Pharyngeal electrical stimulation for early decannulation in tracheotomised stroke patients with dysphagia (PHAST-TRAC): a randomised, single-blind, pivotal, superiority trial

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PHAST-TRAC Stroke RCT

Background

Swallowing problems (dysphagia) common after stroke:

- Admission ~50% of patients to ~15% at 6 months

Associated with poor outcome:

- Dehydration, poor nutrition, aspiration pneumonia, prolonged hospital stay (cost), poor functional outcome; increased death

Intensive Care after stroke (5-10%):

- Swallowing problems in stroke patients that need mechanical ventilation are common
- Tracheotomy for airway protection + severe dysphagia, or long term ventilation
- Long term cannula post-ventilator: uncomfortable, extended ICU/hospital stay (cost), readmission
- Decannulation often delayed because of severe dysphagia

Treatments:

- No definitive treatments
- Pharyngeal electrical stimulation (PES)?

Restoration of swallow control after stroke

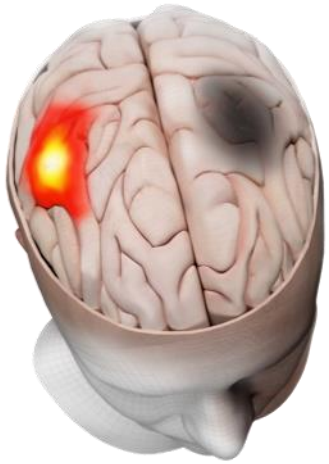
The natural recovery process post stroke involves compensatory reorganisation in the motor cortex of the non-dominant hemisphere

Healthy brain

Both hemispheres active during swallowing but left hemisphere dominates

Post Stroke

Lesion in left hemisphere (dominant side) - patient presents with dysphagia



Recovery

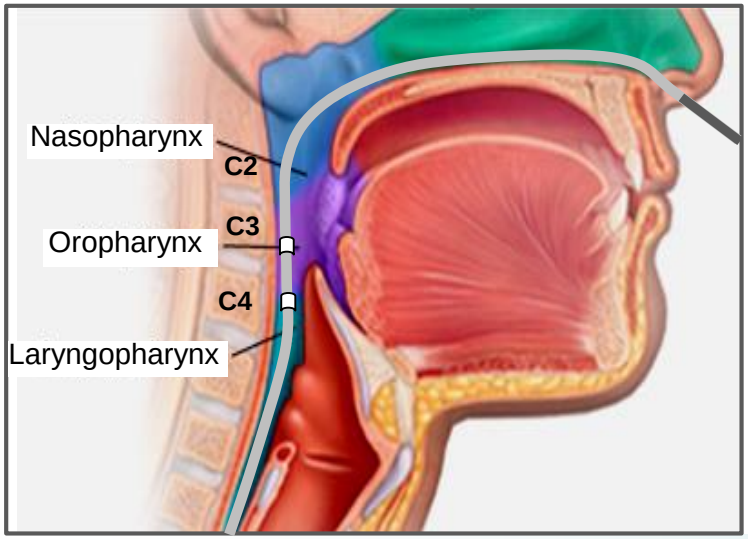
Functional reorganization of control to unaffected hemisphere

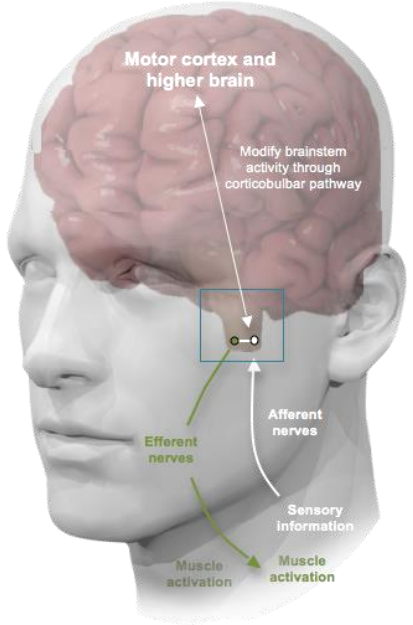
Hamdy, S., Q. Aziz, J. C. Rothwell, M. Power, K. Singh, D. A. Nicholson, R. C. Tallis, D. G. Thompson. Recovery of Swallowing after Dysphagic Stroke Relates to Functional Reorganisation in Intact Motor Cortex. *Gastroenterology* 1998; 115: 1104-1112.

Pharyngeal electrical stimulation (PES)

Catheter

Base station





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

PES studies in neurogenic dysphagia

Condition	Stage	Site	Design	Size	Status	Name	Type
Stroke	Subacute	SU	RCT x3	73	Published	Hamdy *et al*	Academic
	Subacute	SU	RCT	162	Published	STEPS	Commercial
	Subacute	*SU*	*RCT*	*≤225*	*To start*	*PhEED*	*Commercial*
	Subacute	**ICU**	**RCT**	**30**	**Published**	**Suntrup *et al***	**Academic**
	Subacute	ICU	Obs	23	Published	Muhle *et al*	Academic
	Subacute	**ICU**	**RCT**	**≤126**	**Completed**	**PHAST-TRAC**	**Commercial**
	Chronic		RCT	18	Published	Michou *et al*	Academic
MS	Chronic		RCT	20	Published	Resitvo *et al*	Academic
Mixed	*Subacute*	*Hosp*	*Register*	*~300*	*Ongoing*	*† PHADER*	*Commercial*
	Subacute	*ICU*	*RCT*		*Planned*		*Commercial*

† Mixed neurogenic dysphagia: Stroke – ventilation; Stroke – no ventilation; Traumatic brain injury or spinal cord injury; Other – ventilation; Other – no ventilation

Hosp: hospital; ITU: Intensive Care Unit; RCT: randomised controlled trial; SU: Stroke Unit; Obs: Observational study

PHAST-TRAC

Aim

- Safety & efficacy of PES in accelerating readiness for decannulation

Patients (adults)

- Supratentorial stroke (IS or ICH)
- Prior artificial ventilation and tracheotomy; weaned but persistent neurogenic dysphagia with unsafe airway
- Ineligible for decannulation 24-72 hours beforehand
- Cannot take food (FOIS=1)
- No sedation for ≥3 days
- Germany, Italy, Austria

Intervention

- Early PES (Phagenyx, CE Mark)
- PES again if persistent dysphagia

Comparator

- Sham then PES if persistent dysphagia = Late PES

Outcomes

1. Readiness for decannulation using FEES
2. Secondary

- Need for recannulation
- Need for, effect of, retreatment

Design

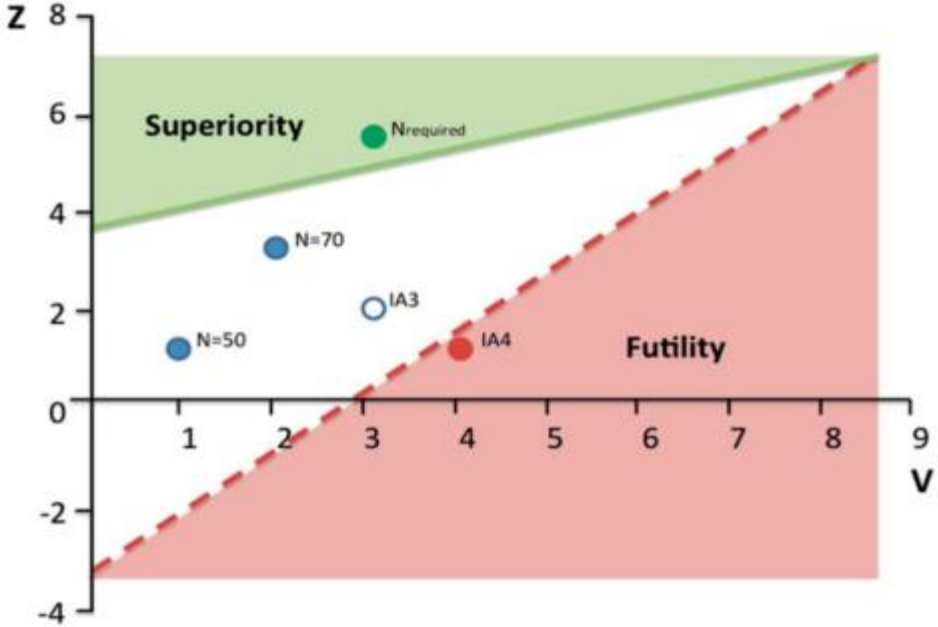
- International, prospective, randomised, single-blind parallel group trial; sequential design
- N=70-140

Funder/sponsor

- Phagenesis Ltd (UK)

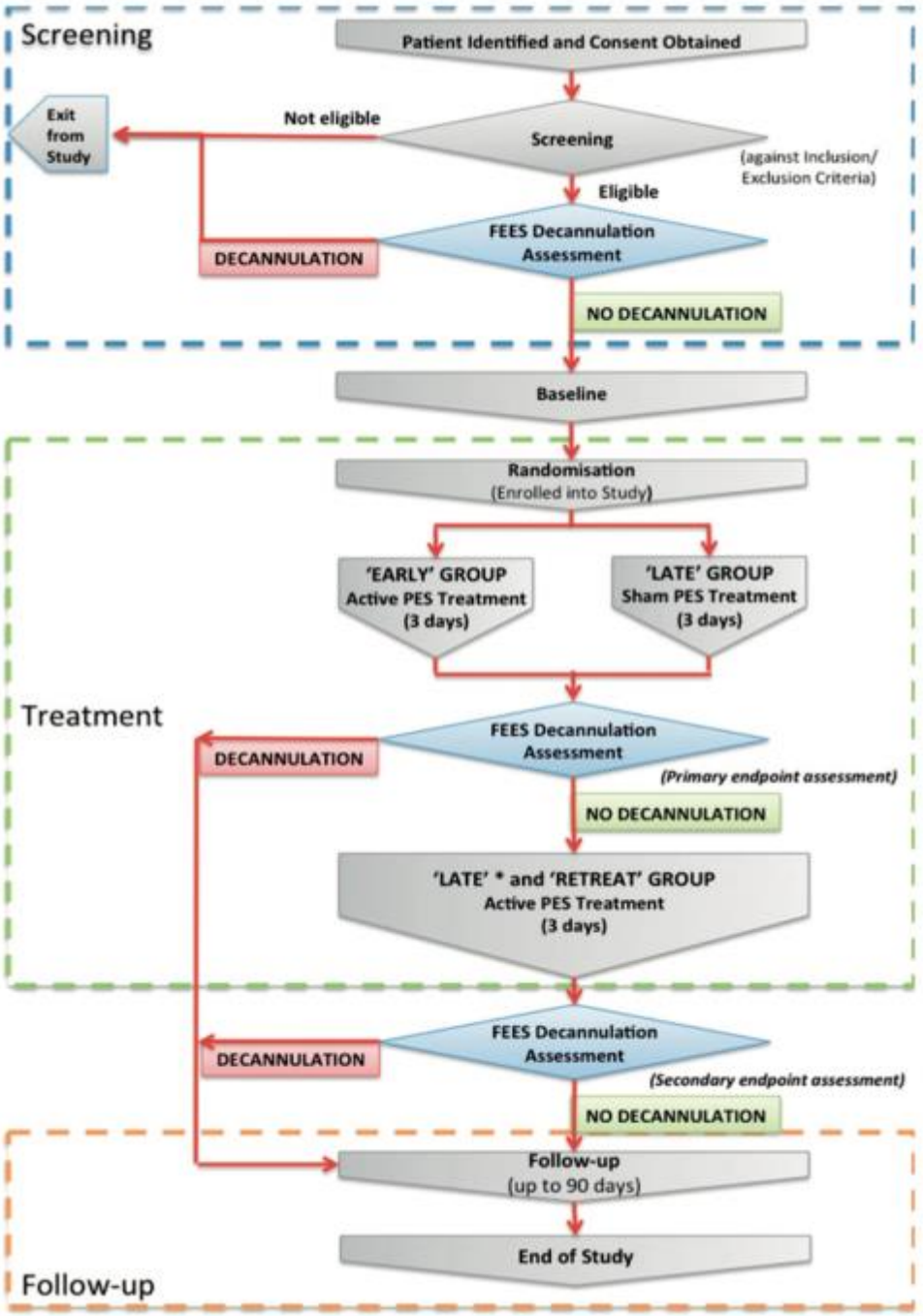
PHAST-TRAC
Stroke RCT

Protocol



Sequential review:

N=50	Futility
N=70	Efficacy / sample size re-estimation
N=140	Maximum

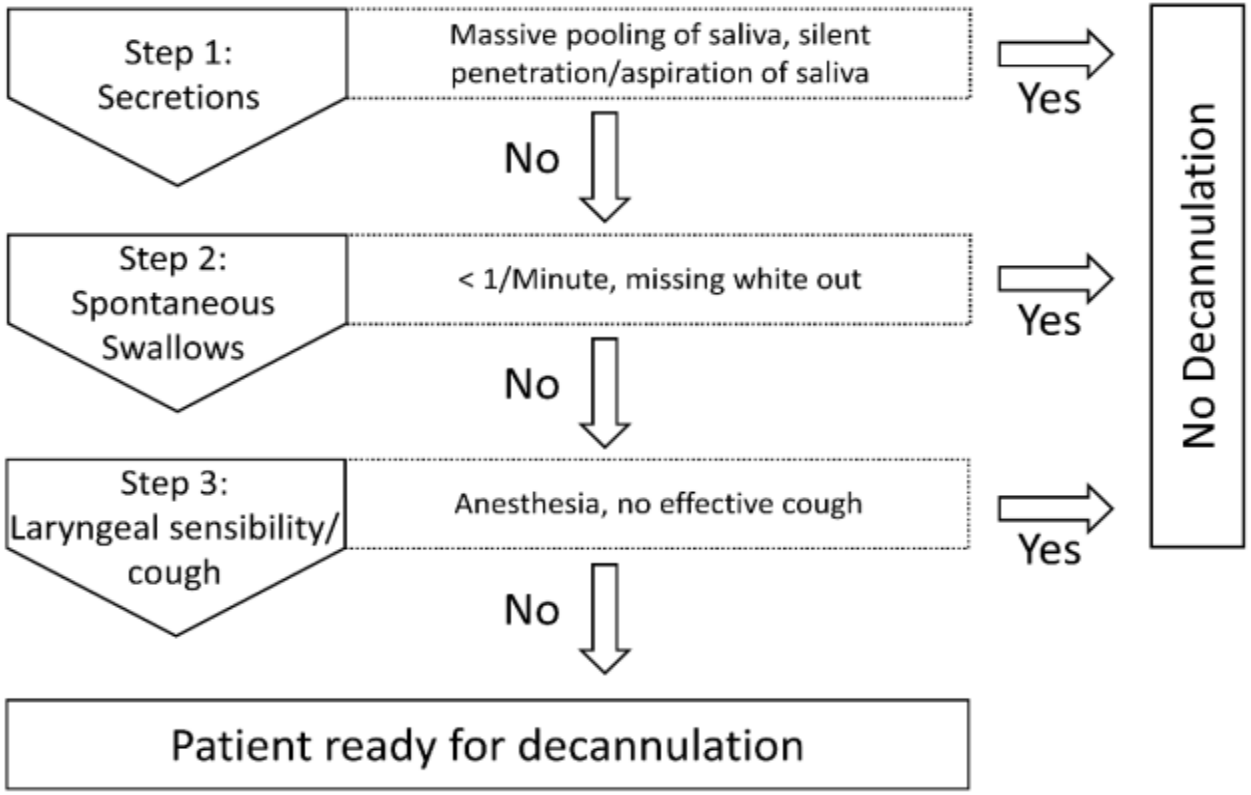


Dziewas *et al*. *Int J Stroke* 2017; 12: 430-7

N=70-140

PHAST-TRAC: Decannulation algorithm

- Protocol for determining readiness for decannulation using instrumental assessment - fibreoptic endoscopic evaluation of swallowing (FEES)
- Assessment made by independent investigator at each site
- Scoring: binary, ordinal



Adapted from: Dziewas *et al*. *Int J Stroke* 2017; 12: 430-7

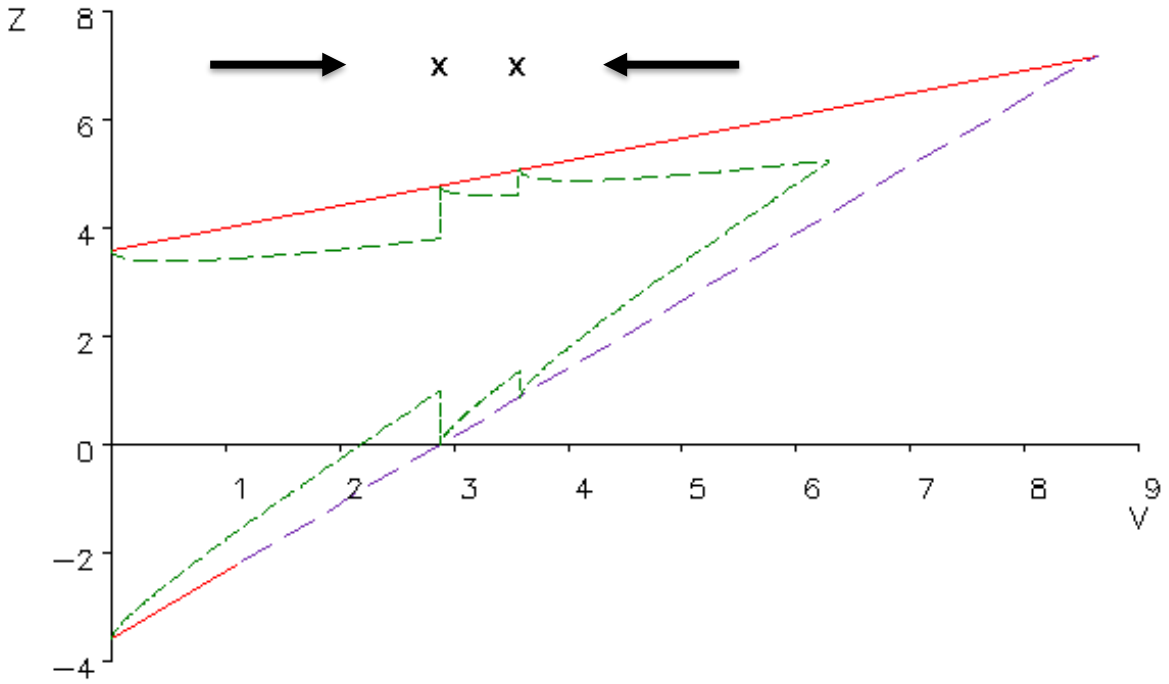
PHAST-TRAC Stroke RCT

PHAST-TRAC: Baseline

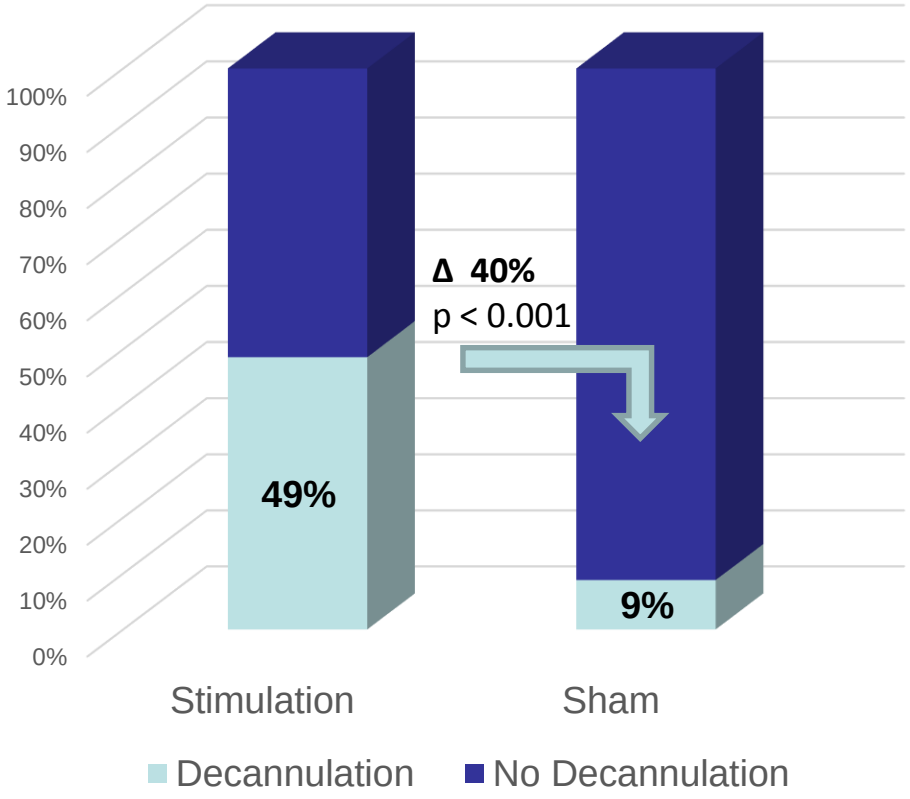
	All	PES	Sham
Patients	69	35	34
Age, years)	**64.2 (11.9)**	**61.7 (13.0)**	**66.8 (10.3)**
Sex, female, %	25 (36.2)	11 (31.4)	14 (41.2)
Premor. mRS>0, %	3 (4.6)	1 (3.0)	2 (6.2)
mRS>4, %	67 (98.5)	34 (100)	33 (97.1)
Previous stroke/TIA	10 (14.5)	7 (20)	3 (8.8)
Smoking, %	8 (11.6)	5 (14.3)	3 (8.8)
OTR, days	**28.0 [22] (11-120)**	**28.0 [29] (11-120)**	**28.0 [22] (11-95)**
Ventilation, days	**15.0 [13] (3-131)**	**15.0 [15] (5, 131)**	**13.5 [13] (3, 60)**
PEG tube, %	9 (20.5)	5 (22.7)	4 (18.2)
NIHSS, /24	**17.5 (4.6)**	**17.6 (5.0)**	**17.5 (4.3)**
Ischaemic stroke	**49 (71.0)**	**27 (77.1)**	**22 (64.7)**

PHAST-TRAC: Sequential analysis

- Two analyses performed: futility at N=50, efficacy at N=70
- Trial continued at N=50, not futile
- Trial stopped at N=70, for efficacy
- 1 patient excluded since catheter not inserted so N=69



PHAST-TRAC: Results



PES increased readiness for decannulation

PHAST-TRAC Stroke RCT

PHAST-TRAC: Results

%	PES	Sham	OR/MD (95% CI)	p
Participants	35	34		
Investigators				
Decannulation ready (%)	**17 (48.6)**	**3 (8.8)**	**7.0 (2.4-19.9)**	**0.00082**
Failing algorithm (/3)	0.5 [0, 3]	2 [2, 2.75]	-1.0 (-2.0, 0.0)	0.018
Independent FEES RV				
Decannulation ready (%)	10 (28.6)	2 (5.9)	6.4 (1.3-31.9)	0.023
Failing algorithm (/3)	1.2 [0.4, 2.0]	2.0 [1.7, 2.7]	-0.7 [-1.0, 0.0]	0.009
Actions				
Patients	17	3		
Re-cannulation ≤48h (%)	**0 (0%)**	**0 (0%)**		

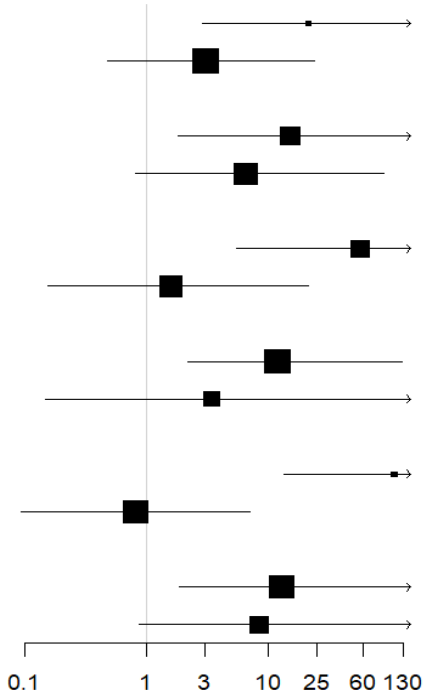
1ry outcome: pre-specified subgroups

Pre-specified subgroups

Significant interactions:

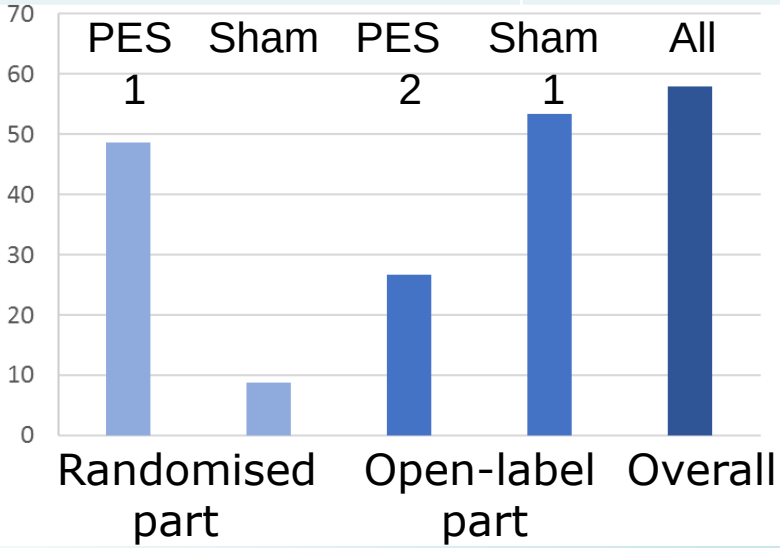
- Onset to randomisation
  - Efficacy if <28 days
- Time on ventilator
  - Efficacy if <15 days

Variable	OR (95% CI)	Interaction p-value
Age		0.168
< 66	21.26 (2.90, Inf)	
≥ 66	3.06 (0.48, 23.95)	
Sex		1.000
Male	15.17 (1.81, 727.78)	
Female	6.58 (0.82, 88.94)	
OTR		0.029
< 28	56.37 (5.47, 3146.36)	
≥ 28	1.58 (0.16, 21.39)	
Stroke type		1.000
Ischaemic	11.85 (2.18, 124.59)	
Haemorrhagic	3.42 (0.15, 235.57)	
Ventilation time		0.000
< 15	108.20 (13.54, Inf)	
≥ 15	0.82 (0.09, 7.17)	
NIHSS		1.000
< 18	12.86 (1.87, 160.45)	
≥ 18	8.51 (0.87, 436.59)	



1ry outcome: After open-label PES

	All	PES	Sham
Participants, open-label part	**45**	**15**	**30**
Ready for decannulation (%)	20 (44.4)	4 (26.7)	16 (53.3)
Participants, randomised & open-label parts	**69**	**35**	**34**
Ready for decannulation (%)	40 (58.0)	21 (60.0)	19 (55.9)
Participants	**69**	**35**	**34**
SAEs	18 (26.1)	10 (28.6)	8 (23.5)
Device-related SAEs	0 (0)	0 (0)	0 (0)



PHAST-TRAC: Limitations & Strengths

Limitations

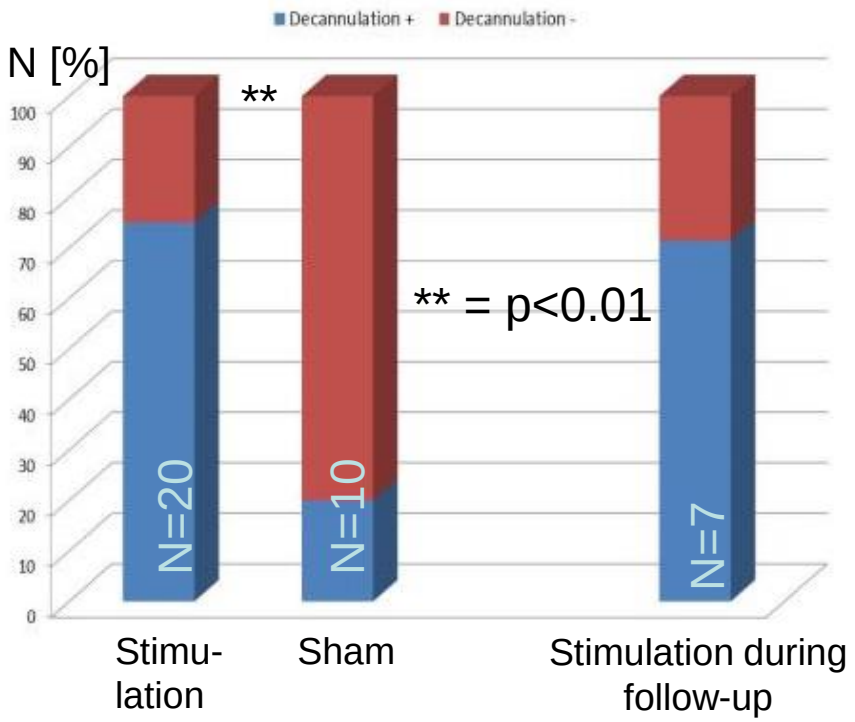
- Small: sequential analysis led to early stopping
- Single-blind: treater was unblinded
- Design meant no long-term follow-up

Strengths

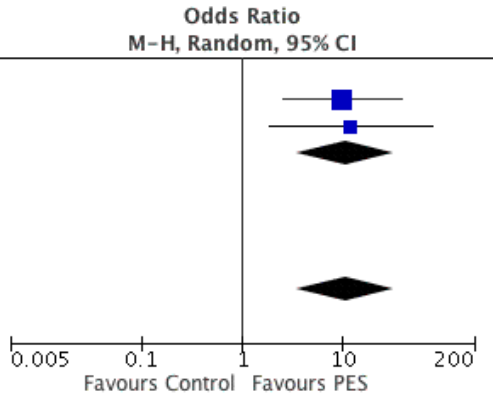
- Multicentre, sham-controlled, well-defined participants
- Robust findings, blinded outcome
- Internal consistency
- External consistency (with pilot trial)
- Most patients offered PES irrespective of randomisation

Summary: Decannulation

- Results similar to Suntrup et al (single centre, N=30)
- Randomised comparison
- Subsequent treatment in sham group



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: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 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: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 4.21 (P < 0.0001)						
Test for subgroup differences: Not applicable						



Suntrup *et al*. *Int Care Med* 2015; 41: 1629-37

Pharyngeal Electrical Stimulation Evaluation for Dysphagia after Stroke (PhEED)

PhEED Stroke RCT

Aim: Pivotal trial

Patients: Post stroke dysphagia, in-patient rehabilitation. In US and Europe

Intervention: Catheter – stimulation PES x 3 days

Comparator: Catheter – no stimulation

Outcome: swallowing safety by videofluoroscopy

Status: Start Q1. Some US and EU sites identified; more interested US sites welcome

If interested, please contact:

- rharvey@sralab.org

  or

- philip.bath@nottingham.ac.uk

Thanks

PHAST-TRAC
Stroke RCT

Thank you

Declaration of Interests: P Bath

Chief Investigator:

- Cochrane post-stroke dysphagia — National Institute Health Res

Trial Steering Committees

• STEPS	CI	Phagenesis Ltd
• **PHAST-TRAC**	**Chair**	**Phagenesis Ltd**
• PHADER	Co-CI	Phagenesis Ltd
• PhEED	Co-CI	Phagenesis Ltd

Advisor

- SONAR — Nestle

PES: Tracheotomised stroke patients

Patients

- N=30, severe stroke; prior artificial ventilation and tracheotomy; weaned but persistent dysphagia with unsafe airway

Intervention

- PES 3 days (n=20)

Comparator

- Sham (n=10). Then PES if persistent dysphagia

Outcomes

1. Decannulation
2. Stimulation intensity; LoS; FOIS; mRS
3. Response in sham group

Design

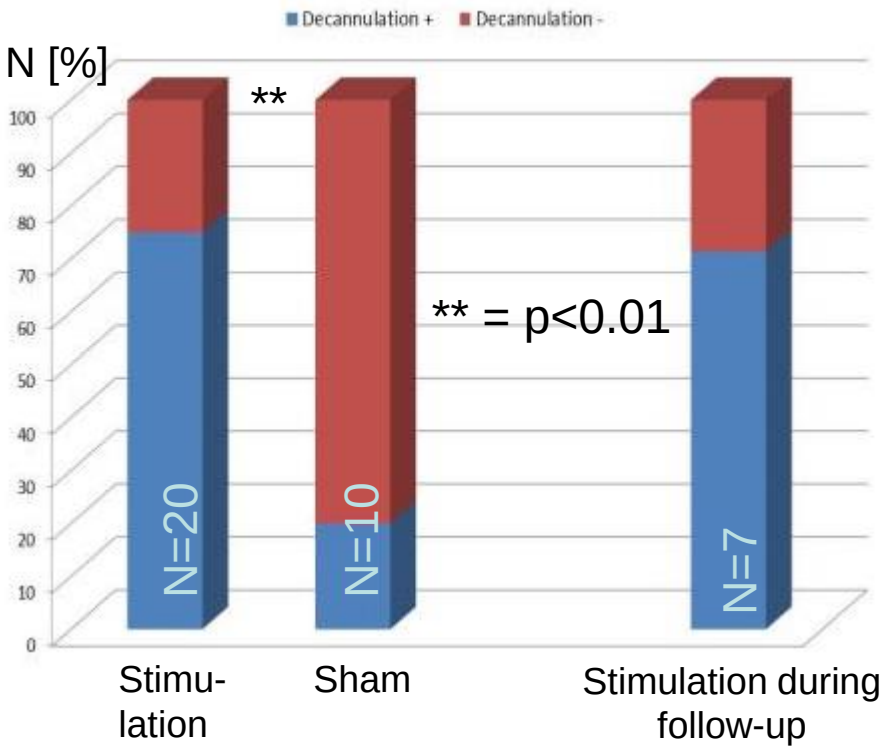
- Parallel RCT

Funding

- Academic

Results

1. Decannulation PES 15/20 v 2/10 ($p<0.01$)
2. LoS, FOIS, mRS all NS
3. PES in sham 5/7



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N=30