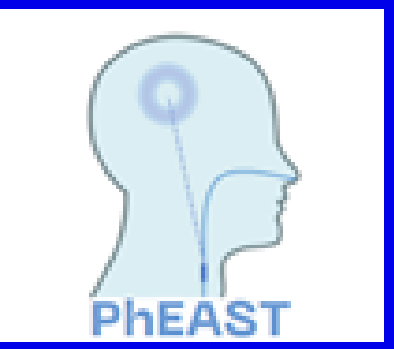

Pharyngeal electrical stimulation for Acute Stroke Trial (PhEAST)

Philip Bath, Chief Investigator

Stroke Association Professor of Stroke Medicine,
University of Nottingham

NIHR | National Institute for Health and Care Research

PhEAST: Trial Team

Chief Investigator: Prof Philip M Bath (Stroke Physician – Nottingham UK)

Co-applicants:

- Prof Shaheen Hamdy (Neuro-gastroenterologist – Manchester UK)
- Assoc Prof Tim England (Stroke Physician – Derby UK)
- Prof Alan Montgomery (Medical Statistician – Nottingham Clinical Trials Unit UK)
- Professor Marilyn James (Health Economist – Nottingham UK)
- Prof Niki Sprigg (Stroke Physician – Nottingham UK)
- Prof Craig Smith (Stroke Physician – Manchester UK)
- Dr Lisa Everton (Speech & Language Therapist – Nottingham UK)
- Mrs Angela Shone (Sponsor – Nottingham UK)
- Assoc Prof Helle Iversen (Stroke Neurologist – Copenhagen DK)
- Assoc Prof Karl Matz (Neurologist – Krems AT)
- Prof Rainer Dziewas (Neurologist, Osnabrück DE)
- Mr Martin Coult (Lay, UK)

Trial Statistician: Mrs Lisa Woodhouse (Medical Statistician –Nottingham)

Trial Coordinating Centre: Stroke Trials Unit (Nottingham)

Trial Management Team (all STU Nottingham):

- Dr Tiff Hamilton (Senior Trials Manager)
- Ms Gemma Squires (Trial Manager)
- Ms Olivia Matthews (Trial Coordinator)
- Ms Carrie Chalmers (Administrator)
- Ms Gwen Wilkinson (Speech & Language Therapist)

Lisa Woodhouse (Statistician, blinded)
Iris Mhlanga (Statistician, unblinded – DMC)
Athfi Mufied (Programmer)

PhEAST: TSC and DMC

TSC Chair: Prof Gary Ford (Stroke Physician, CEO Oxford AHSN).

TSC Members:

- Prof Hugh Markus (Neurologist, Cambridge UK)
- Prof Thorsten Steiner (Neurologist, Heidelberg DE)
- Prof Laura Gray (Statistician, Leicester UK)
- Assoc Prof Nathalie Rommel (SLT, Leuven BE)
- Mr Stephen Hill (Lay, UK)
- Prof Philip Bath (Stroke Physician/CI, Nottingham UK) – non-voting

DMC Chair: Prof Kennedy Lees (Stroke Physician Ret, Glasgow UK)

DMC members:

- Prof Chris Weir (Statistician, Edinburgh UK)
- Prof Marian Brady (SLT, Glasgow UK)
- Ms Iris Mhlanga (supporting Statistician, Stroke Trials Unit, Nottingham) – non-voting

1. PhEAST: Background

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Interventions for stroke

Hyperacute:

- Diagnosis
  - Brain scan CT/MRI
- Stroke Unit
- IS: Reperfusion
  - Thrombolysis
  - Thrombectomy
- ICH: BP lowering

Acute:

- Aspirin
- Hemicraniectomy
- VTE prevention
  - Heparin
  - Intermittent pneumatic compression

Sub-acute/chronic:

- Rehabilitation
  - Physiotherapy
  - Occupational therapy
  - Speech & language therapy
  - Dietetics
  - Social care
- Secondary prevention:
  - Life-style
  - Blood pressure lowering
  - Lipid lowering
  - Antithrombotics
  - Carotid endarterectomy

> But zero for dysphagia

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Post-stroke dysphagia: Background

- 15 million strokes worldwide per year: 5M die, 5M left disabled
- Dysphagia (swallowing problem) common: 60% of patients on admission
- Natural history: Resolves in many patients but some need long-term enteral feed
- Associations: Age, severe stroke, recurrent stroke
- Prognostic marker for: Dependency, disability, death, malnutrition, weight loss, aspiration pneumonia
- Screening/diagnosis: Bed-side water tests, speech & language therapist, videofluoroscopy, FEES, …
- Patients often need feeding through a nasogastric tube (NGT) or percutaneous endoscopically-introduced gastrostomy tube (PEG) thereby prolonging hospital stays or causing long-term institutional care
- Used treatments: Behavioural therapy by Speech & Language Therapists (SLTs)
- Proven treatments: None
- Increased costs: length of stay, investigations, staff (nurses, SLTs)

Cohen *et al*. *Int J Stroke* 2016; 11: 399-411

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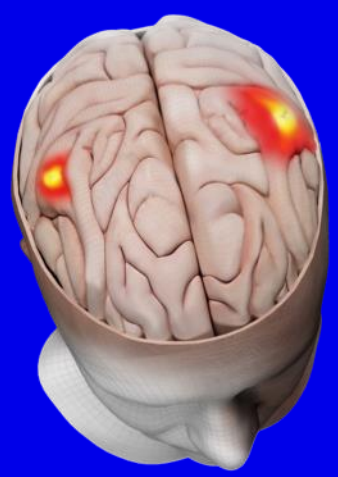
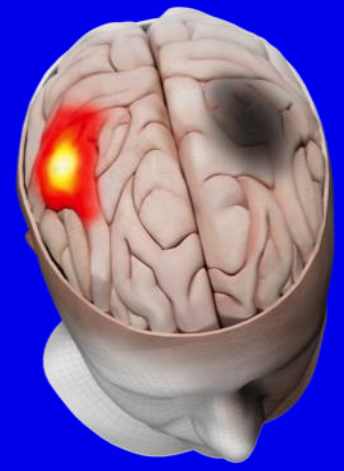
Restoration of swallow control after stroke

- Human swallowing has bilateral representation in the brain with a 'dominant' cortex (unrelated to handedness)
- Natural recovery process post stroke involves compensatory reorganisation in the motor cortex of the non-dominant hemisphere



Healthy brain
Both hemispheres active during swallowing but left hemisphere (could be right) dominates

Post Stroke
Lesion in left hemisphere (dysphagia dominant side) → patient presents with dysphagia



Recovery
Functional reorganisation of control to unaffected hemisphere

Hamdy *et al*. *Gastroenterology* 1998; 115: 1104-1112

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Pharyngeal Electrical Stimulation (PES)

- 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 with reorganisation of the swallowing cortex.

- PES has been developed academically by Prof Shaheen Hamdy and then commercially by a University of Manchester spin-out company, Phagenesis Ltd

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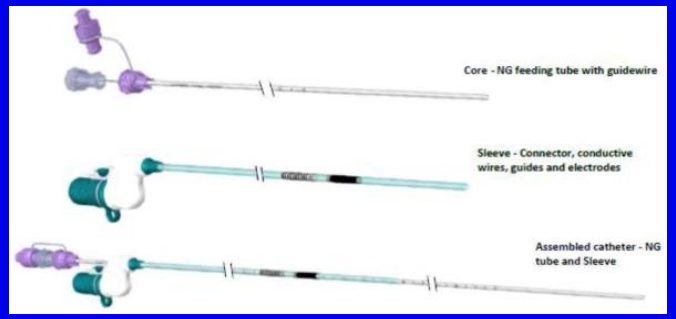
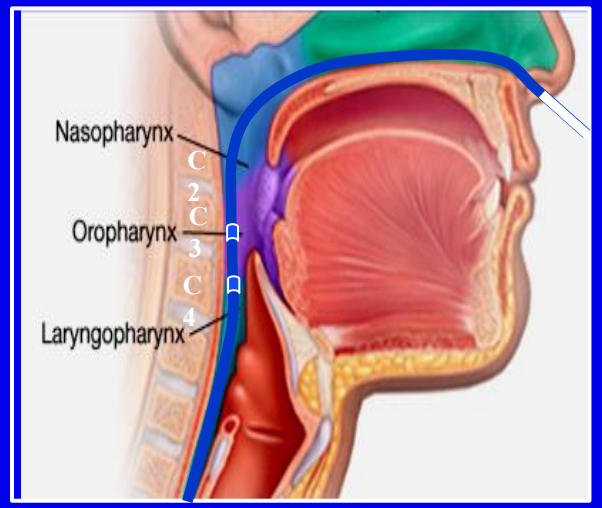
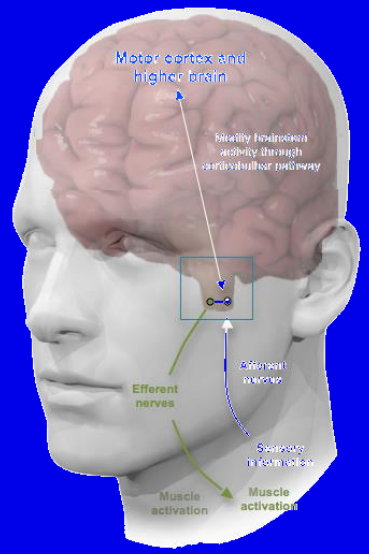
PhEAST: Pharyngeal electrical stimulation

- PES System is indicated for the treatment of neurogenic oropharyngeal dysphagia, which includes post-stroke dysphagia, and comprises a re-usable base-station and a single-use sterile disposable stimulation catheter
- The Base Station provides the user interface and generates, optimises and monitors the delivery of electrical stimulation.
- The catheter design is based on a NGT but incorporates electrodes with appropriate wiring and insulation for delivery of electrical stimulation to the pharyngeal mucosa.
- The Phagenyx system received CE Mark in 2012







Harvey *et al*, Phagenesis. PhEED CIP v1 2017

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PES for PSD – Previous Trials

	Pilot trials x3	STEPS	PHAST-TRAC	PHADER	PhEED	PhEAST
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, Aspiration	Improved	Neutral	/	Improved	N/A	(?)
Effect, Swallowing	Improved	Neutral	Improved	Improved	N/A	?

DSRS: dysphagia severity rating scale

A measure of swallowing impairment

DSRS total score = sum of 3 sub-scales

Score	Fluids	Score	Diet	Score	Supervision
4	No oral fluids	4	Non oral feeding	4	No oral feeding
3	IDDSI level 4	3	IDDSI level 4 and 5	3	Therapeutic feeding (SALT/trained staff)
2	IDDSI level 3	2	IDDSI level 6	2	Feeding by third party (untrained)
1	IDDSI level 1 and level 2	1	IDDSI level 7 easy to chew	1	Eating with supervision
0	IDDSI level 0	0	IDDSI level 7 regular	0	Eating independently

)SRS supervision score 3 is always chosen when a patient is on limited or consistent oral trials and still requires
NG/PEG tube.

Small vol. trials 443 = 11
Large vol. trials 343 = 10
Large vol. trials 434 = 10

Jayasekeran *et al. Gastroenterology* 2010; 138: 1737-46
Everton *et al. Sci Rep* 2020 10: 7268

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PES for PSD – Previous Trials

- **STEPS**: Study feasible (recruitment, compliance and retention), PES was safe but did not reduce aspiration (PAS) or dysphagia (DSRS) relative to sham. Meta-analysis of STEPS and earlier pilot trials showed a reduction in DSRS with PES
- **PHAST-TRAC**: PES was superior to sham at 69 patients and stopped early
- **PHADER**: PES was associated with improved DSRS and PAS, both overall and in each diagnostic group including in both non-ventilated and ventilated stroke.
- **PhEED**: The trial was stopped early due to low US recruitment, explained by the:
  - Need for VFS at baseline and outcome (primary outcome)
  - Presence of clinical dysphagia but only mild radiological aspiration in many screenees; of a target of 120 participants, 50 were consented for screening with VFS but only 17 treated open-label and 3 randomised
- **PhINEST**: Ongoing randomised post-extubation trial in intensive care units in patients with neurogenic dysphagia

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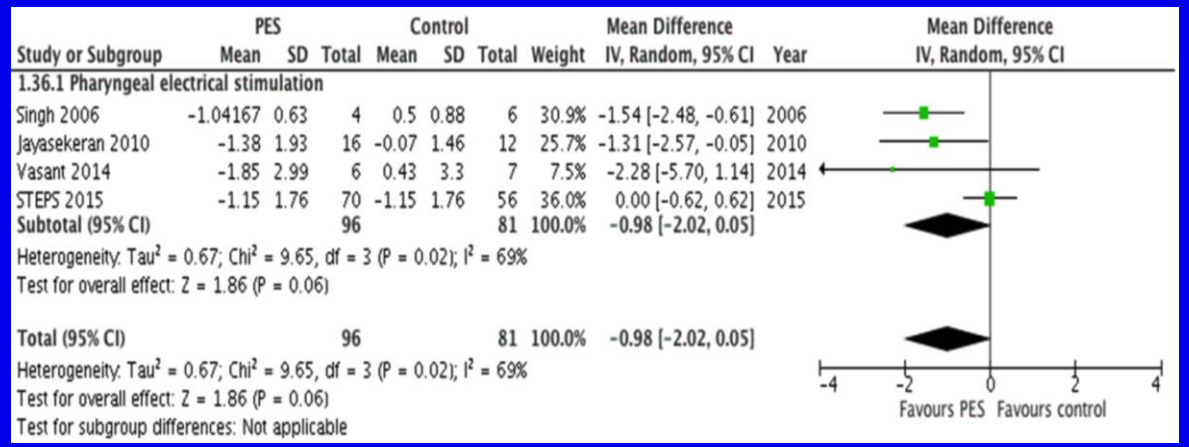
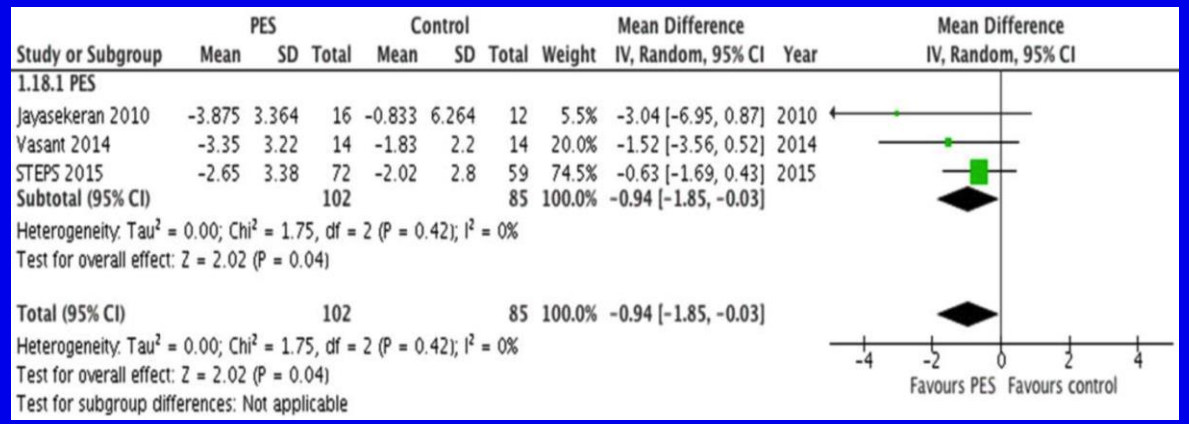
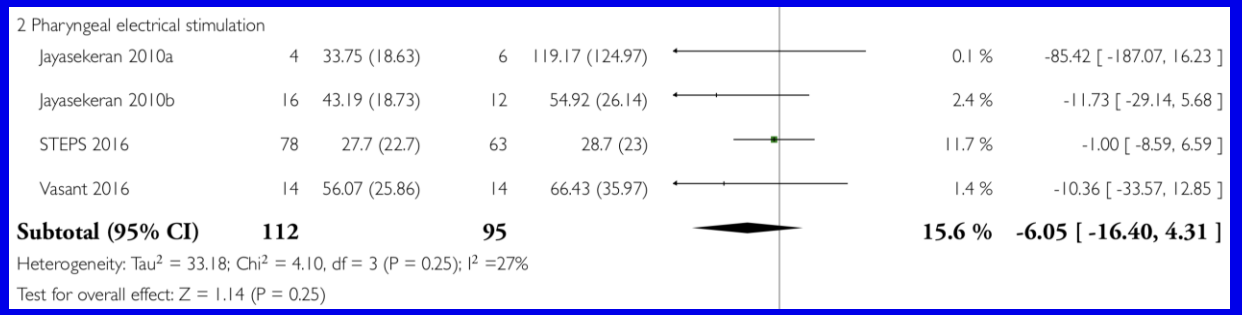
PES on PAS, DSRS & LoS: 3 pilot trials + STEPS



> *Tendency to less aspiration/penetration, PAS*



> *Significant improvement in swallowing, DSRS*



> *Tendency to shorter length of stay (LoS)*

> *More research needed*

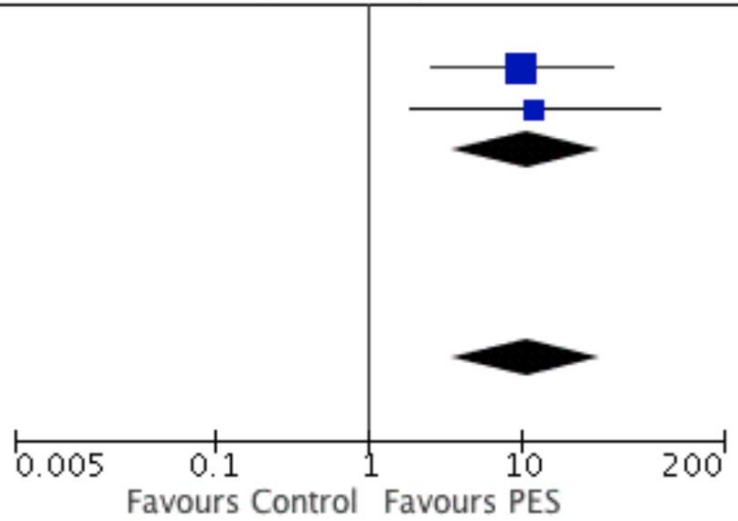
Bath *et al*. *Stroke* 2016;47:1562 N=162
Bath *et al*. *Cochrane Database Systematic Review* 2018; 10: CD000323

PHAST-TRAC Stroke RCT

Decannulation: Suntrup & PHAST-TRAC

Meta-analysis of trials of decannulation after ventilation in stroke patient

Study or Subgroup	PES Events	PES Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Decannulation						
Dziewas 2017	17	35	3	34	65.0%	9.76 [2.51, 37.94]
Suntrup 2015	15	20	2	10	35.0%	12.00 [1.89, 76.38]
Subtotal (95% CI)		**55**		**44**	**100.0%**	**10.49 [3.51, 31.35]**
Total events	32		5			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0\%$						
Test for overall effect: Z = 4.21 (P < 0.0001)						
Total (95% CI)		**55**		**44**	**100.0%**	**10.49 [3.51, 31.35]**
Total events	32		5			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0\%$						
Test for overall effect: Z = 4.21 (P < 0.0001)						
Test for subgroup differences: Not applicable						



> PES increased readiness for decannulation in randomised (and subsequent open-label) phases

> No re-cannulations recorded

Suntrup *et al*. *Neuroimage* 2015; 104: 117-24 N=30

Dziewas *et al*. *Lancet Neurology* 2018; 28 August N=69

PHADER European Registry

PHADER: DSRS

Real world phase IV single-arm (uncontrolled) study of PES in Austria, Germany, UK

	All	Stroke, not ventilated	Stroke, ventilated	Ventilator-related [a]	TBI	p
N		79	98	35	24	
DSRS (/12) [b]						
Baseline	236, 11·4 (1·7)	79, 10·9 (2·4)	98, 11·7 (1·2)	35, 11·9 (0·5)	24, 11·3 (1·8)	0·003
Day 5	229, 10·5 (2·6)	74, 9·9 (2·9)	97, 10·8 (2·4)	35, 10·8 (2·5)	23, 11·0 (2·5)	
Day 9	224, 8·6 (3·9)	70, 7·7 (4·1)	97, 8·9 (3·8)	35, 8·5 (4·1)	22, 10·4 (3·1)	
Day 92	174, 5·1 (4·9)	46, 4·2 (4·2)	78, 5·2 (5·0)	30, 5·3 (5·4)	20, 6·8 (4·8)	0·26
DIM (unpaired)	-6·3 (-7·0, -5·6)[c]	-6·7 (-7·8, -5·5)[c]	-6·5 (-7·6, -5·5)[c]	-6·6 (-8·4, -4·8)[c]	-4·5 (-6·6, -2·4)[c]	0·31
MD (paired)	174, -6·3 (-7·0, -5·6)	46, -6·5 (-7·9, -5·2)[c]	78, -6·5 (-7·6, -5·3)[c]	30, -6·6 (-8·5, -4·6)[c]	20, -4·7 (-6·8, -2·5)[c]	0·033

> Swallowing impairment improved more than expected from natural history in all 4 neurogenic dysphagia groups

> DSRS improved by 6.5 units over 90 days in unventilated stroke patients

Bath *et al. E Clin Med* 2020; 28: 100608

N=79

2. PhEAST:Design

Objectives –

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 and return to work
- PES is cost effective as compared to usual care
- Participant subgroups predict response to PES

PhEAST – Key learnings from previous trials

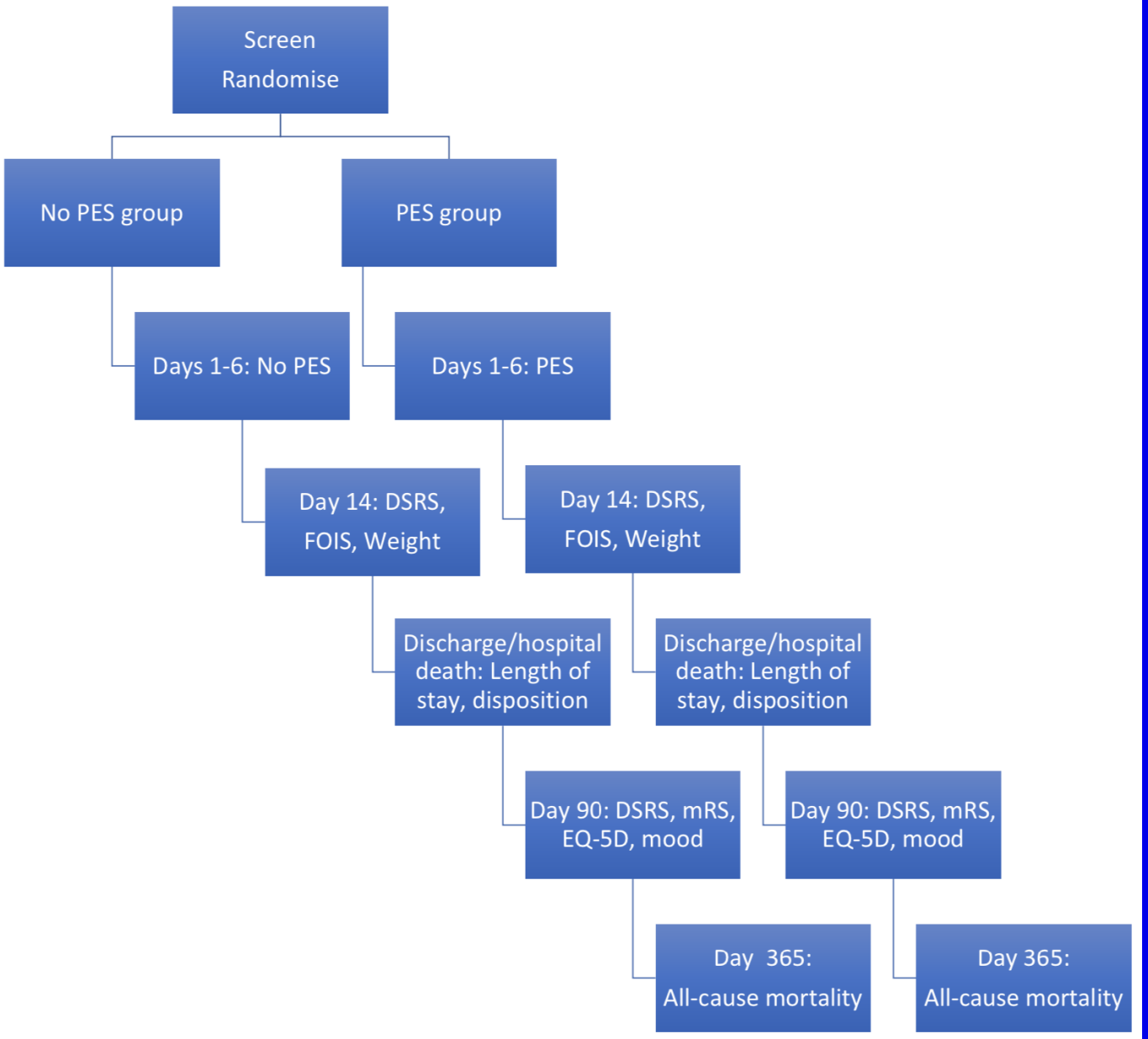
1. Treat within 1 month after stroke onset
2. Recruit both anterior and posterior circulation stroke
3. Ensure investigators are adequately trained and regularly retrained to ensure fidelity
4. Treat with sufficient stimulation current:
    1. At calculated stimulation level
    2. >20 mA
5. Avoid any stimulation in control group
6. Use 6 days of PES treatment, not 3 days
7. Assume 1.1 PES catheters per patient, i.e. to allow for some being pulled out by confused patients
8. Use clinical DSRS swallowing score
    1. It is relevant to patients and can be assessed in all
    2. It is validated and has been shown previously to be improved by PES
9. Measure DSRS at 14 days, i.e. 8 days after end of PES, to allow treatment effect to develop and be assessed

Design

- Investigator-initiated trial (not commercial)
- International
- Prospective randomised open-label blinded-endpoint (PROBE)
- Parallel group: PES vs control 1:1
- Superiority, i.e. test whether PES is superior to control
- Funded by NIHR HTA

- Participants: 800
- Consent: Written informed consent from participant, personal consultee (England & Wales) or a legal representative (Scotland)
- Intervention: 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
- Comparator: Guideline-based standard-of-care

Flowchart



Site: Randomise

Site: Randomised groups

Site: Treatment for 6 days

Site: Primary outcome at 14 days

Site: Discharge/death information

Central: Final follow-up at 90 days

Central: Mortality

Eligibility – Inclusion criteria

- 800 adults
- Age >=18
- Recent stroke 4-31 days
  - *I.e. not too early/not too late*
- IS or ICH
- Anterior or posterior circulation
- 'NIHSS item 1a score of 0, 1 or 2 (where the patient requires repeated stimulation to arouse).'
- Severe dysphagia: Tube fed
  - Functional oral intake scale (FOIS)
  - FOIS=1: nothing by mouth, feeding by NGT/PEG
  - FOIS=2: NGT/PEG-dependent with minimal attempts of food or liquids
  - *Deliberately broad inclusion criteria*

Sites, 50 acute hospitals in

- Austria ~ 8
- Denmark ~ 6
- Germany ~ 6
- UK ~24

- We define a FOIS score of 2 (minimal attempts of food or liquid) as a person receiving no more than 15 teaspoons of any consistency within one day
- e.g. up to 3 teaspoons of level 0 thin water only 3 times a day
- OR up to 5 teaspoons of level 4 puree diet 3 times a day

Eligibility – Exclusion criteria

- Non-stroke dysphagia: TBI, SAH, tumour, MS, head & neck cancer, PD, severe dementia
- Premorbid dysphagia
- Premorbid dependency mRS 4/5
- Ongoing/expected intubation/ventilation and/or tracheostomy
- Ongoing/expected electrical/magnetic stimulation, e.g., NMES, rTMS, TCDS
- Malignant middle cerebral artery syndrome
- Pacemaker
- >35% oxygen
- >=2 NGT pulled out unless nasal bridle in place
- NIHSS item 1a score of 2 (where the patient only responds to pain) or NIHSS item 1a score of 3.'
- Investigator feels participant will not tolerate PES catheter
- Expected to be discharged or transferred to a site not running the trial during the PES treatment period.
- Participating in another randomised controlled treatment trial for post-stroke dysphagia
- **Pregnancy if known at time of enrolment**
- **Participant on palliative pathway**

Participant Screening

- All patients should be screened using the inclusion and exclusion criteria

- Both recruited participants **and** screen failures should be recorded and signed off on the Participant Screening and Enrolment Log (RF1 TA011)

The University of Nottingham	Record Form RF1 TA011 Version 1.0
Title:	PARTICIPANT SCREENING AND ENROLMENT LOG
Reference SOP:	TA011

STRICTLY CONFIDENTIAL

Trial Name:

Trial Reference:

Site:

Date Trial Opened at Site:

Page Number:

Participant name, DOB, hospital number or other unique identifier	Date of consultation*	Entered into trial Y/N	If N give reason**	If Y date consent obtained	Allocated trial number	Investigator Signature and Date

3. PhEAST: CONSENT

Consent

- Written informed (signature, mark, witnessed oral)

If lacks capacity, adapt to local consent rules:

- Austria: Consent from personal legal representative or professional legal representative
- Denmark: Proxy consent (assent) from consultee (relative)
- England & Wales: Proxy consent (assent) from consultee (relative)
- Germany: Proxy consent (assent) from consultee (relative)
- Scotland: Consent from personal legal representative

- May be obtained remotely by tele/video if necessary, e.g., COVID lockdown

Local header

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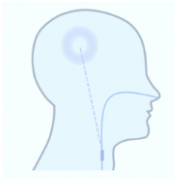


(Form to be printed on local headed paper)

PARTICIPANT CONSENT FORM
(Final version 1.0 23/09/2021)

Study Title: Pharyngeal Electrical stimulation for Acute Stroke dysphagia Trial (PhEAST)

IRAS Project ID: 306761

Name of Researcher:

Name of Participant:

Please initial box

1. I, the above-named participant, confirm that I have read and understand the participant information sheet version number 1.0 dated xxx for the above study and have had the opportunity to ask questions. ☐
2. I understand that I can withdraw from the study at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw from the study then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐
3. I understand that relevant sections of my medical records and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to me taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐
4. I understand that the information held and maintained by NHS Digital, EDRIS and other central UK NHS bodies may be used to help contact me or my named contact to provide information about my health status. ☐
5. I agree to the information collected about me in this study may be used to support other research in the future and may be shared anonymously with other researchers. ☐
6. I agree to my GP being informed of my participation in this study and to be asked to provide information on my status before I am contacted for the Day 90 and Day 365 follow up. ☐
7. I agree to you sending me a letter/email with a summary of the results. Yes/No
8. I consent to take part in the above study. ☐

Consent: Participant regains capacity

Participant to be approached for continued participation in the trial with the:

England, Northern Ireland, Wales
- Participant information sheet, and the participant re-consent form

Scotland
- Regained capacity information sheet, and the participant re-consent form

Denmark
- Participant information sheet, and the participant re-consent form

Germany
- Participant information sheet, and the participant re-consent form

Austria
- Participant information sheet, and the participant re-consent form

ALL CONSENT PROCESSES NEED TO BE RECORDED IN THE PARTICIPANT'S MEDICAL NOTES

4. PhEAST: RANDOMISATION

Randomisation Overview

- Patients who consent (individually, or by personal/professional legal representative) to participate in the trial will be randomised by a member of their local research team within **4 to 31 days** of stroke onset

- 1:1 treatment allocation (PES VS Standard Of Care)

- Done via bespoke, secure web-based system. Maintained by the central Stroke Trials Unit in Nottingham

Baseline data & randomisation

Baseline

- Demographics: Age, sex, …
- Stroke: NIHSS, , type, mRS, …
- Dysphagia: DSRS, FOIS, EAT-10, FSS, …
- Hospital-based treatment: Alteplase, thrombectomy, ICU, ventilation, hemicraniectomy, carotid endarterectomy, …
- Infection at baseline

Randomisation

- On-line, secure internet, real time
- Stratification on:
  - Country
- Minimisation on:
  - Age (<75/75+)
  - Sex
  - DSRS (<12/12)
  - Impairment (NIHSS <15/15+)
  - Stroke type (ischaemic/haemorrhagic)
  - Time to randomisation (<15/15+ days)
  - 5% simple randomisation

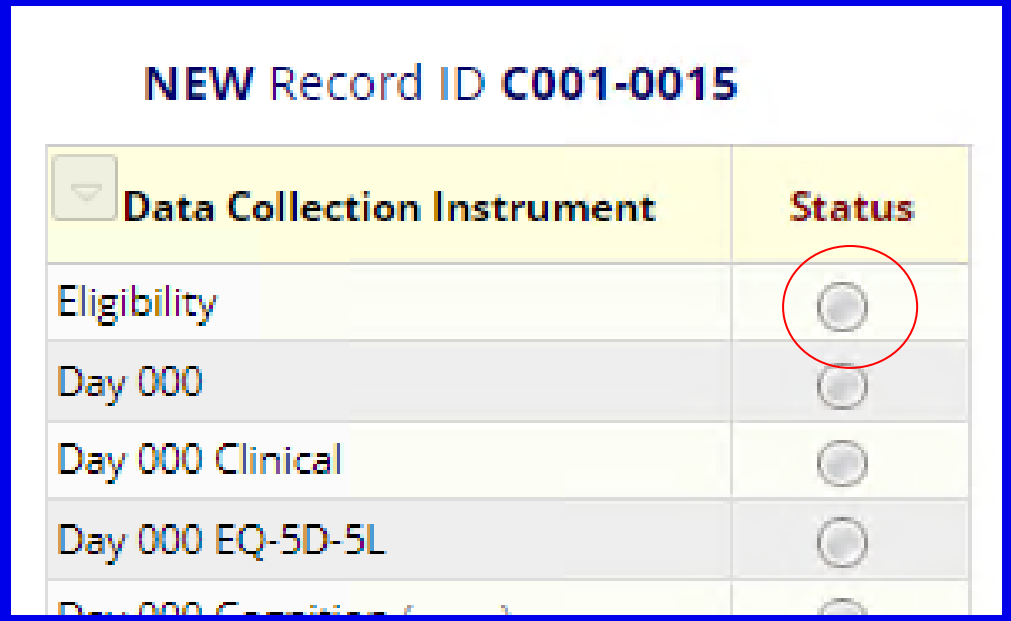
Randomisation instructions, 1

1. In REDCAP, select ‘Add / Edit records’

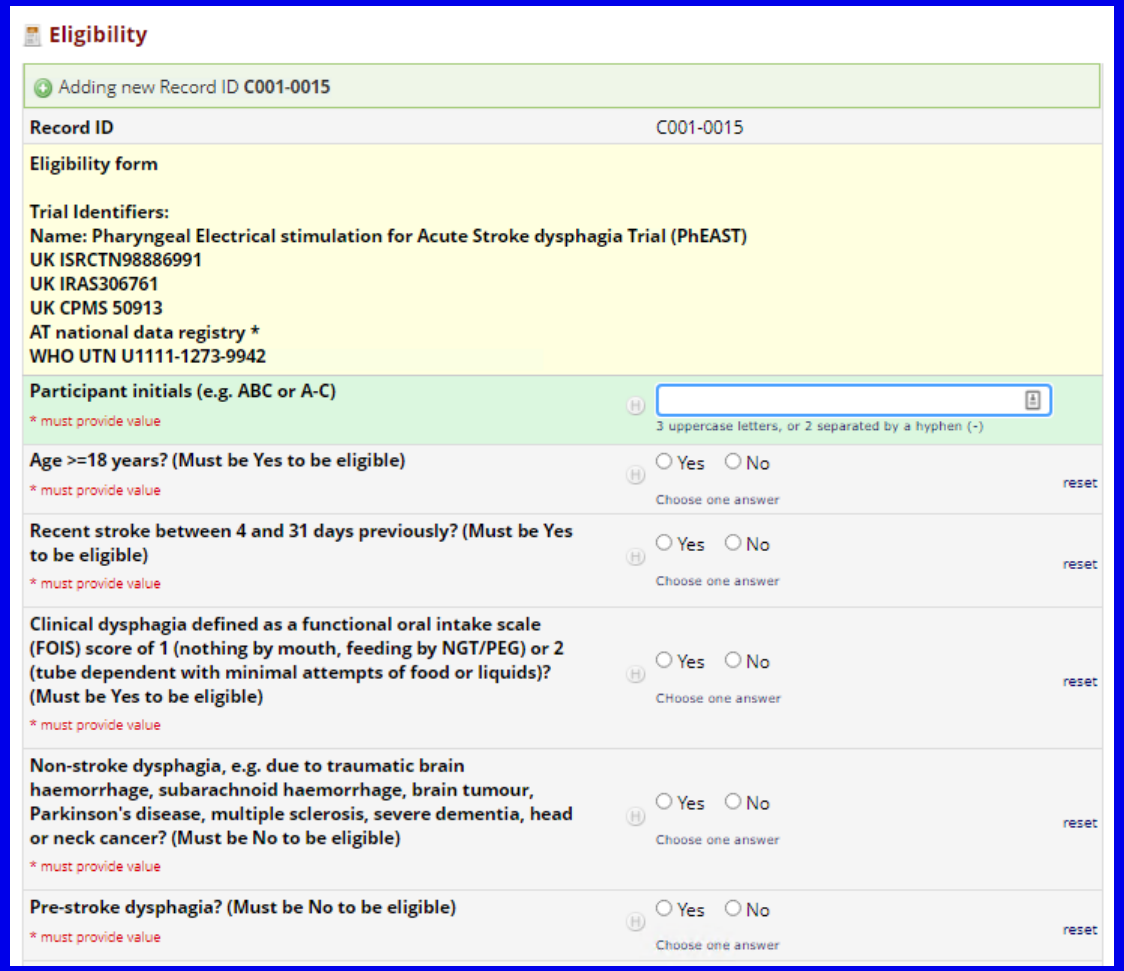
2. Add a new record

Randomisation instructions, 2

3. In the new data entry, select 'Eligibility'

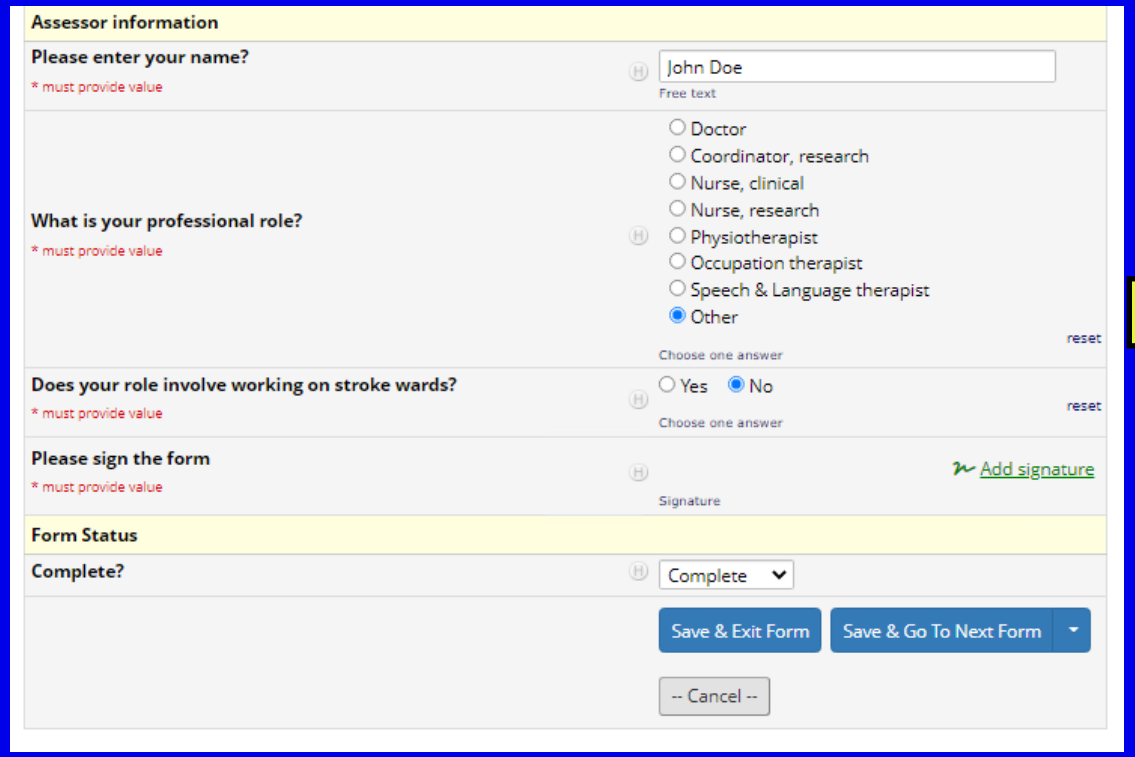


4. Complete the Eligibility form

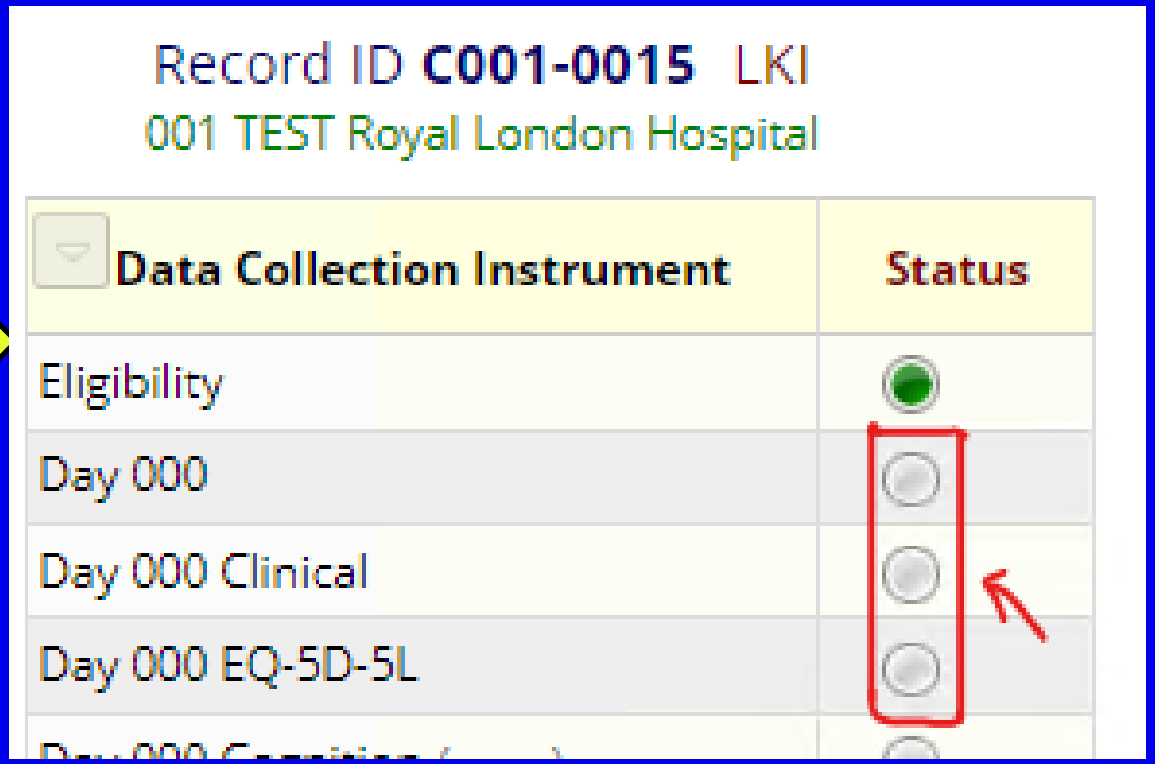


Randomisation instructions, 3

5. Once complete, click 'save and exit form'

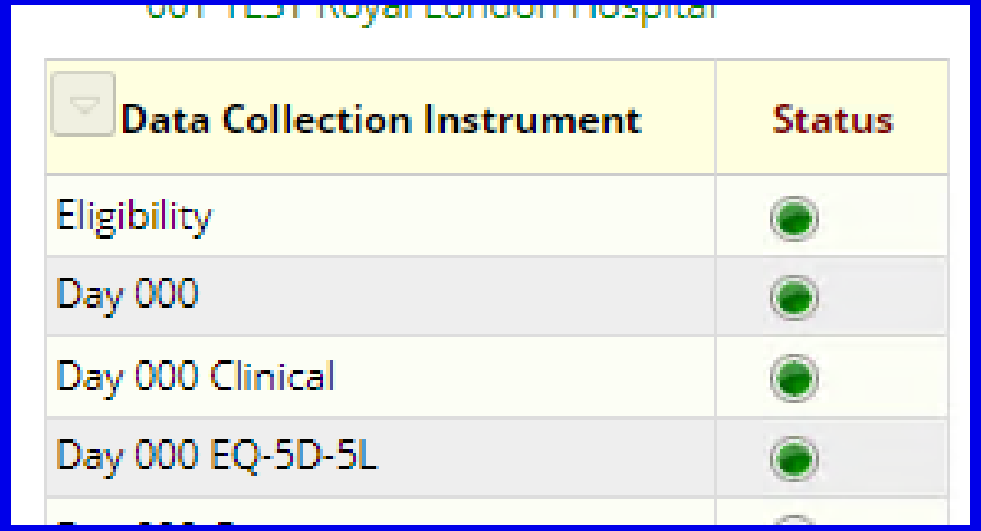


6. Open and complete the 'Day 000', 'Day 000 Clinical', and 'Day 000 EQ-5D-5L' form.

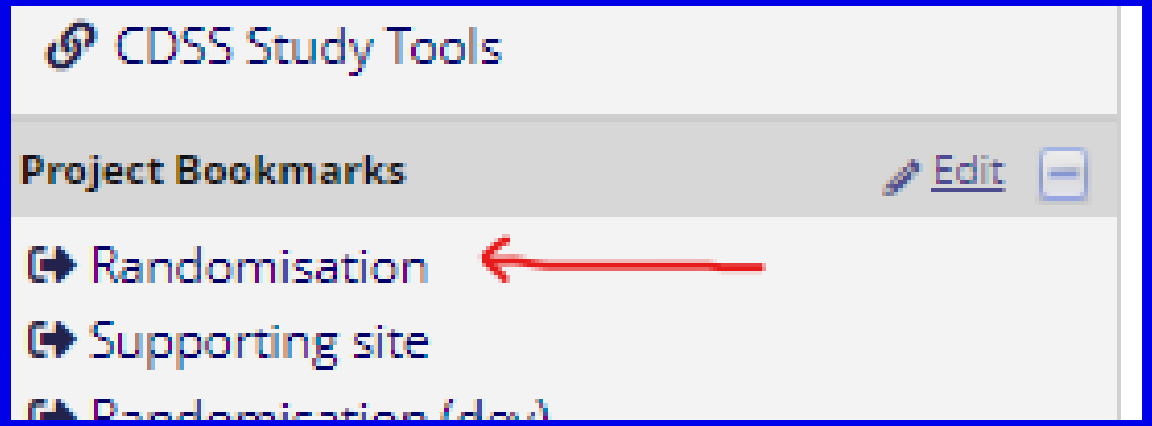


Randomisation instructions, 4

5. Once ‘Eligibility’, ‘Day 000’, ‘Day 000 Clinical’, and ‘Day 000 EQ-5D-5L’ forms are complete



6. Click the ‘Randomisation’ link under Project Bookmarks



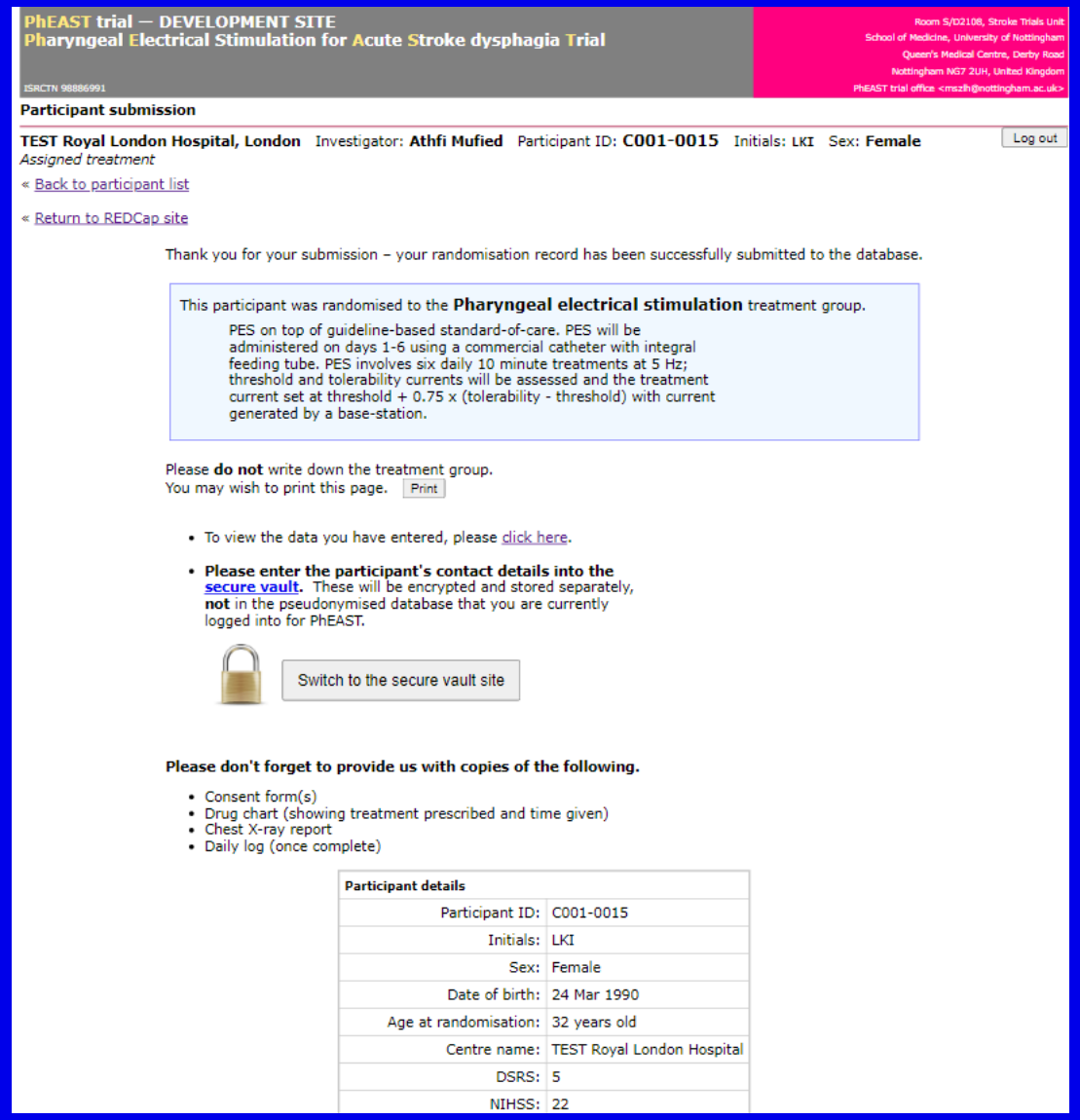
Randomisation instructions, 5

7. Check the information in the randomisation summary and then click ‘Randomise this participant’.

8. Once complete, the following page should appear:

9. Click the link to get to the ‘success page’.

Randomisation Instructions



PhEAST trial – DEVELOPMENT SITE
Pharyngeal Electrical Stimulation for Acute Stroke dysphagia Trial
ISRCTN 98886991

Room 5/D2108, Stroke Trials Unit
School of Medicine, University of Nottingham
Queen's Medical Centre, Derby Road
Nottingham NG7 2UH, United Kingdom
PhEAST trial office <mszlh@nottingham.ac.uk>

Participant submission

TEST Royal London Hospital, London Investigator: **Athfi Mufied** Participant ID: **C001-0015** Initials: **LKI** Sex: **Female** Log out
Assigned treatment

« Back to participant list

« Return to REDCap site

Thank you for your submission – your randomisation record has been successfully submitted to the database.

This participant was randomised to the **Pharyngeal electrical stimulation** treatment group.

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.

Please **do not** write down the treatment group.
You may wish to print this page. Print

- To view the data you have entered, please click here.
- **Please enter the participant's contact details into the secure vault.** These will be encrypted and stored separately, **not** in the pseudonymised database that you are currently logged into for PhEAST.

Switch to the secure vault site

Please don't forget to provide us with copies of the following.

- Consent form(s)
- Drug chart (showing treatment prescribed and time given)
- Chest X-ray report
- Daily log (once complete)

Participant details	
Participant ID:	C001-0015
Initials:	LKI
Sex:	Female
Date of birth:	24 Mar 1990
Age at randomisation:	32 years old
Centre name:	TEST Royal London Hospital
DSRS:	5
NIHSS:	22

10. The left page should be displayed, which shows a summary of all of the participant's randomisation information.

This shows:

- Participant's trial ID number
- The name of the randomising investigator
- Participant's their allocated treatment arm.

11. Click into the secure vault site to enter the participant's contact details, which will be required for follow-up.

12. Identifiable data will be kept separately in the secure vault, whereas all other data will be kept in the REDCap database.

Manual Randomisation

If the randomisation database is not working, please see the manual randomisation details found:

- On the trial website
- In WPD 003

Blinding

- Whilst investigators, participants and their family will be unblinded, outcome assessors will be blinded to treatment
- Please ensure that outcome assessors are not inadvertently unblinded
- They should not be members of the the stroke delivery team

- Research staff should complete the treatment

- A blinded SLT should then complete a day 14 bedside assessment

- A blinded day 14 follow up should then be completed, with the participant and using the information from the day 14 bedside assessment, by either a blinded SLT or blinded researcher
- Please refer to WPD 008 for more advice on blinding in the PhEAST trial

5. PHEAST: PHAGENESIS

Phagenesis device: Base station and catheter

DETAILS OF DEVICE

Manufacture

- Phagenyx® system manufactured by Phagenesis Ltd (Manchester UK).
- Has an EU CE Mark and FDA breakthrough device designation.
- Phagenesis will provide catheters and loan a base stations to each site, and training in their use without charge.
- If a site has an existing base station, this can be used.

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.
- The tray and contents are terminally sterilized using ethylene oxide.
- There are two accessory parts supplied with the catheter:
  - A Garment Clip to secure the external parts of the catheter to alleviate weight
  - A Transition Adaptor to enable standard connections for feeding delivery

Base Station

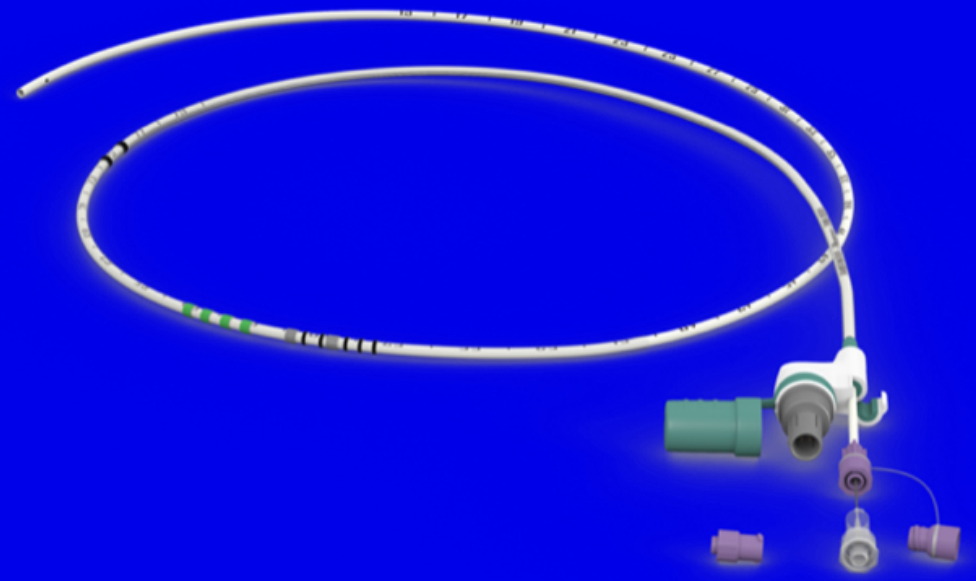
- The Base Station is used to generate, optimise and monitor the delivery of electrical stimulation.
- All devices are mains operated only.
- Please refer to your Phagenesis face-to-face training & handouts for further instructions.

Catheters

- Catheter combines a nasogastric feeding Tube (NGT) with electrodes with appropriate wiring and insulation for delivery of electrical stimulation to the lining of the pharynx.

- The catheter can be used as an NGT alongside its use for stimulation, delivering enteral nutrition to the patient as needed.

- Only one replacement catheter will be inserted, if pulled out before 3 treatments have been administered. If a second catheter is removed prior to completion of the treatment, no further catheters will be provided and treatment will stop.



How To Determine Treatment Level

1. THRESHOLD

The lowest stimulation level at which the participant can feel the PES in their throat.

Increment stimulation levels mA by mA until the participant feels the stimulation

2. TOLERABILITY

The highest level of stimulation that the participant can tolerate.

This is not the treatment stimulation level

3. STIMULATION

Base station calculates treatment stimulation level = threshold + 0.75 x (tolerability – threshold).

Avoid using a lower stimulation level unless participant conveys that they cannot tolerate treatment for 10 minutes. NB. The lower levels will reduce the effectiveness of PES.

Look for visual cues that the participant is uncomfortable

Intervention

Active

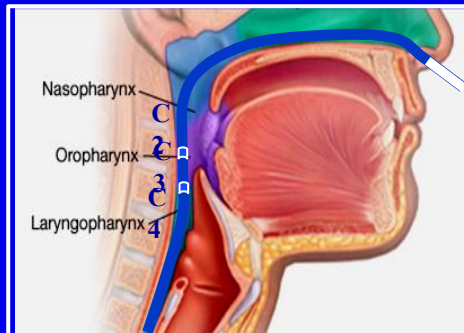
- Randomised group starts with NGT
- PES on top of guideline-care
- Independent treater
- Commercial “Phagenyx” system
- Days 1-6 10 mins, 5 Hz
- Threshold, tolerance, calculated stimulation, actual stimulation all recorded(mA)
  - Calculated = threshold + (0.75 x (tolerance-threshold))
- Stop treatment early if participant ready for discharge
- If tube pulled out, replace x1
  - Use mittens, nasal bridle as necessary; assess/record deprivation of liberties

Comparator

- Randomised group starts with NGT
- No PES tube on top of guideline care
- Normal NGT left in place as necessary

Training at start and twice yearly

- By trial SLT, e.g., sufficient current
- By Phagenesis representative…
- Monitor TTS currents



Intervention

- The treatment cycle should be 6 consecutive days.
- If this is not possible, a treatment cycle should not be less than 3 consecutive days.

Mon	Tues	Wed	Thurs	Fri	Sat	Sun	Mon	Tues	Wed
Day 1	2	3	4	5			6		
	Day 1	2	3	4			5	6	
		Day 1	2	3			4	5	6

Phagenesis Training

- All potential ’treaters’ will have face-to-face training on the base station and catheters.
- This includes a competency assessment and a handout for future reference.
- Trial staff who will only be involved in the blinded outcomes do not need to attend this training.

Study within a trial (SWAT)

- To ensure maximal stimulation on active PES group
- Sites will be randomised to enhanced support or normal support

Enhanced support

- If actual < calculated stimulation, 2 catheters pulled out, or <9 min 50 sec
- Trial SLT will contact site to retrain on treatment delivery

- Interim analysis
- If SWAT shows enhanced support group have higher PES stimulation, then all sites will receive it.

6. PHEAST: DATA COLLECTION

Data Collection Flow

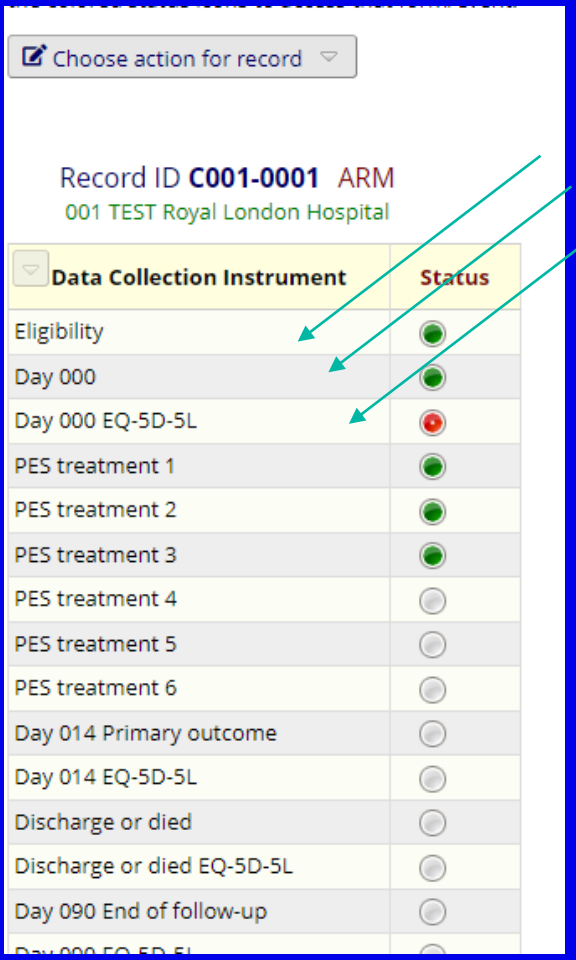
	Screen	Baseline	Day 1-6	Day 14	Discharge or death	Day 90 †	Day 365 ‡
Location	Hospital	Hospital	Hospital	Hosp. or outside	Hospital	Hosp. or outside	Centrally
Eligibility	+						
Consent/proxy consent	+						
DSRS FOIS EAT-10 FSS		+		+		+	
NIHSS, GCS		+		+			
Randomisation		+					
PES vs no PES			<>	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

DSRS: The Dysphagia Severity Rating Scale
FOIS: The Functional Oral Intake Scale
EAT-10: Eating Assessment Tool
FSS: Feeding Status Scale
NIHSS: NIH Stroke Scale
mRS: Modified Rankin Scale
BI: Barthel Index
EQ-5D: EuroQoL Five Dimensional
EQ-VAS: EuroQoL Visual Analogue Scale
TICS: Telephone Interview for Cognitive Status
ZDS: Zung Depression Scale

Eligibility and Day 000 CRF

- Trial staff will receive login details for the PhEAST RedCap database

- The eligibility, and baseline (day 000) forms must be complete and signed to proceed to randomisation



Treatment eCRFs

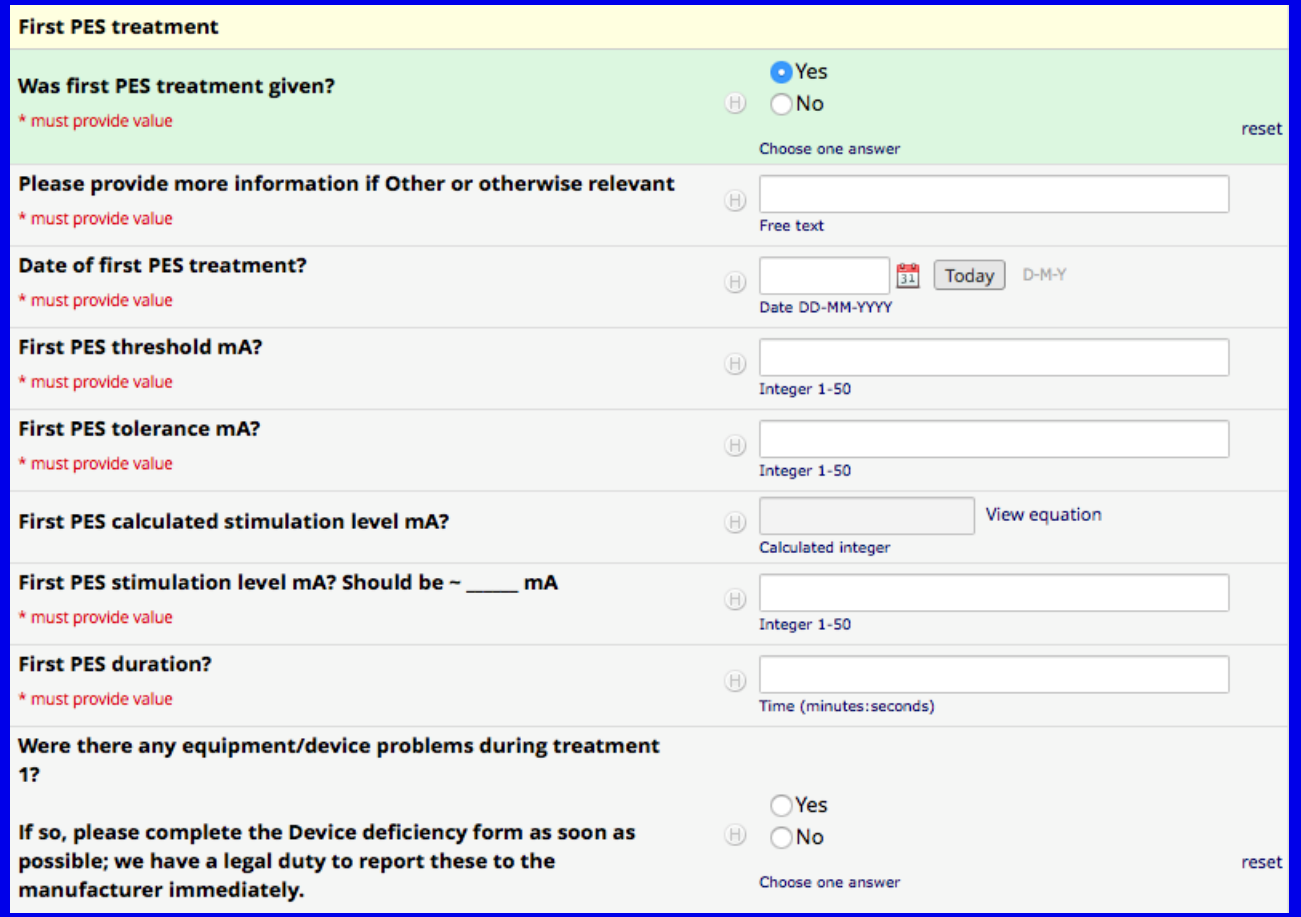
- A treatment eCRF form is filled out for each day of treatment, as soon as possible after PES finishes
- By treater

Data entered

- PES threshold
- PES tolerability
- Calculated PES stimulation
- Actual PES stimulation
- Catheters used
- Catheter LOT number; base station serial number

SWOT: The site may be contacted if:

- Actual PES stimulation < calculated, or
- Actual PES stimulation < 20 mA



First PES treatment

Was first PES treatment given? * must provide value
Yes / No — Choose one answer — reset

Please provide more information if Other or otherwise relevant * must provide value
Free text

Date of first PES treatment? * must provide value
Today D-M-Y — Date DD-MM-YYYY

First PES threshold mA? * must provide value
Integer 1-50

First PES tolerance mA? * must provide value
Integer 1-50

First PES calculated stimulation level mA?
View equation — Calculated integer

First PES stimulation level mA? Should be ~ ____ mA * must provide value
Integer 1-50

First PES duration? * must provide value
Time (minutes:seconds)

Were there any equipment/device problems during treatment 1?

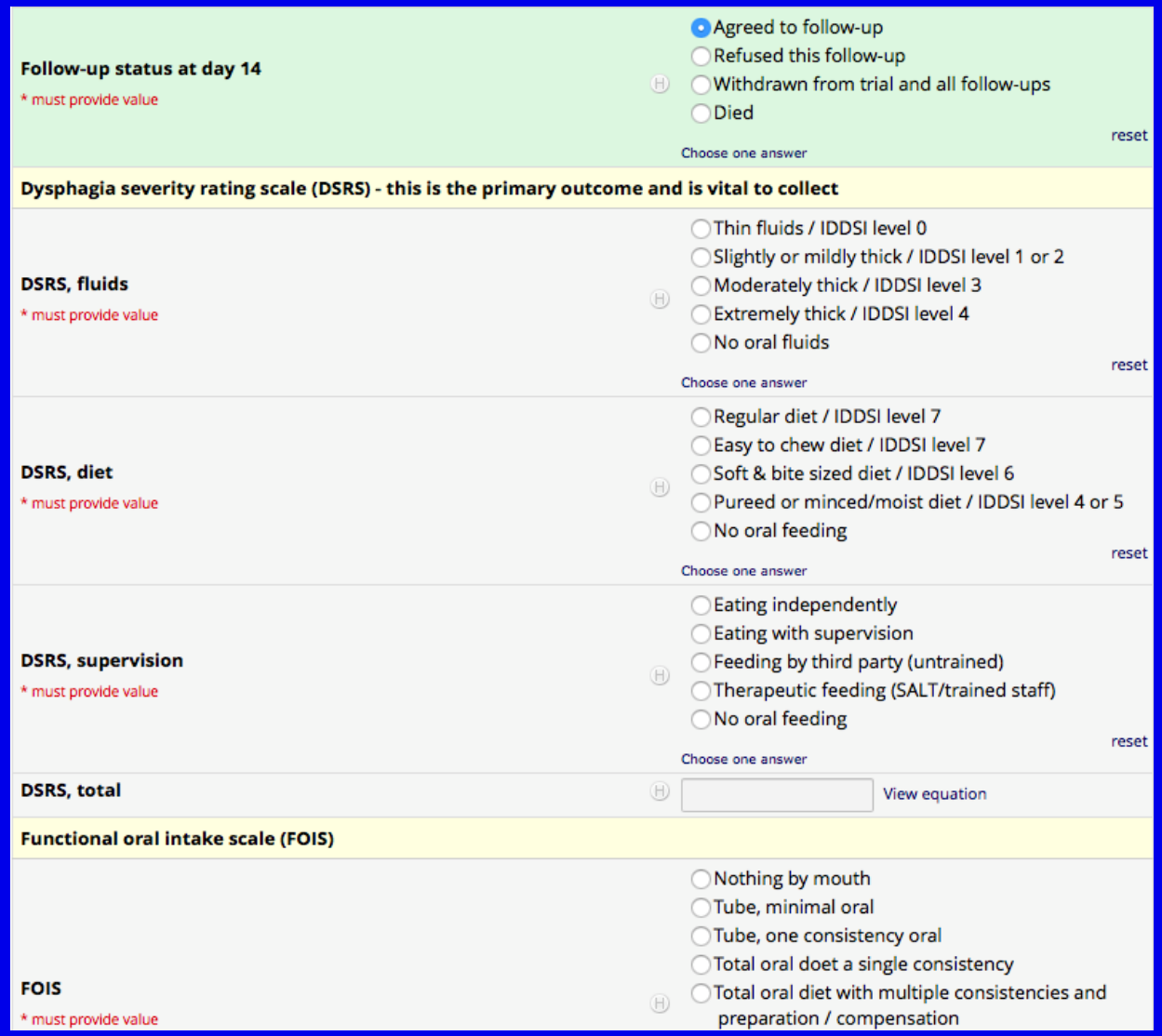
If so, please complete the Device deficiency form as soon as possible; we have a legal duty to report these to the manufacturer immediately.
Yes / No — Choose one answer — reset

Day 14 Follow Up CRF

- Primary outcome: DSRS
  - Effect in subgroups: age, sex, NIHSS, DSRS, stroke type, anterior vs posterior circulation, time onset-randomisation
- Secondary outcomes:
  - DSRS <=4, FOIS, EAT-10, feeding status score (FSS); EQ-VAS; chest infection; antibiotic use; weight

It is vital that these are:

- Completed for each participant
- Done by a blinded observer - someone not on the stroke team



Follow-up status at day 14
* must provide value
- (•) Agreed to follow-up
- ( ) Refused this follow-up
- ( ) Withdrawn from trial and all follow-ups
- ( ) Died

reset
Choose one answer

Dysphagia severity rating scale (DSRS) - this is the primary outcome and is vital to collect

DSRS, fluids
* must provide value
- ( ) Thin fluids / IDDSI level 0
- ( ) Slightly or mildly thick / IDDSI level 1 or 2
- ( ) Moderately thick / IDDSI level 3
- ( ) Extremely thick / IDDSI level 4
- ( ) No oral fluids

reset
Choose one answer

DSRS, diet
* must provide value
- ( ) Regular diet / IDDSI level 7
- ( ) Easy to chew diet / IDDSI level 7
- ( ) Soft & bite sized diet / IDDSI level 6
- ( ) Pureed or minced/moist diet / IDDSI level 4 or 5
- ( ) No oral feeding

reset
Choose one answer

DSRS, supervision
* must provide value
- ( ) Eating independently
- ( ) Eating with supervision
- ( ) Feeding by third party (untrained)
- ( ) Therapeutic feeding (SALT/trained staff)
- ( ) No oral feeding

reset
Choose one answer

DSRS, total View equation

Functional oral intake scale (FOIS)

FOIS
* must provide value
- ( ) Nothing by mouth
- ( ) Tube, minimal oral
- ( ) Tube, one consistency oral
- ( ) Total oral doet a single consistency
- ( ) Total oral diet with multiple consistencies and preparation / compensation

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UK | CHINA | MALAYSIA

DSRS: dysphagia severity rating scale

A measure of swallowing impairment

DSRS total score = sum of 3 sub-scales

Score	Fluids	Score	Diet	Score	Supervision
4	No oral fluids	4	Non oral feeding	4	No oral feeding
3	IDDSI level 4	3	IDDSI level 4 and 5	3	Therapeutic feeding (SALT/trained staff)
2	IDDSI level 3	2	IDDSI level 6	2	Feeding by third party (untrained)
1	IDDSI level 1 and level 2	1	IDDSI level 7 easy to chew	1	Eating with supervision
0	IDDSI level 0	0	IDDSI level 7 regular	0	Eating independently

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

Small vol. trials 443 = 11
Large vol. trials 343 = 10
Large vol. trials 434 = 10

Jayasekeran *et al. Gastroenterology* 2010; 138: 1737-46
Everton *et al. Sci Rep* 2020 10: 7268

DSRS: dysphagia severity rating scale

- Oral trials of fluid and/or food are commonly recommended for patients with post-stroke dysphagia. Scoring the DSRS can feel more difficult with patients on oral trials. We suggest the following criteria:

- **Minimal amount trials**
- This is equivalent to a score of 2 on the FOIS with no more than 15 teaspoons of any consistency within one day.
- Fluid and food items should be scored as 4, with a supervision score of 3 to indicate trials are taking place = DSRS 11 (4,4,3)
- e.g. 5 teaspoons of level 3 moderately thick fluids 3 times daily
- OR 3 teaspoons of level 4 puree yoghurt only 3 times daily

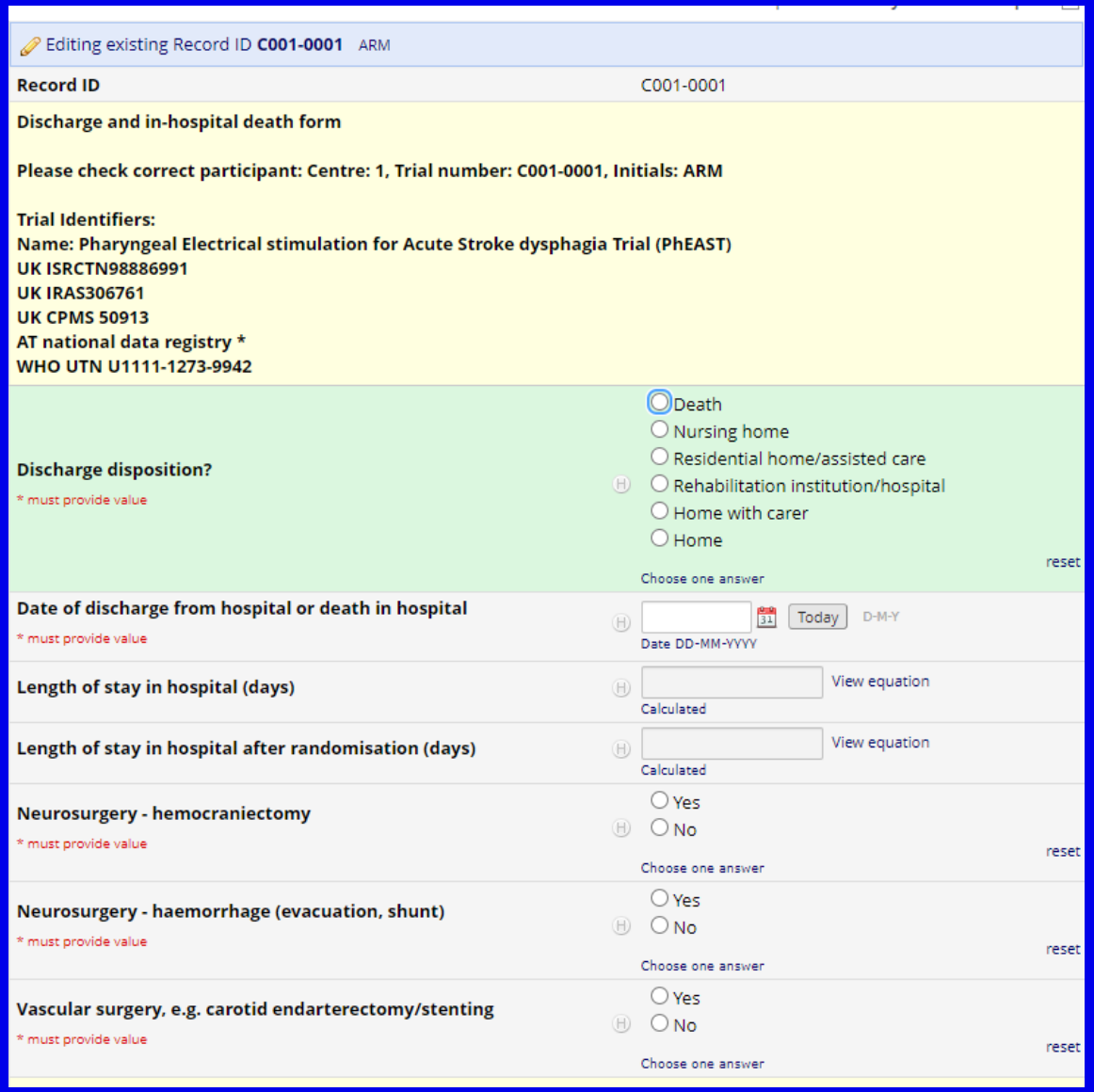
- **Consistent amount trials**
- This is equivalent to a score of 3 on the FOIS
- Fluid and food should be scored as per the consistency advised with a supervision score of 3 to indicate trials are taking place
- e.g. ½ portions of level 4 puree diet separate to 100mls of level 2 mildly thick fluids 3 times daily = DSRS 7
- OR 10 tspns of level 4 puree diet separate to up to 10 sips of level 1 slightly thick fluids 3 times daily = DSRS 6

Discharge / Death eCRF

All participants need a discharge / death CRF completed

This collects information on

- Discharge disposition: home, care home, nursing home, another hospital, death
- Length of stay
- Final diagnosis
- Time to removal of NGT /PEG
- Whether discharged with PEG
- Time in ICU, to intubation, disposition



Editing existing Record ID **C001-0001** ARM

Record ID	C001-0001
Discharge and in-hospital death form **Please check correct participant: Centre: 1, Trial number: C001-0001, Initials: ARM** **Trial Identifiers:** **Name: Pharyngeal Electrical stimulation for Acute Stroke dysphagia Trial (PhEAST)** **UK ISRCTN98886991** **UK IRAS306761** **UK CPMS 50913** **AT national data registry *** **WHO UTN U1111-1273-9942**	
Discharge disposition? * must provide value	○ Death ○ Nursing home ○ Residential home/assisted care ○ Rehabilitation institution/hospital ○ Home with carer ○ Home reset Choose one answer
Date of discharge from hospital or death in hospital * must provide value	Today D-M-Y Date DD-MM-YYYY
Length of stay in hospital (days)	View equation Calculated
Length of stay in hospital after randomisation (days)	View equation Calculated
Neurosurgery - hemocraniectomy * must provide value	○ Yes ○ No reset Choose one answer
Neurosurgery - haemorrhage (evacuation, shunt) * must provide value	○ Yes ○ No reset Choose one answer
Vascular surgery, e.g. carotid endarterectomy/stenting * must provide value	○ Yes ○ No reset Choose one answer

7. PHEAST: LOCAL SITE INFORMATION

Local Site File Contents

- Please see the PhEAST website where you can download an index page for the local investigator site file
- The coordinating centre will not send local (investigator) hardcopy site files in the post for reasons of sustainability and version control
- All documents will be available on the PhEAST website – if the local site want to print their own local site file then they must keep both the hardcopy and electronic site file up to date
- The coordinating centre will send any amendment notifications electronically with guidance of if any documents need superseding, we will then put the updated documentation on the PhEAST website

https://stroke.nottingham.ac.uk/pheast/docs

Delegation Log

- Anyone who is involved in the trial needs to be on the delegation log
- Includes nurses, doctors, speech and language therapists, administrators entering data onto online platform etc
- You can have as many people on the delegation log as required
- The training and roles delegated should be appropriate to the respective job role.

Local team members listed on the PhEAST delegation log need:

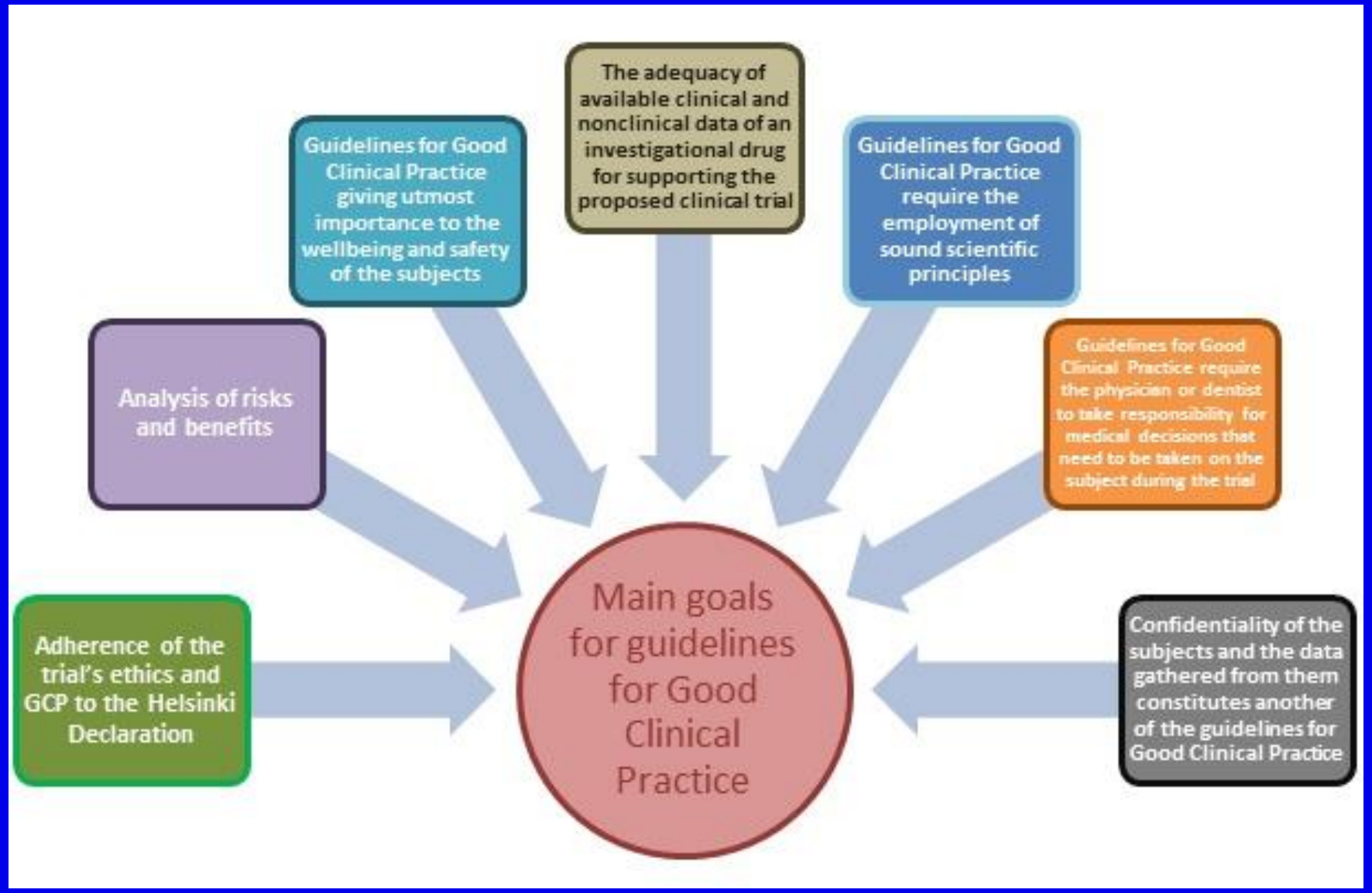
- Up to date CV
- Up to date GCP
- Completion of training

It is the local PI's responsibility to check the CV and GCP are up to date (within previous 2 years) for each team member before they can be signed off on the delegation log

Online delegation log:

- Add new team members to the delegation log before they can start working on PhEAST
- Alter the record of departing team members: sign and date 'role finished' against their name

Good Clinical Practice (GCP)



Good Clinical Practice (GCP)

- Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, conduct and record of research involving humans.
- There are 13 principles of GCP (listed below) and compliance with GCP provides public assurance that the rights, safety and well-being of research subjects are protected and respected, in line with the principles enunciated in the Declaration of Helsinki and other internationally recognized ethical guidelines. It also ensures the integrity of research data.

- Further reading:
- https://learn.nihr.ac.uk/
- https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/ema-gcp-guidance.pdf
- https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/good-clinical-practice/

Associate PI Scheme (UK only)

PhEAST (CPMS ID: 50913) is registered for the Associate PI Scheme. This scheme is a great opportunity for doctors, nurses, SLTs and other healthcare professionals to gain knowledge about delivery of an NIHR portfolio trial

See the Associate PI scheme page on the NIHR website

Applicants may register to be Associate PIs for this study, having obtained approval from their local PI, using the NIHR Associate PI Scheme Applicant Registration Form

Please consider who might be an associate PI at your site

NIHR | National Institute for Health Research

8. PHEAST SAFETY REPORTING

SAFETY EVENTS

- 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:

- All SAEs over 0-9 days
- Procedure/device-related (serious) adverse device events, (S)ADEs, over days 0-14
- Fatal SAEs over days 10-90 days
- All-cause mortality to day 365

Serious Adverse Event Reporting

- All SAEs will be assessed for causality using the following criteria:

1. **Not related / improbable** to device = SAE
2. **Unlikely** related to device = SAE
3. **Possibly** related to device = SAE
4. **Probably** related to device = (U)SADE serious adverse device effect
5. **Definitely** related to device = (U)SADE serious adverse device effect

ADEs, SADEs, USADEs

ADE = adverse device effect

- Adverse event related to the use of an investigational medical device (cf AE)
- Includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device
- Includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

SADE = serious adverse device effect (SADE)

- Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (cf SAE)

USADE = unanticipated serious adverse device effect (cf SUSAR)

- Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (cf SUSAR)
- Must be entered into the database within 24 hours of knowledge of the event

SADEs and USADEs

- Will trigger an email sent directly to the CI, who will review the event

- Sites should record and monitor all SAEs / SADEs until resolution, stabilisation or until the AE has been found to **not** be caused by study treatment

Serious Adverse Event Reporting

- Any AE occurring following study mandated procedures, having received the treatment, that results in any of the following outcomes:

1. **Death**
2. **A life-threatening adverse event**
3. **Inpatient hospitalisation or prolongation of existing hospitalization**
4. **A disability / incapacity**
5. **A congenital anomaly in the offspring of a participant**
6. **Medically important**
   - Events that jeopardise the participant and may require medical / surgical intervention to prevent one of the above criterion

What to do in Case of Device Defect

ADEs/SADEs and device defects are not the same!

Report any device defect (relating to either the base station or the catheter) on RedCap using device deficiency form

Information:

- Item: base-station, catheter
- Timing: Before PES, during PES, after PES
- Failure type: e.g., cable, break, base-station, feeding port (photo)
- Associated SAE form
- Plan to return to Phagenesis

This information will be reported automatically to the manufacture (Phagenesis)

9. PHEAST: PROTOCOL VIOLATIONS

Protocol Violation

A protocol violation is a major variation in practice from the trial protocol, for example where a participant is enrolled in spite of not fulfilling all the inclusion and exclusion criteria (e.g. lack of consent, randomisation before 4 days), or where deviations from the protocol could affect participant safety, the trial delivery or interpretation significantly.

Important to report any protocol violations to coordinating centre straight away

All protocol violations must be reported to the Chief Investigator, via email or telephone call to the trial office.

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

10. PHEAST: MONITORING

Site Monitoring Plan by Nottingham STU

Investigator Site File checklist

- This will check, but is not limited to:

1. Delegation & training logs in the ISF
2. Correct versions of patient-facing documents (PIS, RIS, GP letter, etc)
3. Ethical approval letters
4. Printed CRFs
5. SAE forms
6. Signed consent forms
7. CVs / GCPs

Patient File checklist

- This will check, but is not limited to:

1. Randomisation result and eligibility
2. Consent form and GP letter
3. Treatment levels
4. Adverse event log
5. Protocol violations affecting participant

Monitoring Plan

Entries on the eCRF will be verified by:

- Inspection against the source data
- A small random sample of data entries will be checked on a regular basis for verification of all entries made
- Central data analysis looking for outliers, digit preference, logic errors, non-normality etc

- On-site visits will only be performed if there are concerns about a site's performance.

SDV will be done via:

1. Document uploading / sharing through secure vault.
2. Secure video conference screen sharing but not copying or recording.
3. Pseudonymised documents uploaded onto database.

- Any discrepancies identified in the eCRF will be clarified with the site and resolved. Any changes to source data should be recorded, initialled and dated, as per GCP guidelines

Co-enrolment

Co-enrolment between certain trials is allowed

- An up-to-date list of trials that PhEAST can co-enroll with, and their respective time windows, will be given on the PhEAST website

Current list of trials	Delay to PhEAST
ENOS-2: IS/ICH	>= 7 days
MAPS-2: IS/ICH	>= 21 days
RECAST-3: IS	>= 14 days
TICH-3: ICH	>= 14 days

11. PhEAST: SUMMARY

PhEAST Key Points

Population

- Total 800 participants with recent stroke (4-31 days) with FOIS score of 1 or 2

Intervention

- PES administered over six-day period

Comparison

- Standard of care

Outcome

- DSRS (day 14) (primary)

12. PHEAST: CONTACT INFORMATION

PhEAST Trial Team

Name	Role	Contact Information email
Philip Bath	Chief Investigator	philip.bath@nottingham.ac.uk
Tiffany Hamilton	Senior Trial Manager	tiffany.Hamilton@nottingham.ac.uk
Gemma Squires	Trial Manager	gemma.squires1@nottingham.ac.uk
Olivia Matthews	Follow Up Coordinator	olivia.Matthews@nottingham.ac.uk
Carrie Chalmers	Research Administrator	Carrie.chalmers@nottingham.ac.uk

Trial Coordinating Centre contact information:

+44 115 823 1255

pheast@nottingham.ac.uk

Q&A

13. PHEAST: FAQS

FAQs

- Q: Is there any additional radiological imaging required for the PhEAST study?
- A: No. All imaging for the PhEAST study (i.e., CT head scans at admission to assess type of stroke and chest x-rays for pneumonia diagnosis) should be performed as per standard of care. No specific scans are required but results from standard of care scans will be collected.

- Q: Who can take consent?
- A: Consent can be taken by NIHR CRN nurses/co-ordinators to recruit, all must be GCP-trained and on the delegation log. Written informed consent will be sought but a documented, witnessed mark or oral consent due to physical inability to sign is permitted.

- Q: Will imaging be required for placement of catheters?
- A: Confirmation of correct NG placement should follow local best practice guidelines.

- Q: Can we recruit participants who have COVID-19?
- A: Yes, participants withCOVID-19 can be recruited as long as they do not require more than 35% of oxygen. Researchers must follow their hospital policies and procedures with regards to PPE, and ensure the base station is adequately cleaned between participants.

FAQs

- Q: Who is liable for the Phagenesis base station?
- A: For the duration of the trial, sites will have their own base station under a loan agreement from the manufacturer, Phagenesis. In terms of the Loan agreement, the site is liable for any loss or damage arising out of or in connection with any negligence, misuse or mishandling of the device(s).

- Q: What constitutes a recruit?
- A: Once you have randomised a participant, this will count as a recruit. The catheter should be inserted, and treatment should begin as soon as possible after randomisation, if randomised to PES.

- Q: If a participant has a further stroke, can they remain in the trial?
- A: Yes, please report this via the E-CRF.

- Q: Do 'treaters' need to be GCP trained and have a Research CV?
- A: Yes, all members of staff who work on the trial need to be GCP trained and have an up-to-date Research CV.

Thanks – Q&A?

More information from:

pheast@nottingham.ac.uk