trial computer system will record what treatment each participant is assigned to.

The trial will have a prospective randomised open-label blinded-endpoint (PROBE) design so participants randomised to control will receive standard care. Outcomes will be assessed blinded to treatment assignment.

Investigators who are not involved in outcome assessment can determine, if necessary, what treatment is being received by seeing if they have a PES tube inserted. Masked outcome assessors should never need to unblind themselves.

TRIAL MANAGEMENT

The Chief Investigator has overall responsibility for the study and will oversee all study management and is the data custodian.

The trial will be overseen by a Trial Steering Committee (TSC) and independent Data Monitoring Committee (DMC) and run by a Trial Management Group (TMG). It will be managed from the International Coordinating Centre (ICC) based in the Nottingham Stroke Trials Unit (STU); the ICC will also manage UK sites whilst National Coordinating Centres (NCC) will manage sites in Austria, Denmark and Germany. Each country will be responsible for obtaining and managing local approvals. Funded trial staff will be based at the ICC; NCCs will use existing local staff, as done in ENOS and TARDIS. NCCs will join the TMC for regular videoconferences to ensure timely recruitment and follow-up, and to address developing problems. Sites will be trained on trial processes by the ICC and NCCs, videos on the website and via the protocol and manual; specific training on PES will be given by Phagenesis and the trial SLT. Specific trial materials (protocol summary, PIS/RIS, consent forms, manual, videos) will be translated into German and Danish. Further details are given below.

Trial Steering Committee
This will lead the trial strategically, reviewing recruitment rate, treatment delivery, data integrity and trial event rates. Any new data emergent from other trials will be discussed for potential impact on PhEAST. The TSC will work according to a charter.
Independent members: Chair, the independent PPI member and remaining members will be appointed from UK/AT/DE/DK from non-participating institutions as per NIHR rules.
Dependent members: Applicants, Sponsor.
Observers: HTA representative, Phagenesis representative, Sponsor representative, Trial Manager, Speech therapist.

Trial Management Group
This will manage the trial daily and will meet every three weeks. The group will monitor trial accrual, centre management (with local CRN research nurses/practitioners) and ensure recruitment strategy remains on target. Centres will be regularly contacted in the event of participant attrition. This approach will be mirrored in the National Coordinating Centres in AT, DE and DK.
Members: CI, senior trial manager, coordinators, trial statistician, programmer and trial manager.

Independent Data Monitoring Committee
This will review safety as well as the validity and scientific merit of the trial. Unblinded data will be provided by a statistician with no other role in the study and discussed twice yearly. A DMC Charter will be drawn up in line with the Damocles Study Group Guidance.[40] The Charter will define the schedule and format of twice yearly meetings (or scheduled as necessary), the method and timing of interim reports and stopping rules:
Members: We propose Prof Ken Lees (Chair, Glasgow UK; who approves of this stopping approach); the remaining 4 members will be appointed from UK/AT/DE/DK from non-participating institutions as per NIHR rules.

Serious adverse events adjudication
Since there are considerable safety data on PES already and taking note that the trial is open-label, we will adjudicate all serious adverse events up to 7 days, and fatal SAEs for days 8-90, and all procedure/device-related (serious) adverse events.

Sites, investigators and monitoring
Investigators will be trained in trial procedures via a site initiation teleconference after obtaining all the necessary regulatory approvals. New investigators who join the study after site initiation training

will be required to complete on-line training and a brief assessment covering the trial protocol and good clinical practice relative to their role in the study. We will perform central monitoring on consent forms and treatment allocation for all participants, and primary endpoint data for a subset. In a proportional approach, we will not perform local onsite monitoring unless triggered at sites due to concerns over data quality or integrity.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Participant Duration: 12 months

Study Duration:

- 39 months

End of the Trial

Final follow-up assessment at 12 months post randomisation (all cause mortality).

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Trial setting: Secondary/tertiary care (district or teaching hospital). These hospitals host comprehensive and acute stroke services.

Participants will be recruited from hospital stroke service wards. The initial approach will be from a member of the patient's usual care team (which may include the investigator or stroke research nurses/coordinators).

The investigator or their designee, e.g. from the research team or a member of the participant's usual care team, will inform the participant or their consultee/representative (other individual or other body with appropriate jurisdiction), of all aspects pertaining to participation in the study. The consultee/representative will also be asked whether any advance decisions may have made about participating in research as this should take precedence.

Historically women and patients from Black, Asian and minority ethnic communities have been underrepresented in stroke trials. Our pragmatic inclusion criteria have no exclusions based on protected characteristics (including age, sex, ethnicity, religion, socioeconomic status) or geography and this should increase inclusivity and fairness (and negates the need for an Equality Impact Assessment). Recruiting staff will be reminded about the importance of inclusivity and fairness. The baseline eCRF will collect information on these and other participant characteristics. In the absence of relevant safety data, pregnancy will be excluded.

There are no healthy volunteers in the trial.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial. The participant information sheets, and consent forms, will be available printed in other languages as appropriate for the recruiting countries.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time, but attempts will be made to avoid this occurrence. In the event of their

withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Eligibility criteria

Inclusion criteria

1. 800 hospitalised adults:
2. Age >=18 years.
3. Recent (4-31 days) ischaemic or haemorrhagic, anterior or posterior circulation, stroke (as diagnosed clinico-radiologically) at a stroke centre.
4. Clinical dysphagia defined as a functional oral intake scale (FOIS [41]) score of 1 (nothing by mouth, feeding by NGT/PEG) or 2 (tube dependent with minimal attempts of food or liquids).

Women of childbearing age may be included since the treatment time is short (6 daily 10 minute sessions) with no residual effects.

Exclusion criteria

1. Non-stroke dysphagia, e.g. due to traumatic brain haemorrhage, subarachnoid haemorrhage, brain tumour, Parkinson's disease, multiple sclerosis, severe dementia, head or neck cancer.
2. Pre-stroke dysphagia or dependency (modified Rankin scale, mRS 4/5).
3. Ongoing or anticipated ventilation/intubation/tracheostomy.
4. Use or planned use of electrical or magnetic stimulation (e.g. NMES, rTMS).
5. Malignant middle cerebral artery syndrome (although this typically presents before 4 days).
6. Pacemaker.
7. Need for >2 litres of oxygen.
8. Two or more NGT tubes pulled out unless nasal bridle in place.
9. Investigator feels patient will not tolerate PES catheter.
10. Expected to be discharged or transferred to a site not running the trial during the PES treatment period.
11. Pregnancy if known at time of enrolment
12. Participating in another randomised controlled treatment trial for post-stroke dysphagia.

Expected duration of participant participation

Study participants will be participating in the study for 12 months.

Removal of participants from therapy or assessments

Discontinuation and withdrawal

Once enrolled, participants, their relative (if the participant still lacks capacity), the site PI, or the CI, may:

- Temporarily discontinue the 6 days of PES, e.g., if they transiently deteriorate;
- Discontinue further PES, e.g., if they suffer an adverse event and decide they no longer want PES;
- Temporarily discontinue follow-up, e.g., refuse follow-up at a particular timepoint;
- Withdraw from the trial, including from further PES (if still in the treatment phase) and from all further follow-up, e.g., if they withdraw consent from the trial. Participants must be withdrawn from study if they withdraw consent. Site and trial staff may discuss with the participant the importance of collecting the primary outcome and so limiting the effect of withdrawal. Participants should be told that withdrawal:

- Will not affect their future care.
- Will not affect data collected up to the date of withdrawal, i.e., it cannot be erased and may still be used in the final analysis.

eCRF forms will record (temporary) discontinuation of PES or follow-up, or withdrawal from the trial.

Participants who withdraw after randomisation will not be replaced.

Lost to follow-up
Participants will be deemed to be lost to follow-up once at least four attempts to make contact, e.g., involving phone calls, letters, have been fruitless.

Informed consent

Consent and proxy consent
The investigator (or designee) is responsible for performing consent procedures for each patient enrolled in the study. Written informed consent will be obtained, or a consultee declaration in England, Wales and Northern Ireland from a relative consultee (by phone if not allowed in hospital) if patient lacks capacity. Personal consultees will be asked whether they know of any advance decisions by the patient with regards to participating in research as these should take precedence. In Scotland consent from a legal representative will be sought where potential participants lack capacity. Since patients with dysphagia typically have severe stroke and so may have parallel cognitive, language (dysphasia) or wakefulness problems, it is vital that consultee opinion/legal representative consent may be sought where the patient lacks capacity. This approach has been used in previous trials in patients with acute stroke and/or dysphagia: STEPS, TARDIS, TICH-2, RIGHT-2, PHAST-TRAC, PHADER.[7-9,22-24] Participant consent will be sought if the participant regains capacity.

Information
Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. The investigator (or designee including doctors, nurses, speech therapists and research health professionals) will all be trained in consent and assessing capacity. Capacity will be assessed by the Investigator or designate to ensure the potential participant understands the purpose, procedures and potential risks of the study. If the patient is deemed by the Investigator or designate to lack capacity (e.g. due to confusion, cognitive impairment or severe dysphasia), an opinion will be obtained from their consultee or consent from a legal representative in Scotland. The Investigator or designate will then provide the patient or consultee/legal representative a Participant Information Sheet and explain the research study, and then answer any questions that may arise. If the consultee/legal representative cannot attend the hospital, the consultee's opinion or legal representative consent, may be obtained remotely by videoconference or telephone/teleconference means; the Participant Information Sheet will be sent by email or post.

Consent will be explicit and cover both participation and use and retention of the trial data. A verbal explanation will be provided in terms suited to the patient's or consultee's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research patients. Pictures and simplified written language will be used where relevant to facilitate comprehension of information. Patients or consultees will have the opportunity to carefully review the written consent/declaration forms and ask questions prior to signing. Patients should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

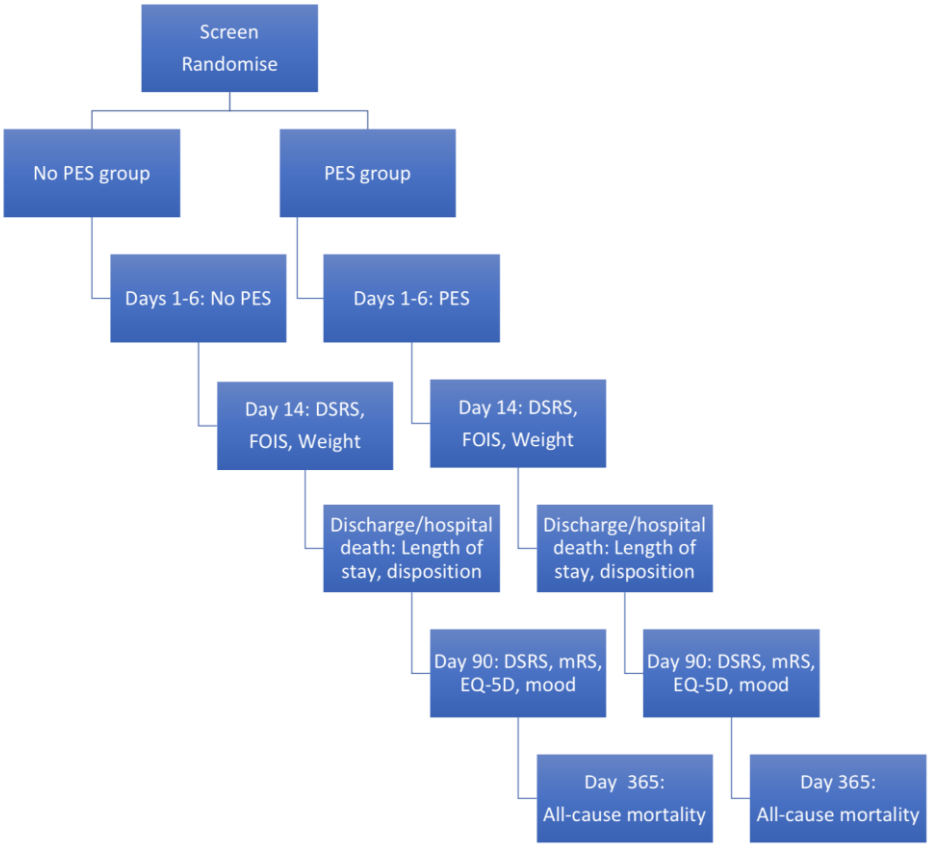
The patient or consultee will sign the consent/declaration form prior to any procedures being done specifically for the study. Consent will be witnessed by a third party if the patient lacks the ability to write a signature (e.g., due to dominant hand weakness) or where approval is provided by a consultee by phone. Patients must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. One copy of the consent form will be kept by the participant or consultee, one will be kept by the Investigator, and a third will be retained in the patient's hospital records. The informed consent process will be conducted and documented in the patient's medical notes. The rights and welfare of the patients will be protected by emphasising to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Should there be any subsequent amendment (e.g., to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant or consultee.

TRIAL / STUDY TREATMENT AND REGIMEN

Design

International prospective randomised open-label blinded-endpoint (PROBE) parallel group superiority phase IV effectiveness trial of PES vs no PES in hospitalised patients with subacute stroke and dysphagia. The design is based on previous trial experience (including one funded by NIHR RfPB [20]), a NIHR-funded Cochrane systematic review,[14] and two NIHR Stroke Research Network-funded planning workshops.[11] We will embed a Study Within A Trial (SWAT) aimed at maximising PES treatment current.

Trial flow



Patient flow
Participants will receive treatment (if randomised to PES) and follow-up as shown in *Table 4*.

Table 4. Flow of participants

	Screen	Baseline	Day 1-6	Day 14	Discharge or death	Day 90 †	Day 365 ‡
Location	Hospital	Hospital	Hospital	Hosp. or outside	Hospital	Hosp. or outside	Centrally
Eligibility	+						
Consent/proxy consent	+						
DSRS FOIS EAT-10 FSS		+		+		+	
NIHSS, GCS		+		+			
Randomisation		+					
PES vs no PES			<>				

Targeted outcomes: pneumonia			<	>			
All SAEs			<>				
Device-related (S)AEs			<	>			
Fatal SAEs			<	=	=	>	
All-cause mortality						+	+
Disposition					+	+	
QoL: EQ-5D, EQ-VAS				+	+	+	
mRS, BI, TICS, ZDS, home-time						+	
Resource use					+	+	

BI: Barthel index; DSRS: dysphagia severity rating scale;[32] EAT-10: eating questionnaire; EQ-5D: EuroQoL-5-dimension; EQ-VAS: EuroQoL visual analogue scale; FOIS: functional oral intake scale;[41] FSS; feeding status scale;[34] GCS: Glasgow coma scale; Hosp: hospital; NIHSS: National Institutes of Health stroke scale; QoL: quality of life; ZDS: Zung depression scale, abbreviated.[4]
† telephone (postal) follow-up ‡ office for national statistics

These measures will be recorded at baseline and after randomisation by the Investigator or designate with information provided by the patient if able, or consultee or carer if the patient is deemed not to be a reliable source of information. Information will be collected:

- From the patient/consultee in hospital: screening, baseline, day 1-6, day 14
- From the patient/consultee in hospital or wherever they have been discharged to (another hospital, rehabilitation institution, care home, own home): Day 14, day 90
- Centrally using routine national data: Day 365

Information on death, including date and cause, will be collected using the hospital's data or central routine data.

Participants randomised to PES will receive it as described above and on top of standard care. Participants randomised to no PES will receive standard care alone.

Health technologies being assessed

Intervention arm: PES on top of guideline-based standard-of-care. PES will be administered on days 1-6 using a commercial catheter (Phagenyx®, Phagenesis Ltd, Manchester UK) with integral feeding tube. PES involves six once-daily 10 minute treatments over 6 days with treatment at 5 Hz; treatment will cease if participants regain normal feeding or are discharged early. Threshold and tolerability currents will be assessed prior to each daily treatment and the PES current set at threshold + 0.75 x (tolerability - threshold) with current generated by a base-station.[19-25] Dosing levels will be monitored and sites informed if the stimulation current is too low, i.e. <20 mA; sites will be re-trained on the importance of delivering adequate current, if necessary. The catheter will be replaced once only if pulled out before 3 treatments have been administered. Treatment will be administered by PES-trained research coordinators, nurses or SLTs who are not involved in outcome data collection. Treatment will be stopped if there is no further need for tube feeding. See below for Training.

Comparator arm: No PES catheter/stimulation on top of best guideline-based dysphagia

management. A standard NGT will be used for feeding as necessary.
Durations: From randomisation: treatment for 6 days, primary outcome at day 14, final follow-up at day 90. Day 365 , all cause mortality. Trial and funding 3.25 years.
Blinding of treatment arms: PROBE design - open-label with blinded outcomes.[23]
Note 1: The value of treatment blinding has been challenged recently.[42]
Dysphagia management: Guideline/standard-of-care will be recommended and recorded using a structured questionnaire encompassing type and duration of dysphagia treatment. Test feeding will be managed as per local practice.
Study Within A Trial: We will embed a SWAT aimed at maximising PES treatment current (see later section describing this).

Concomitant and Rescue Medications and Treatments

PES does not influence any decisions relating to drug administration or other routine treatments (including physiotherapy, occupational therapy, speech therapy), including use of low flow oxygen (2 litres/minute). Other stimulatory techniques (neuromuscular electrical stimulation, transcranial magnetic stimulation, transcranial direct current stimulation) should not be used. Concomitant medications present at baseline should be kept constant from screening throughout the study.

There are no rescue interventions save stopping further PES treatment cycles.

Adherence

Six daily 10 minute PES treatments will be administered by a researcher trained in PES delivery (e.g., doctor, nurse, speech therapist, research health care professional for participants randomised to PES. Participants randomised to no PES will not receive any additional treatment.

Information on PES treatments will be recorded on the eCRF for each daily treatment cycle: threshold level (mA), tolerability level (mA), calculated stimulation level (mA), delivered stimulation level (mA), and length of treatment (minutes). Tolerability level is best assessed by watching the participants face and body for evidence of discomfort rather than repeatedly asking if the current level is excessive (which often leads to lower stimulation levels). Delivered stimulation is expected to be >= 20 mA and the same as calculated stimulation level.

Information on deviations from the treatment protocol - delivered stimulation level < calculated stimulation level, delivered stimulation level < 20 mA, treatment for < 10 minutes - will be recorded on the eCRF.

Accountability for the device

Accountability logs will be used at each site to log the location of each device as well as the number and location of catheters. Catheter use will be recorded with participant anonymised identifier using the catheter. All devices will be returned to the coordinating centre at the end of the trial.
*Unused catheters should be returned to the company/kept for future open-label use.

Management of study treatment overdose

Potential causes of over treatment include PES given:

- For more than 10 minutes - the base station prevents this;
- For more than 6 days - the device catheters prevent this;
- At too high a current - the participant would indicate this as severe discomfort. Correct calculation of treatment current from threshold and tolerance currents will prevent this.

In each case, turning the base station off will prevent over-treatment.

Urgent Safety Measures

An Urgent Safety Measure is a procedure taken to protect a research participant when that participant is identified as being at risk of harm in relation to their involvement in a research project and urgent action, which deviates from the approved protocol, is required to manage the event and protect the participant.

PES treatment may be stopped at any time by the press of a button on the control base station. Any urgent safety measures will be conveyed as soon as possible to the sponsor and device manufacturer.

Protocol Deviations and Violations

Protocol Deviation: These are minor deviations from the protocol that affect the conduct of the trial in a minor way. This includes any deviation from the trial protocol that is not listed as a Protocol Violation. Due to the wealth of published knowledge about PES, deviations will not be recorded.

Protocol violation: These are a major deviation from the trial protocol, for example where a participant is enrolled in spite of not fulfilling all the inclusion and exclusion criteria, or where deviations from the protocol could affect participant safety, the trial delivery or interpretation significantly. Listed protocol violations are:

1. Treatment without consent.
2. Treatment but ineligible.
3. Non-reporting of primary outcome measure.
4. Non-reporting of serious adverse event (SAE), serious adverse device event (SADE), serious unanticipated adverse device event (SUADE).

All protocol violations must be reported immediately to the Chief Investigator, via the online electronic case report form. The CI will notify the Sponsor if a violation has an impact on participant safety or integrity of the trial data. The Sponsor will advise on appropriate measures to address the occurrence, which may include reporting of a serious GCP breach, internal audit of the trial and seeking counsel of the trial committees.

Criteria for terminating trial

The trial may be terminated by either the TSC, the sponsor or the funders if there is overwhelming evidence of major safety concerns, new information, or issues with trial conduct (e.g. poor recruitment, loss of resources). The trial may be stopped at individual centres due to unacceptable performance in recruitment and/or failure to comply with protocol.

Any unused and partially used devices shall be returned to the manufacturer.

RADIATION EXPOSURE

No study-specific radiation procedures will be undertaken.

Details of diagnostic or therapeutic ionising radiation

No trial-specific diagnostic or therapeutic ionising radiation procedures will be untaken. The admission CT scan is routine for clinical diagnosis and part of normal care and will have antedated enrolment into the trial by at least a week.

Clinical Assessment

No study-specific radiation procedures will be undertaken so the only radiation exposure is that associated with normal clinical procedures, e.g., admission head CT scan.

STATISTICS and DATA MANAGEMENT PLAN

DATA MANAGEMENT PLAN (DMP)

The DMP will be written as a separate document. It will cover:

- Contact details for relevant trial staff including roles and responsibilities with regard to data management, indicate access controls and restrictions.
- Details of the flow of data from investigator site to archiving.
- Trial database to be used, including data audit trail, maintenance, disaster recovery plans and data backup system.
- Data coding.
- Data monitoring plans e.g. frequency, source data verification.
- Data protection procedures, including electronic transfer requirements.
- Data storage.

Data Capture and Data Queries

Data will be captured using an electronic case record form (eCRF) built using the REDCap database system. eCRF 'pages' will comprise:

- ***Baseline***: demographic (including information on some protected characteristics - age, sex, ethnicity); stroke (type, severity, syndrome); CT scan (lesion type/size, small vessel disease, atrophy, old lesions - information from report on routine admission scan). Information will be used for randomisation.
- ***Day 7±1 (end of treatment) by hospital treater blinded to baseline***: treatment-related (PES threshold, tolerability and stimulation currents; number of catheters used).
- ***Day 14±1 by hospital (or telephone) assessor blinded to treatment***:[11] Primary outcome (DSRS), secondary outcomes (FOIS, EAT-10,[33] feeding status,[34] NGT/PEG in situ; pneumonia; antibiotic use; weight; EQ-VAS).
- ***Discharge/death by hospital assessor blinded to treatment***: Length of stay; swallowing therapy contact time; pneumonia; antibiotics; time to removal of NGT/PEG; admitted to ICU; discharged with PEG; disposition (home, residential home, nursing home, hospital, death).
- ***Secondary at day 90±7 by central telephone assessor blinded to baseline, treatment and in-hospital data (or by post)***: DSRS, FOIS, EAT-10, FSS; home time;[35] dependency (modified Rankin Scale [2]), disability (Barthel Index), quality of life (EQ-5D5L/EQ-VAS.), cognition (TICS [3]), mood (Zung [4]);[2,5-9] disposition.
- ***Day 365 – all cause mortality.***

Investigators will access the database over the internet using an encrypted link and via a log-in/password system. They will be trained via a training slide set and manual (covering the eCRF).

The database will check and query in real time for logic and range errors. Essential fields will require mandatory data entry. This approach will reduce missing data and prevent protocol violations related to inclusion/exclusion criteria. Any remaining protocol violations will lead to exclusion of the participant from the per protocol data set.

Description of Data Entry Validation

The REDCap database system will be used to collect clinical and trial data. Test data will be entered for validation purposes. Logic checks (e.g., PES treatment levels cannot vary by >30% between treatment sessions) and range checks (e.g., age>=18 and <105) will be built in to reduce errors. Regular assessments of exported pseudo-anonymised data will test for incorrect data; identified errors will be passed back by trial staff to the recruiting site for correction. Data corrections will be recorded.

Data Cleaning and Database Lock

The database with be regularly downloaded and assessed for logical or range inaccuracies. The same will be performed after data lock. Database lock will comprise copying the database from REDCap and preventing further changes. Anonymised data will be archived and shared for legitimate tertiary analyses and meta-analyses.

Monitoring

Remote monitoring will be carried out with analyses of data logic and range checks by sites, and assessment for unusual data patterns (e.g., digit preference, non-random data). Where there is uncertainty about the veracity or accuracy of data, a site will be visited and monitored with data comparison against source data.

STATISTICS

Methods

The analysis and presentation of the trial results will be in accordance with the CONSORT guidelines. The primary outcome will be compared as randomised without imputation of missing data. Due emphasis will be placed on the confidence intervals for the between arm comparisons. A full Statistical Analysis Plan (SAP) will be developed and published prior to database lock.

Characteristics of randomised participants will be compared between the two trial arms at baseline, using appropriate descriptive statistics: number %, median [interquartile range], mean (standard deviation). Analysis of the primary outcome will be performed by intention-to-treat using multiple linear regression, with adjustment for stratification/minimisation factors (country, age, sex, DSRS, NIHSS, stroke type, circulation/syndrome, time onset to randomisation), and fully specified in the SAP. Secondary outcomes will similarly be compared using multiple linear regression (e.g. Barthel index), ordinal logistic regression (e.g. mRS, FOIS), and Cox proportional hazards regression (e.g. time to NGT/PEG removal, death), again each with adjustment for randomisation factors. Absolute and relative measures of effect and 95% confidence intervals will be presented for each analysis. A worst score will be assigned at day 90 for people who die (e.g. DSRS=13, FOIS=0, mRS=6) to avoid losing participants in analyses and missing a “kill or cure” effect, and to anchor analyses, as we did in ENOS, TARDIS and RIGHT-2.

The primary outcome, DSRS, will be assessed in pre-specified subgroups, as specified in the SAP, using interaction tests to identify responder subgroups (as we did in STEPS, PHAST-TRAC and PHADER): country, age, sex, NIHSS, DSRS, stroke type (ischaemic, haemorrhagic), anterior vs

posterior circulation, onset to randomisation time; lesion side (right, bilateral, left). Since the trial is powered to detect overall differences between groups rather than subgroup interactions, these analyses will be regarded as hypothesis generating. The importance of these subgroup analyses is highlighted by identical findings in PHAST-TRAC and PHADER that PES appears to more effective if treatment is started within the first month after stroke.

The trial statistician will perform statistical analyses using code written in the R language. One formal interim analysis will be performed to guide the DMC at the stop-go time-point. The stopping rules for effectiveness are based on the combination of presence of 'proof beyond a reasonable doubt' and the likelihood that the results would change clinical practice. The possible DMC recommendations at any assessment are:

1. *Stop enrolment if the study is negative*: statistical evidence that DSRS or fatal SAE rates are significantly higher in the PES than sham group ($p<0.01$);
2. *Stop enrolment if the study is positive:* the combination of statistical evidence that DSRS is significantly lower in the PES than sham group "beyond reasonable doubt" (i.e. Haybittle-Peto boundary rule, $p<0.001$ [36]) and the overall trial results will lead to a change in clinical practice, e.g. by taking account of delta DSRS and evidence that at least some secondary outcomes are also being benefitted (some of, e.g. FOIS, length of hospital stay, pneumonia, antibiotic use).
3. *Continue enrolment if the study is neutral:* or if conditions 1 and 2 are not present.
4. *Modify study design* – if it appears that:
    a. Sample size calculation assumptions were incorrect, e.g., if standard deviation exceeds 6.0;
    b. Apparent study design aspects will lead to incorrect study conclusions;
    c. Specific clinical procedures jeopardise the safe execution of the study.

Formal statistical analyses will be used as "stopping guidelines" rather than absolute rules. In the light of interim data, and other evidence from relevant studies (including updated overviews of relevant randomised controlled trials), the DMC will inform the TSC, if in their view there is proof beyond reasonable doubt that the data indicate that the intervention is either clearly indicated or contra-indicated, either for all or for a particular subgroup of study participants. A decision to inform the TSC will in part be based on statistical considerations. Appropriate criteria for proof beyond reasonable doubt are not specified precisely. A difference of at least 3 standard errors in the primary endpoint may be needed to justify halting, or modifying, the study prematurely. This approach has the practical advantage that the exact number of analyses are of little importance, and so no fixed schedule is proposed. The DMC may also consider supporting evidence from secondary outcomes in their decision making, but the overall guidance remains that the results should be sufficiently convincing to change practice.

Sample size and justification

The primary outcome, DSRS, will be compared between PES and no PES using multiple linear regression with adjustment for stratification and minimisation variables. The null hypothesis is that PES does not alter DSRS at day 14 in participants with PSD.

Assuming 1:1 randomisation; alpha 5% (two-tailed); power 90%; DSRS difference 1.2 (this target difference lies in the minimal clinically important difference range of 0.3-2.5 [32]); standard deviation 5.0; losses 3% (greater than seen in previous PES trials); crossovers 3%; sample rounded up; a sample size of N=800 is needed (PES n=400, control n=400) (assumptions based on pilot trials and STEPS [19-22]) (using standard t test sample size formula). We and others have shown that adjustment for covariates improves statistical power [43-45] and so can reduce sample size; however, we have not taken account of this in the above sample size calculation since the relevance of these findings to analysis of DSRS remains unclear. Nevertheless, it is likely that covariate adjustment will improve statistical power so that the final power will probably be greater than assumed here.

Recalculation of sample size: We will investigate our assumptions for the standard deviation of the primary outcome and for the proportion of participants with missing primary outcome data. We will discuss any variation in these parameters with the DMC and TSC and any proposed revision to the target sample size.

Sensitivity calculations
The sample size varies by the difference in DSRS between PES and no PES (***Table 5***).

Table 5. Sample size for a variety of mean differences in DSRS between PES and no PES.

Mean difference	0.7	0.8	0.9	1.0	1.1	**1.2**	1.3	1.4	1.5	1.6	1.7
Total trial size	2300	1800	1400	1200	1000	**800**	700	600	500	500	400

Conversely, the power varies by the final achieved sample size, assuming delta 1.2 (***Table 6***).

Table 6. Power of trial by achieved final sample size

Size	1000	900	800	700	600	500	400
Power (%)	0.97	0.95	0.92	0.89	0.84	0.76	0.67

HEALTH ECONOMICS

Measurement of costs and outcomes - Health-economic analyses

The health economic analysis will be conducted from a health and social services perspective but because of the nature of this intervention and the target age group will include the broad perspective on the individual and their families. This will enable a broader societal perspective to be reported alongside a health service perspective.

The incremental cost for pharyngeal electrical stimulation (PES) versus usual care will be calculated. The assumption is the costs for this option will be over and above that for usual care, so is an additional incremental costs. A subset of patients for each treatment will be selected to allow participating staff to record the grade of staff involved in the treatment and intervention. It would be an unnecessary burden on participating staff to collect these data on all individual patients. It is hoped such detailed intervention costing would give an average or point estimate of direct treatment cost and a range of possible costs.

Key collection points for health economic data are day 14: EQ5D-5l (VAS and form) by patient or proxy. Discharge: EQ5D-5l (VAS and form), Health Care Resource use. Day 90: EQ5D-5l (VAS and form), Resource Use.

The CRF data collection will collect data on hospital admissions, length of stay, QALYs (EQ5D) but in addition for the economic analysis use the trial primary outcome of DSRS. A purposely designed patient health economic resource proforma will enable the broad resource profile for the PES versus treatment as usual group to be recorded. Hospital resources and as such cost and ongoing treatment at either hospital, home or alternative destination will be collected and it is important that the CRF captures these resource inputs to establish the full follow-up profile for the patient group. It will be especially important to record the intervention and consequences of complications. The proforma will be developed with the PPI and seek to minimise patient and family burden.

Costs will be applied to resource use using data from sources such as NHS reference costs and the Unit Costs of Social Care (PSSRU Kent), alongside the detailed costing of interventions as outlined above. The purposely designed health economic resource proforma (to be lodged in the UK health economists DiRUM database) will ensure the key resource implications are captured. This enables the full economic consequences and costs of the treatment alternatives to be determined.

Outcome data at baseline and 90 days will be collected using the EQ5D and DSRS. The baseline EQ5D may necessitate a proxy value being used for QoL at baseline. The EQ5D is an important outcome of choice to measure patient utility and will aid in capturing the multiple effects that swallowing has on quality of life. To try and address the specific effects of treatment on swallowing alone the analysis will in addition conduct a separate cost effectiveness analysis of PES versus usual care using the DSRS.

The resource use data and subsequent calculation of health service and societal cost will be combined with the primary outcome DSRS and the EQ5D to provide a measure of cost effectiveness and cost utility. An incremental approach will be used and the Incremental Cost Effectiveness Ratio (ICER will be calculated. Cost Effectiveness Acceptability Curves (CEACs) showing the probability of effectiveness versus willingness to pay at the NICE threshold of £20-30k per QALY will be plotted. Probabilistic sensitivity analysis to test the robustness of the findings for key cost drivers will be undertaken.

Assessment of efficacy

Primary outcome at day 14±1 by hospital (or telephone) assessor blinded to treatment
Dysphagia assessed using DSRS (***Table 2***), based on bedside clinical assessment/management conducted at day 14±1. Outcome assessment will be assessed by DSRS/FOIS-trained research coordinators, nurses or SLTs who are not involved in treatment.
Justification of DSRS: DSRS is a pseudo-continuous dysphagia scale that measures fluids, diet and feeding supervision. It is validated;[32] can be assessed remotely by telephone; and improved with PES in meta-analysis of pilot trials and STEPS,[21,22] and in PHADER.[24]
Justification of 14 days: 14 days is a balance between allowing sufficient time for PES to work and not allowing sufficient time for any natural recovery to become apparent.
Analysis: Analysis of the primary outcome will be performed by intention-to-treat using multiple linear regression, with adjustment for stratification/minimisation factors (country, age, sex, DSRS, NIHSS, stroke type, circulation/syndrome, time onset to randomisation). The result will be difference in mean DSRS between PES vs no PES adjusted for baseline.
Day 90: DSRS will also be assessed at day 90 as a secondary outcome to assess whether efficacy at day 14 is sustained longer-term or whether it simply accelerates the return of swallowing; accelerated return to oral swallowing is still important since it should still reduce complications such as pneumonia and hospital length of stay and so may still be cost-effective. An accelerated return to oral feeding will improve the patients' quality of life.

Secondary outcomes
Secondary at day 7±1 (end-of-treatment) by hospital treater blinded to baseline: PES threshold, tolerability and stimulation currents; number of catheters used.
Secondary at day 14±1 by hospital (or telephone) assessor blinded to treatment:[11] DSRS >3,[21] FOIS, EAT-10 [33] and feeding status score (FSS);[34] NGT/PEG in situ; pneumonia; antibiotic use; weight; EQ-VAS/EQ5D-5l.(patient/proxy).
Note 1: We have included several measures of dysphagia and feeding: DSRS, FOIS, EAT-10 and FSS to triangulate the presence and magnitude of dysphagia and effects on feeding. These will be analysed together using the Wei-Lachin test.[1]

Secondary at discharge/death by hospital assessor blinded to treatment: Length of stay; swallowing therapy contact time; time to removal of NGT/PEG; admitted to ICU; discharged with PEG; disposition (home, residential home, nursing home, hospital, death).
Secondary at day 90±7 by central telephone assessor blinded to baseline, treatment and in-hospital data (or by post): DSRS, FOIS, EAT-10, FSS; home time;[35] dependency (modified Rankin Scale [2]), disability (Barthel Index), quality of life (EQ-5D5L/EQ-VAS.), cognition (TICS [3]), mood (Zung [4]);[2,5-9] disposition.
Note 1: These outcomes are all sensitive to therapeutic change.
Health economic: Costs, health resource use at discharge, resource use at day 90.

Secondary at day 365 all cause mortality.

Assessment of safety

The process for recording and reporting safety takes account that PES has an excellent safety record in previous trials, participants with PSD (who usually have severe stroke) are likely to have multiple adverse events and SAEs, and the trial is open-label in design. Hence, we will limit recording to:

- SAEs over 0-7 days
- Procedure/device-related (serious) adverse device events, (S)ADEs, over days 0-14
- Fatal SAEs over days 8-90 days
- All-cause mortality to day 365.

We will not record non-device-related adverse events. This pragmatic approach is appropriate for an intervention which already has much recorded safety data, and follows that in our BHF RIGHT-2 trial.[9] (S)AE information will be entered into the eCRF directly by the local site investigator or designate. Events will be adjudicated blinded to participant information and treatment assignment. Expected (S)ADEs associated with PES and SAEs associated with stroke are listed below; SAEs that are not expected, i.e. not listed below, will be reported as serious unexpected suspected adverse reactions (SUSARs).

Procedures for missing, unused and spurious data

Many fields in the electronic case report form will be mandatory, especially those relating to baseline covariates, treatment and primary and secondary outcomes; further, the primary and most secondary outcomes include a value for death. Hence, there should be minimal missing data in the primary and key secondary analyses, and we will not impute data. A sensitivity analysis of the primary outcome will use regression imputation of missing data.

Definition of populations analysed

Safety set: All randomised participants who receive at least one dose of pharyngeal electrical stimulation.
Full Analysis set: All randomised participants, who take at least one dose of pharyngeal electrical stimulation and for whom at least one post-baseline assessment of the primary endpoint is available.
Per protocol set: All participants in the Full Analysis set who are deemed to have no major protocol violations that could interfere with the objectives of the study.

Protocol violations are defined above.

Study Within A Trial (SWAT)
A Study Within A Trial (SWAT) will investigate the effects of a package to improve awareness and communication with investigators to improve PES delivery, and especially delivered current.

Intervention: Enhanced training and re-training of investigators with the trial Speech & Language Therapist monitoring PES treatment on each day for each participant.
Control: Standard trial training and re-training if necessary.

Method of allocation: Cluster randomisation of sites to either the SWAT intervention or SWAT control with minimisation on site characteristics (country, prior PES experience, stroke volume).

Outcome measures: The primary outcome will be the mean treatment current over the first 3 days. The secondary outcomes will be the proportions of participants who:

(i) have a mean current >20 mA
(ii) require only one PES catheter.

Analysis: One interim analysis is planned at 200 PES participants (i.e. 400 total randomised) in the main trial. If there is strong evidence of an effect of the SWAT intervention on treatment current, the strategy showing the greatest treatment current would then be implemented for the remaining participants. Otherwise, the SWAT will continue until the end of the trial. Analyses will include appropriate descriptive statistics and between-group comparisons for each strategy using multivariate regression models. These will be detailed in the SAP.

Success criteria:

1. Increased treatment current over first three days in participants randomised to PES.
2. Increased proportion of participants randomised to PES with mean treatment current >20 mA.
3. Increased proportion of participants randomised to PES who only require one PES catheter.

ADVERSE EVENTS

Definitions

Adverse event

This is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.
An AE does include a / an:

1. exacerbation of a pre-existing illness.
2. increase in frequency or intensity of a pre-existing episodic event or condition.
3. condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.
4. continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

Serious Adverse Event (SAE)

This is any adverse event occurring following study mandated procedures, having received the study intervention or control that results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalisation or prolongation of existing hospitalisation
4. A disability / incapacity
5. A congenital anomaly in the offspring of a participant

Important medical events

These, that may not result in death, be life-threatening, or require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardise the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed here.

All adverse events will be assessed for seriousness, expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Anticipated (serious) adverse events
These are associated with PES and so are only relevant to the active treatment group; they include, but are not limited to, the following:

- Sensation of stimulation at back of throat

Anticipated (serious) adverse events
These are associated with usual treatment other than PES, e.g., naso-gastric tube insertion, and so are relevant to both active and control treatment groups; they include, but are not limited to, the following:

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

Anticipated (serious) adverse events, (S)AEs
These are associated with the index stroke or underlying co-morbid conditions associated with stroke, are also to be expected. These may include, but are not limited to, the following:

- Agitation
- Anaemia
- Angina/myocardial infarction/cardiac ischaemia

- Anxiety
- Atrial fibrillation/flutter
- Bradycardia
- Cardiac arrest
- Cardiac dysrhythmia
- Cellulitis
- Cerebral oedema
- Cerebral herniation
- Cerebral infarct extension/recurrence
- Coma/diminished level of consciousness
- Confusion
- Congestive heart failure/heart failure
- Constipation
- Death
- Deep venous thrombosis
- Dehydration
- Diarrhoea
- Dizziness/vertigo
- Dyspepsia
- Dysphagia
- Dyspnoea
- Extracranial bleeding
- Fever
- Gastritis or gastric/duodenal ulcer
- Gastrointestinal bleed
- Headache/migraine
- Haemorrhagic transformation of cerebral infarct
- Hydrocephalus
- Hypokalaemia
- Hyperglycaemia/hypoglycaemia
- Hypoxia
- Insomnia
- Intracerebral haemorrhage expansion
- Intraventricular haemorrhage
- Joint pain (arthralgia)
- Musculoskeletal pain
- Nausea
- Neurologic worsening
- Peripheral vascular disorder
- Peripheral oedema
- Pneumonia
- Pressure sore
- Pulmonary oedema
- Pulmonary embolism
- Seizure
- Sepsis
- Sleep apnoea
- Skin rash
- Limb spasticity
- Transient ischemic attack
- Urinary incontinence
- Urinary tract infection
- Vomiting

Reference safety information
These known (S)AEs occurred in the STEPS, PHAST-Trac and PHADER studies and were listed in the PhEED protocol.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the study intervention is assessed by the Chief Investigator as "possible", "probable", or "definite" is a trial intervention related SAE.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Recording and Reporting of Adverse Events

PES has an excellent safety record in previous trials. Participants with PSD, who usually have severe stroke, will have multiple adverse events and SAEs. Hence, we will limit recording to: SAEs over 0-7 days, procedure/device-related (S)AEs over days 0-14; fatal SAEs over days 8-90 days; and all-cause mortality to day 365. Hence, non-serious adverse events (AEs) will not be recorded. SAEs will be reported whether spontaneously volunteered or in response to questioning about wellbeing at trial visits. The questioning about SAEs will cover the current visit as well as the period of time between the previous and the current visit. A note of any concomitant medication will also be made so that a full assessment of the AE can be made.

Abnormal laboratory test results that are deemed clinically significant by the investigator and that lead to a change or temporary or permanent discontinuation in the use of the device,or require intervention or diagnostic evaluation to assess the risk to the subject will be recorded as adverse events in the CRF and instigate further investigation and follow up as appropriate.

All SAEs will be documented in the subject's medical records and CRF. All events must be followed until resolution, or for at least 30 days after discontinuation in use of the device, whichever comes first.

Participants will be asked to contact the study site immediately in the event of any SAEs. The Chief Investigator shall be informed immediately of any serious events and shall determine seriousness and relationship in conjunction with any treating medical practitioners.

In the event of a pregnancy occurring in a trial participant monitoring shall occur during the pregnancy and after delivery to ascertain any trial related adverse events in the mother or the offspring.

All serious adverse events will be recorded and reported to the REC as part of the annual reports.

SAEs will be reported within the statutory timeframes to the REC as stated below. The Chief Investigator will be responsible for all adverse event reporting.

Urgent Safety Measures

An Urgent Safety Measure is a procedure taken to protect a research participant when that participant is identified as being at risk of harm in relation to their involvement in a research project and urgent action, which deviates from the approved protocol, is required to manage the event and protect the participant.

Trial Intervention Related SAEs

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial intervention shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

Assess the event for seriousness, expectedness and relatedness to the trial device.
Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
If the event is deemed serious, related and/or unanticipated to the trial device, shall inform the REC using the reporting form found on the HRA web page within 15 days of knowledge of the event and report to the manufacturer via the yellow card scheme.
Shall, within a further eight days send any follow-up information and reports to the REC.
Make any amendments as required to the study protocol and inform the REC as required

Participant removal from the study due to adverse events

Any participant who experiences a serious adverse event may be withdrawn from the study at the discretion of the Investigator.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the R&D and REC are notified as soon as possible, and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the UK Department of Health Policy Framework for Health and Social Care, 2017.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent or assent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legally authorised representative shall both sign and date the Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Device accountability

Devices will be kept in a secure, limited access storage area.

The investigator shall maintain records of the study device's delivery to the hospital site, an inventory at the site, the distribution to each participant, and then final disposition of unused devices. These records will include dates, quantities received, batch / serial numbers, expiration dates, and the unique code numbers (patient trial number) assigned to the trial participant. Investigators will maintain records that document adequately that the participants were provided with the correct study medication. These records will be part of each patient's Case Report Form (CRF). All study devices shall be accounted for.

Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation, for use on the eCRF and other trial documents. The documents and database will use a trial code consisting of centre number/initials/trial participant number
eCRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or national health number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial in accordance with regulatory requirements and for follow-up as required.
Entry of data into CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results, pharmacy records and the eCRF. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities.

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The eCRF will only collect the minimum required information for the purposes of the trial. Printed eCRF pages will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer-held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

*Phagenesis Ltd, who manufacture the Phagenyx® PES system, indemnify their equipment.

TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; drug accountability, pharmacy records and equipment calibration logs.

The Trial Coordinator or, where required, a nominated designee of the Sponsor shall carry out a site systems audit at least yearly, and an audit report shall be made to the Trial Steering Committee.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on eCRFs will be verified by inspection against the source data. A sample of CRFs (square root of the number of participants recruited at each centre) will be checked for verification of key variables:

- Consent: Electronic.
- Demographic: Age, sex, onset to randomisation, stroke severity, dysphagia severity (DSRS, FOIS).
- PES treatment: Number and length of treatments administered; threshold, tolerance and treatment currents.
- Name of treating investigator and outcome assessor.

In addition, the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

Presentations and publications will comprise:

- Ongoing trial presentations at UK Stroke Forum, European Stroke Organisation Conference, International Stroke Conference and World Stroke Conference.
- Protocol, statistical analysis plan and baseline characteristic publications in open access journal (e.g. International Journal of Stroke, European Stroke Journal).
- Primary results: Oral presentation at a large international stroke conference times as per one of the above conferences. Open access publication in high impact journal to ensure maximum impact and rapid dissemination.
- Publication in HTA monograph.
- Secondary/tertiary/post hoc analyses: In appropriate journals (e.g. Stroke).
- Subsequent presentations to inform UK, European and International guidelines.
- Provide evidence for NICE single technology appraisal (STA) assessment and guidance.
- Data sharing with the VISTA Stroke archive.[46]

USER AND PUBLIC INVOLVEMENT

A Patient-Public Involvement (PPI) representative (who is a stroke survivor with residual mild swallowing problems) contributed to the development of the grant application leading to funding of this trial through participating in planning meetings and then leading on the development of PPI text for this application. He provided guidance on issues related to consent and proxy consent with family member consultees, and the need for separate information sheets and consent forms for these. A second PPI member (to be appointed) will be added as an independent member of the TSC.

The PPI member, with support from the Senior Trial Manager, will work with the Independent PPI member of the Trial Steering Committee on areas where there is no conflict of interest. Their focus will be on the writing of the participant and family-facing materials, including participant/consultee information sheets, consent forms (paper and electronic for participants and consultees) and trial leaflets. They will also support development of participant and relative-facing materials on the trial website, including a PowerPoint training slide set. At trial end, they will lead on PPI dissemination of the results.

STUDY FINANCES

Funding source

This study is funded by National Institute of Health Research (NIHR) Health Technology Assessment (HTA) programme (NIHR132016). The Phagenyx® system is provided free of charge by Phagenesis Ltd (Manchester UK).

Participant stipends and payments

Participants will not be paid to participate in the trial. Travel expenses will be offered for any hospital visits in excess of usual care.

SIGNATURE PAGES

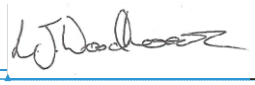
Signatories to Protocol:

Chief Investigator: (name) Philip M Bath

Signature:_ 
_____

Date: _02/02/2022_____

Trial Statistician: (name) Lisa J Woodhouse

Signature: 

Date: _02/02/22_____

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