NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of pharyngeal electrical stimulation for neurogenic dysphagia

Neurogenic dysphagia is difficulty swallowing (dysphagia) caused by conditions that affect the nervous system (neurogenic), for example stroke, multiple sclerosis and Parkinson's. It can also be caused by major head and neck surgery (for example, to remove cancer), trauma, and intensive care treatment (intubation and tracheostomy). Dysphagia can cause coughing and choking, and food, drink or saliva may go into the lungs (aspiration), which can lead to chest infections. People with severe dysphagia may need a tracheostomy to help prevent saliva going into the lungs.

In this procedure, a catheter (tube) is passed through the nose and into the throat (pharynx). The catheter delivers small amounts of electrical current to the pharynx. The electrical current travels to the brain and stimulates the areas involved in swallowing. The aim is to reduce aspiration and improve secretion management and quality of life.

Contents

Introduction

Description of the procedure

Efficacy summary

Safety summary

The evidence assessed

Validity and generalisability of the studies

Existing assessments of this procedure

Related NICE guidance

Additional information considered by IPAC

References

Literature search strategy

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Appendix

Abbreviations

Word or phrase	Abbreviation
Amyotrophic lateral sclerosis	ALS
ALS functional rating scale revised	ALSFRS-R
Analysis of variance	ANOVA
Barthel Index	BI
Confidence interval	CI
Dysphagia severity rating scale	DSRS
EuroQol 5-dimensions	EQ-5D
Fibreoptic endoscopic evaluation of swallowing	FEES
Functional oral intake scale	FOIS
Mean difference	MD
Minimal clinically important difference	MCID
modified Rankin Scale	mRS
Multiple sclerosis	MS
National Institutes of Health Stroke Scale	NIHSS
Odds ratio	OR
Penetration-aspiration scale	PAS
Pharyngeal electrical stimulation	PES
Quality of life	QoL
Randomised controlled trial	RCT
Serious adverse event	SAE
Standard deviation	SD
Standard logopaedic therapy	SLT
Standardised mean difference	SMD
Swallowing quality of life	SWAL-QOL
Traumatic brain injury	TBI

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

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Date prepared

This overview was prepared in May 2022. The final version was done in November 2023.

Procedure name

- Pharyngeal electrical stimulation for neurogenic dysphagia

Professional societies

- Royal College of Speech and Language Therapists
- British Association of Stroke Physicians
- British Association of Otorhinolaryngologists, Head and Neck Surgeons (ENT UK)
- British Society of Rehabilitation Medicine

Description of the procedure

Indications and current treatment

Difficulty in swallowing (dysphagia) is caused by neurological impairment. It can happen because of several conditions, including stroke, traumatic brain injury (TBI), disorders of cerebral development, neurodegenerative diseases, major head and neck surgery (for example, to remove cancer), trauma and intensive care treatment (intubation and tracheostomy). Dysphagia may lead to malnutrition, dehydration, aspiration pneumonia and death.

Treatment options depend on the cause and severity of the dysphagia. Compensatory strategies include modifying diet (including thicker fluids and foods) and in moderate or severe dysphagia, nasogastric tubes, percutaneous endoscopic gastrostomy tubes or jejunostomy tubes may be used to provide nutritional support. Rehabilitation strategies include swallowing therapy (to help relearn swallowing and strengthen muscles) and for some people, transcutaneous neuromuscular stimulation.

What the procedure involves

A catheter with 2 electrodes on the outside is passed through the nose into the pharynx. Guide marks on the catheter are used to ensure it is correctly positioned to deliver low-level pharyngeal electrical stimulation (PES). The catheter is connected to a portable base station, which stores the person's information and adjusts the stimulation variables. The exact stimulation level is calculated for each person at the start of each treatment session. Treatment is given by a healthcare professional with appropriate training and typically a treatment cycle consists of 10 minutes of stimulation each day for 3 consecutive days, for up to 2 cycles. People may experience a fizzing or tingling sensation in the

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throat during the procedure. The focused stimulation aims to increase brain activity in the swallowing control centre and restore neurological control of the swallowing function. The dual function catheter can also be used to administer enteral nutrition and fluids, if needed, as well as delivering electrical stimulation.

Unmet need

Dysphagia is associated with delayed decannulation, prolonged intensive care unit stays and increased dependence upon discharge. People who experience dysphagia report negative emotional and quality-of-life effects (such as from having to have a tracheostomy or feeding tube for a prolonged period of time). Treatment options are limited, particularly for people with post-stroke dysphagia, because these need active engagement from the person.

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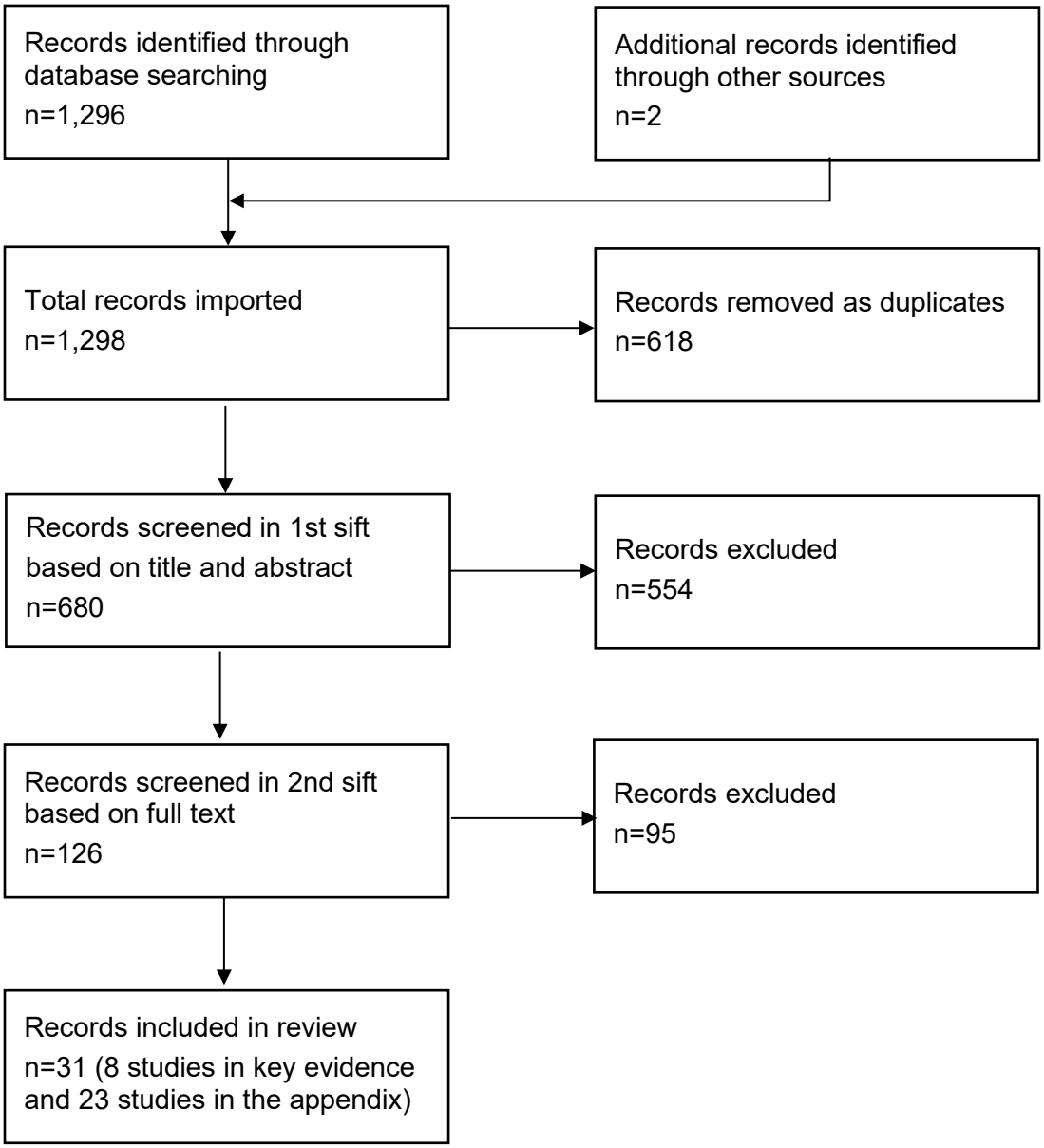
Figure 1 Flow chart of study selection



Outcome measures

Decannulation

Readiness for decannulation is assessed with a standardised technique called the fibreoptic endoscopic evaluation of swallowing (FEES). Clinicians use this technique to check for pooling of

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saliva, spontaneous swallowing and sensation of the endoscope in the laryngeal vestibule. An algorithm is followed to determine whether a person is ready for their tracheostomy to be removed.

Swallowing

PAS

The penetration-aspiration scale (PAS) is an 8-point scale that assesses the safety of swallowing. PAS score is assessed by endoscopic exam or videofluoroscopy and ranges from 1 (material does not enter the airway) to 8 (material enters the airway, passes below the vocal folds and no effort is made to eject). Higher scores indicate worse swallows and a PAS score of 3 or more is considered an abnormal swallow.

DSRS

The dysphagia severity rating scale (DSRS) provides an estimate of the severity of dysphagia post stroke, based on the amount of food and fluid modification people with the condition need as well as the level of supervision required. The subscales range from 0 to 4 (0= normal and eating independently; 4= no oral fluids and feeding). Higher scores indicate more severe dysphagia.

FOIS

The functional oral intake scale (FOIS) is a 7-point scale that assesses oral intake capacity. The scale ranges from 1= no oral intake, to 7= total oral intake with no restrictions. Lower scores indicate more severe dysphagia.

MCID

The minimal clinically important difference (MCID) is the minimum difference in a score that is considered valuable and changes management of the person's condition. The MCID for the DSRS was determined to be 1.0 point. It demonstrates a mean change in DSRS in people having active treatment of greater than 1.0 point just a few days after completing treatment.

Dependence and disability

NIHSS

The National Institutes of Health Stroke Scale (NIHSS) is a 15-item scale that assesses the level of neurological impairment in people with stroke. Subscales include the following: consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria and sensory loss. Each subscale is scored on a 3-point to 5-point scale, with a total score of 42. Higher scores indicate worse impairment, with scores of more than 25 considered very severe and scores of 15 to 24 considered severe.

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mRS

The modified Rankin Scale (mRS) is a 6-item scale that assesses dependence and disability. The scale ranges from 0= no symptoms, to 6= dead. Higher scores indicate more severe disability.

Barthel Index

The Barthel Index (BI) assesses activities of daily living across 10 items: feeding, personal toileting, bathing, dressing and undressing, getting on and off a toilet, controlling the bladder, controlling the bowel, moving from a wheelchair to bed and returning, walking on level surface (or propelling a wheelchair if unable to walk) and ascending and descending stairs. Each item is scored from 0 (unable) to 2 (independent). The final score is multiplied by 5 to get a total score out of 100. Lower scores indicate higher levels of dependency.

ALSFRS-R

The amyotrophic lateral sclerosis (ALS) Functional Rating Scale Revised (ALSFRS-R) assesses the severity of ALS across several functional domains. Lower scores indicate higher severity.

Quality of life

EQ-5D

The EuroQol 5-dimensions (EQ-5D) assesses health-related quality of life (QoL) across 5 domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Higher scores indicate worse QoL. The second part of the EQ-5D includes the EQ visual analogue scale (EQ VAS). This is a vertical line that ranges from 0 (the worst health you can imagine) to 100 (the best health you can imagine). People mark the line to indicate how their health is that day. Higher scores indicate better health.

SWAL-QOL

The swallowing quality of life (SWAL-QOL) is a 44-item scale that assesses 10 aspects of QoL in people with dysphagia. Lower scores indicate worse QoL.

Efficacy summary

Decannulation

The PHAST-TRAC RCT (Dziewas, 2018) found a statistically significant effect that people who had PES had a higher likelihood of readiness for decannulation 24 to 72 hours after the treatment (49% [17 of 35]) compared with sham (9% [3 of 34]; OR=7·00 [95% CI 2·4–19·8]; p=0·0008). This was a crossover trial, meaning that people in the sham arm who were not decannulated within the first 24 to 72 hours were then treated with PES. Of the 30 people who crossed over to have PES, 53% (16 of 30) were ready for decannulation within 24 to 72 hours. No one who was decannulated was recannulated within 30 days or before hospital discharge.

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In the RCT of 30 people (Suntrup, 2015) there was a statistically significantly higher likelihood of decannulation within 72 hours of treatment completion in the PES group (75% [15 of 20]) compared with sham (20% [2 of 10]; p<0.01). This was also a crossover trial, and 71% (5 of 8) of people in the sham group who had severe persistent dysphagia and went on to have PES were ready for decannulation 72 hours after treatment.

In the PHADER prospective registry study (Bath, 2020), 66% (66 of 99) of people with tracheostomy could be decannulated after PES. The magnitude of improvement at 3 months was greater (7.5 compared with 2.1 points on the DSRS) in the decannulated group compared with the non-decannulated group (note MCID=1). Most people who were decannulated were post stroke (38 of 66), but 18 people had ventilator associated dysphagia and 10 had traumatic brain injury.

Overall treatment effect

In a meta-analysis of 8 RCTs, there was a statistically significant overall moderate effect size of PES compared with sham with substantial heterogeneity: standardised mean difference (SMD) 0.68 (95% confidence interval [CI] 0.22 to 1.14; p=0.004; I^2=65%). Further meta-analyses were done for early (up to 2 weeks) and late (3 months or more) treatment effects (Cheng, 2021):

- Early (8 studies): there was a statistically significant overall moderate effect size of PES compared with sham with substantial heterogeneity: SMD 0.68 (95% CI 0.22 to 1.14; p=0.004; I^2=65%).
- Late (2 studies): there was no statistically significant effect size of PES compared with sham with no heterogeneity: SMD -0.04 (95% CI -0.46 to 0.38; p=0.86; I^2=0%).

The authors note that the number of studies that published data on late treatment effect was limited. Interpretation of the overall treatment effect reported in this meta-analysis is challenging because multiple outcome measures (percentage of people decannulated, PAS, DSRS) were combined in the description of ‘overall treatment effect’.

Swallowing outcomes

PAS

In a meta-analysis of 5 RCTs, treatment with PES had a statistically significant moderate effect size on PAS scores from before to after treatment: effect size 0.527 (z[4]=3.983, p=0.000, 95% CI 0.268 to 0.786). When comparing the change in PAS score between PES and sham groups, there was no statistically significant difference in PAS score change from baseline to after treatment (z[4]=0.718, p=0.473, Hedges’ g=0.099, and 95% CI -0.170 to 0.368; Speyer 2022).

In an RCT of 162 people (87 active treatment) with post-stroke dysphagia, there were no statistically significant differences in the change in PAS score from baseline to 2 weeks or 12 weeks in PAS scores between the PES and sham groups (Bath 2016):

- 2 weeks: mean difference=0.14; 95% CI -0.37 to 0.64; p=0.60

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- 12 weeks: mean difference=0.29; 95% CI -0.04 to 0.99; p=0.41.

In an analysis of a prospective registry of 252 people with dysphagia from various neurological causes, there was a statistically significant decrease in PAS score from 6.7 at baseline to 3.2 at day 92 after PES treatment (mean difference -4.1; 95% CI -4.8 to -3.3; p<0.001). Similar decreases were observed in diagnostic subgroups (stroke, not ventilated; stroke, ventilated; ventilator-related; but not observed in TBI; Bath 2020).

In a pilot RCT of 20 people (10 active treatment) with dysphagia related to multiple sclerosis (MS), there was a statistically significant decrease in PAS score from baseline to each post-stimulation period (p<0.001). A similar decrease was not observed in the sham group (Restivo 2013).

In a pilot RCT of 20 people (10 people PES plus SLT) with dysphagia related to ALS, there were no statistically significant differences in PAS score improvement between the PES plus SLT and SLT alone treatment groups at any of the follow-up visits (all p>0.05; Herrmann 2022).

DSRS

In the RCT of 162 people (87 on active treatment) with post-stroke dysphagia, there were no statistically significant differences in the change in DSRS score from baseline to 2 weeks or 12 weeks between the PES and sham groups (Bath 2016):

- 2 weeks: mean difference 0.31; 95% CI -0.56 to 1.18; p=0.49
- 12 weeks: mean difference 1.01; 95% CI -0.44 to 2.46; p=0.17.

In an RCT of 69 people (35 on active treatment) with post-stroke dysphagia and tracheostomy, there were no statistically significant differences in the change in DSRS score from baseline to 2 days, 30 days (or hospital discharge, whichever was first), or 90 days after treatment between the PES and sham groups. Note that this RCT was stopped early for superiority in the primary outcome (readiness for decannulation; Dziewas 2018):

- baseline DSRS: PES 12, sham 12
- 2 days: mean difference 0.27; 95% CI -1.05 to 1.59; p=0.6873
- 30 days (or hospital discharge): mean difference -0.88; 95% CI -3.17 to 1.41; p=0.4437
- 90 days: mean difference -1.10; 95% CI -3.97, 1.77; p=0.4449.

In the analysis of a prospective registry of 252 people with dysphagia from various neurological causes, there was a statistically significant decrease in DSRS score from 11.4 at baseline to 5.1 at day 92 after PES treatment (mean difference -6.3; 95% CI -7.0 to -5.6; p<0.001). Similar decreases were observed in diagnostic subgroups (stroke, not ventilated; stroke, ventilated; ventilator-related; and TBI; Bath 2020).

In the pilot RCT of 20 people (10 people PES plus SLT) with dysphagia related to ALS, there were no statistically significant differences in DSRS score improvement between the PES plus SLT and SLT alone treatment groups at any of the follow-up visits (all p>0.05; Herrmann 2022).

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FOIS

In the RCT of 69 people (35 on active treatment) with post-stroke dysphagia and tracheostomy, there were no statistically significant differences in the change in FOIS score from baseline to 2 days, 30 days (or hospital discharge), or 90 days after treatment between the PES and sham groups. Note that this RCT was stopped early for superiority in the primary outcome (readiness for decannulation; Dziewas 2018):

- baseline FOIS: PES 1, sham 1
- 2 days: mean difference -0.191; 95% CI -0.878 to 0.495; p=0.5789
- 30 days (or hospital discharge): mean difference 0.560; 95% CI -0.61 to 1.73; p=0.3407
- 90 days: mean difference 0.745, 95% CI -0.660 to 2.150; p=0.2922.

In the analysis of a prospective registry of 252 people with dysphagia from various neurological causes, there was a statistically significant increase in FOIS score from 1.4 at baseline to 4.3 at day 92 after PES treatment (mean difference 2.9; 95% CI 2.5 to 3.3; p<0.001). Similar increases were observed in diagnostic subgroups (stroke, not ventilated; stroke, ventilated; ventilator-related; but not observed in TBI; Bath 2020).

Leaking and residues

In the pilot RCT of 20 people (10 people PES plus SLT) with dysphagia related to ALS, there were no statistically significant differences in leaking and residues between the PES plus SLT and SLT alone treatment groups at any of the follow-up visits (all p>0.05). Residues are parts of the bolus that remain in the pharynx after swallowing and put the person at risk of aspiration. Leaking is when solid or fluid food enters the pharynx before triggering the swallowing reflex (Herrmann 2022).

Dependence/disability outcomes

NIHSS

In the RCT of 162 people (87 on active treatment) with post-stroke dysphagia, there was no statistically significant difference in the change from baseline to 2 weeks in NIHSS scores between the PES and sham groups (Bath 2016): at 2 weeks the mean difference was -0.05; 95% CI -1.42 to 1.32; p=0.94.

In the RCT of 69 people (35 on active treatment) with post-stroke dysphagia and tracheostomy, there were no statistically significant differences in the change in NIHSS score from baseline to 2 days, 30 days (or hospital discharge), or 90 days after treatment between the PES and sham groups. Note that this RCT was stopped early for superiority in the primary outcome (readiness for decannulation; Dziewas 2018):

- baseline NIHSS score: PES 17.6, sham 17.5
- 2 days: mean difference -0.027; 95% CI -3.287 to 3.233; p=0.9867

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- 30 days (or hospital discharge): mean difference 0.292; 95% CI -2.865 to 3.448; p=0.8533
- 90 days: mean difference -6.750; 95% CI -16.281 to 2.781; p=0.1510.

mRS

In the RCT of 162 people (87 active treatment) with post-stroke dysphagia, there was no statistically significant difference in the change from baseline to 2 weeks in mRS scores between the PES and sham groups (Bath 2016): at 2 weeks the mean difference was 0.53; 95% CI 0.23 to 1.22; p=0.14.

In the RCT of 69 people (35 on active treatment) with post-stroke dysphagia and tracheostomy, there were no statistically significant differences in the change in mRS score from baseline to 2 days, 30 days (or hospital discharge), or 90 days after treatment between the PES and sham groups. Note that this RCT was stopped early for superiority in the primary outcome (readiness for decannulation; Dziewas 2018):

- baseline NIHSS score: PES 5.0, sham=5.0
- 2 days: mean difference 0.078; 95% CI -0.570 to 0.727; p=0.8094
- 30 days (or hospital discharge): mean difference 0.091; 95% CI -0.163 to 0.345; p=0.4769
- 90 days: mean difference -0.203; 95% CI -0.730 to 0.324; p=0.4421.

BI

In the RCT of 162 people (87 active treatment) with post-stroke dysphagia, there was no statistically significant difference in the change from baseline to 2 weeks in BI scores between the PES and sham groups (Bath 2016): at 2 weeks the mean difference was 1.57; 95% CI -3.60 to 6.73; p=0.55.

Quality of life outcomes

EQ-5D

In the RCT of 162 people (87 on active treatment) with post-stroke dysphagia, there were no statistically significant differences in change from baseline in EQ-5D (as health utility status) or EQ-5D VAS between the PES and sham groups (Bath 2016):

- EQ-5D (as health utility status): mean difference 0.13; 95% CI 0.00 to 0.27; p=0.054
- EQ-5D VAS: mean difference -4.17; 95% CI -15.22 to 6.88; p=0.46.

SWAL-QOL

In the pilot RCT of 20 people (10 people on PES plus SLT) with dysphagia related to ALS, there were no statistically significant differences in SWAL-QOL scores between the PES plus SLT and SLT alone treatment groups at any of the follow-up visits (all p>0.05; Herrmann 2022).

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ALSFRS-R

In the pilot RCT of 20 people (10 people PES plus SLT) with dysphagia related to ALS, there were no statistically significant differences in ALSFRS-R scores between the PES plus SLT and SLT alone treatment groups at any of the follow-up visits (all p>0.05; Herrmann 2022).

Safety summary

Overall rate of adverse events

In the RCT of 162 people (87 on active treatment) with post-stroke dysphagia, there was no statistically significant difference in the rate of serious adverse events (SAEs) at the end of follow up: PES n=22 (25.9%), sham n=18 (26.9%); p=1.00; (Bath 2016).

In the RCT of 69 people (35 on active treatment) with post-stroke dysphagia and tracheostomy, there was no statistically significant difference between the number of people with at least 1 SAE between the PES and sham groups: PES n=12 (10 people, 29%), sham n=9 (8 people, 24%; Dziewas 2018).

In the analysis of a prospective registry of 252 people with dysphagia from various neurological causes, there were 74 SAEs in 60 people (24.5%; Bath 2020).

Device-related and treatment-related adverse events

In the RCT of 69 people (35 on active treatment) with post-stroke dysphagia and tracheostomy, there were 8 non-serious device-related adverse events in 5 people in the PES group (14%) and 4 non-serious device-related adverse events in 3 people (9%). The most common device-related adverse event in both the PES and sham groups was medical device complication (Dziewas 2018).

In the analysis of a prospective registry of 252 people with dysphagia from various neurological causes, there was 1 SAE (0.4%) that was considered possibly related to PES: pneumonia related to catheter insertion leading to sepsis (Bath 2020).

Device-unrelated and treatment-unrelated adverse events

In the RCT of 162 people (87 on active treatment) with post-stroke dysphagia, there were 22 SAEs in the PES group that were deemed unrelated to the device. These included SAEs in the following categories: cardiac n=6 (7.1%), gastrointestinal n=2 (2.4%), hepatobiliary n=1 (1.2%), infections n=6 (7.1%), investigations n=1 (1.2%), neoplasms n=1 (1.2%), nervous system n=4 (4.7%), renal and urinary n=1 (1.2%), respiratory n=5 (5.9%), and surgical or medical n=2 (2.4%; Bath 2016).

In the RCT of 69 people (35 on active treatment) with post-stroke dysphagia and tracheostomy, there were 12 SAEs in the PES group that were deemed unrelated to the device. The most common SAEs were pneumonia n=2 (6%), cardiac arrest n=2 (6%), sepsis n=3 (9%), hydrocephalus n=2 (6%), and death n=7 (20%; Dziewas 2018).

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In the analysis of a prospective registry of 252 people with dysphagia from various neurological causes, there were 73 SAEs considered unrelated to treatment. The most common SAEs were pneumonia n=26 (10.6%), cardiac arrest n=5 (2.0%), respiratory failure n=4 (1.6%), stroke n=3 (1.2%), and infection including sepsis. 'Other' SAEs accounted for n=3 (1.2%; Bath 2020).

In the pilot RCT of 20 people (10 people on PES plus SLT) with dysphagia related to ALS, there were 2 adverse events reported: uncomfortable feeling in the pharynx while using non-invasive ventilation after PES, n=1 (10%), mild burning pain in the nasopharynx after PES caused by an erythema, n=1 (10%; Herrmann 2022).

Death

In the RCT of 162 people (87 on active treatment) with post-stroke dysphagia, there was no statistically significant difference in the cumulative risk of all-cause death between the PES and sham groups (Bath 2016): the time to event hazard ratio was 1.11; 95% CI 0.34 to 3.59; p=0.86.

In the RCT of 69 people (35 on active treatment) with post-stroke dysphagia and tracheostomy, 7 people in the PES group, 3 people in the sham group and 1 person before randomisation died during the study. None of the deaths were judged to be PES treatment or investigational device (base station and catheter) related (Dziewas 2018).

In the analysis of a prospective registry of 252 people with dysphagia from various neurological causes, there were 29 fatal SAEs (Bath 2020).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events that they have heard about) and about theoretical adverse events (events that they think might possibly occur, even if they have never happened).

For this procedure, professional experts listed the following anecdotal adverse events: discomfort, hypersalivation, reddening of mucosa, pain in the ear and eye, local oedema.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to pharyngeal electrical stimulation for neurogenic dysphagia. The following databases were searched, covering the period from their start to 18 October 2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

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The inclusion criteria were applied to the abstracts identified by the literature search. If selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded if no clinical outcomes were reported, or if the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with neurogenic dysphagia.
Intervention or test	Pharyngeal electrical stimulation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 524 people from 2 systematic reviews and meta-analyses, 3 RCTs, 1 registry analysis, and 2 pilot studies. There was considerable overlap between the systematic reviews and meta-analyses. All 3 RCTs were identified in the systematic reviews: Bath (2016) and Suntrup (2015) were included in both meta-analyses; Dziewas (2018) was only included in Cheng (2021).

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

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Summary of key evidence on pharyngeal electrical stimulation for neurogenic dysphagia

Study 1 Speyer R (2022)

Study details

Study type	Systematic review and meta-analysis
Country	Not reported for individual studies
Recruitment period	Not reported for individual studies
Study population and number	n=10 studies, 428 people (252 active treatment), 5 studies were included in the meta-analysis People with neurogenic dysphagia.
Age and sex or gender (as reported by the study)	Mean 64.7 years; 56.7% male
Patient selection criteria	Inclusion criteria: • Population: People with a diagnosis of oropharyngeal dysphagia based on instrumental assessment. • Intervention: PES or NMES (only data on PES included in this summary). • Comparator: any control or comparison group. • Study design: RCTs Exclusion criteria: non-electrical peripheral stimulation (for example air-puff or gustatory stimulation), pharmacological interventions and acupuncture, invasive techniques and/or those that did not specifically target oropharyngeal dysphagia (for example, deep-brain stimulation studies after neurosurgical implementation of a neurostimulator), conference abstracts, doctoral theses, editorials, and reviews were excluded.
Technique	PES. Typically delivered as 10-minute stimulation over 1 to 5 days (varying between studies).
Follow up	Not reported for individual studies
Conflict of interest or source of funding	Conflict of interest: The authors disclose no conflict of interest, however, 1 author is the co-founder of Phagenesis, the manufacturer of a PES device. Source of funding: No external funding was received.

Analysis

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Study design issues: This systematic review and meta-analysis assessed the efficacy of PES for people with oropharyngeal dysphagia. The methods and reporting of the systematic review were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Study quality was assessed by the Cochrane Risk of Bias 2 (RoB 2) tool. The overall risk of bias for PES studies was assessed as 'low risk' for 6 studies and 'some concerns' for 4 studies. Five studies were included in the meta-analysis for PES, reasons for exclusion were given for 3 studies: overlap in population between studies, insufficient data for meta-analyses, and no confirmation of dysphagia diagnosis prior to treatment. It is not reported for which studies these reasons relate to.

Two meta-analyses were conducted to compare:

- pre-post outcome measures of dysphagia.
- mean difference between neurostimulation and comparison controls in outcome measures from pre- to post-intervention.

Effect sizes were calculated using a random-effects model were generated using the Hedges' g formula for standardised mean difference with a 95% CI. Effects sizes were interpreted using Cohen's d convention as follows: g of 0.2 or less as no or negligible effect; g more than 0.2 and 0.5 or less as small effect; g more than 0.5 and 0.8 or less as moderate effect; and g more than 0.8 as large effect. Heterogeneity was estimated using the Q statistic. I^2 values of less than 50%, 50% to 74%, and higher than 75% denote low, moderate, and high heterogeneity, respectively. Publication bias was also assessed, and the authors concluded that there was no evidence of publication bias.

Study population issues: all studies included in the meta-analyses included people with post-stroke dysphagia.

Key efficacy findings

Pre-post meta-analysis

Number of people analysed: 5 studies

- Five studies using PAS to assess dysphagia were included in the meta-analysis.
- The pre-post intervention effect sizes for the included studies ranged from 0.265 (small effect) to 0.802 (large effect), with a statistically significant overall moderate effect size of 0.527 (z(4)=3.983, p=0.000, 95% CI 0.268 to 0.786).

Between group meta-analysis

Number of people analysed: 5 studies

- Five studies using PAS to assess dysphagia were included in the meta-analysis.

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- There was no statistically significant difference in PAS scores between PES and sham groups (z(4)=0.718, p=0.473, Hedges' g=0.099, and 95% CI -0.170 to 0.368), suggesting no improvement in PAS outcomes following PES neurostimulation versus sham.

Key safety findings

Safety findings were not reported.

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Study 2 Cheng I (2021)

Study details

Study type	Systematic review and meta-analysis
Country	Not reported for individual studies
Recruitment period	Not reported for individual studies
Study population and number	n=8 studies, 334 people (187 active treatment) People with post-stroke neurogenic dysphagia.
Age and sex (or gender, as reported by the study)	Mean age of people in the studies ranged from 60.3 to 74.4; sex not reported
Patient selection criteria	Inclusion criteria: • Population: People diagnosed with post-stroke dysphagia regardless of the time of onset or type of stroke (ischemic, haemorrhagic or brainstem infarction). • Intervention: PES • Comparator: any control or comparison group. • Outcomes: swallowing, which included swallowing physiology measurement, clinical swallowing function ratings, functional dysphagia symptom scales or health outcomes related to swallowing or pharyngeal functions. • Study design: RCTs Exclusion criteria: Studies with people whose dysphagia was caused by other aetiologies, case studies, open-label studies, animal studies, observational studies, quasi-experimental studies, studies on healthy volunteers, studies that did not include original data, non-English studies.
Technique	PES. 5 Hz, 75% tolerated threshold for 10 minutes over 1 or 3 days (varying between studies)
Follow up	Perioperative to 3 months
Conflict of interest or source of funding	Conflict of interest: Not reported, however, 1 author is the co-founder of Phagenesis, the manufacturer of a PES device. Source of funding: The authors declare no financial support.

Analysis

Study design issues: This systematic review and meta-analysis assessed the efficacy of PES for people with post-stroke neurogenic dysphagia. The methods and reporting of the systematic review were based on the PRISMA statement. Study quality was assessed by the Cochrane RoB 2 tool. The authors note that there was insufficient information to determine the risk of selective reporting and other risks so these 2 aspects were not assessed. Most studies had low risk of bias in most aspects. The following studies were assessed as high risk of bias for the following domains: blinding of

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participants and personnel (Cabib, 2020; Jayasekeran, 2010; Vasant, 2016), incomplete outcome data (Bath, 2016). Three meta-analyses were conducted using PES studies:

- Overall treatment effect vs. sham
- Early (up to 2 weeks) effects vs. sham
- Late (3 months or more) effects vs. sham

A weighted average of standardised mean difference across studies was computed using random effects model analysis. For the interpretation of effect sizes, standardised mean difference of 0.2 represented a small effect, 0.5 a moderate effect, and 0.8 a large effect. $p<0.05$ was considered statistically significant. Heterogeneity was assessed with Cochrane's Q statistic and I^2 test in which heterogeneity was considered substantial with $p<0.05$ and I^2 higher than 50%.

Key efficacy findings

Overall treatment effect meta-analysis

Number of people analysed: 8 studies

- There was a statistically significant overall moderate effect size of PES compared to sham with substantial heterogeneity: SMD=0.68 (95% CI 0.22, 1.14; p=0.004; I^2=65%; figure below).
- As a sensitivity analysis, Bath, 2016 was removed from the analysis. This resulted in a statistically significant large effect size without substantial heterogeneity: SMD=0.83 (95% CI 0.43, 1.42; $p<0.001$; I^2=34%).

Early treatment effect meta-analysis

Number of people analysed: 8 studies

- There was a statistically significant overall moderate effect size of PES compared to sham with substantial heterogeneity: SMD=0.68 (95% CI 0.22, 1.14; p=0.004; I^2=65%; figure below).

Late treatment effect meta-analysis

Number of people analysed: 2 studies

- There was no statistically significant effect size of PES compared to sham with no heterogeneity: SMD=−0.04 (95% CI −0.46, 0.38; p=0.86; I^2=0).

Key safety findings

Safety findings were not reported.

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Study 3 Bath PM (2016)

Study details

Study type	Multicentre, double-blinded (patients, assessors), sham-controlled RCT
Country	Denmark, France, Germany, Spain, and the UK
Recruitment period	2012 to 2014
Study population and number	n=162 (87 active treatment) People with recent stroke and videofluoroscopy-confirmed dysphagia
Age and sex (or gender, as reported by the study)	Mean (all randomised) 74.0 years; 55.2% male
Patient selection criteria	Inclusion criteria: people who were admitted to hospital with a clinical stroke syndrome because of ischemic or haemorrhagic stroke, were aged 18 or above, had clinical dysphagia identified using bedside testing, were alert or rousable, had a PAS of 3 or more for at least 1 swallow, and could be treated within 42 days of stroke onset. Exclusion criteria: a history of dysphagia, dysphagia from a condition other than stroke, advanced dementia, implanted pacemaker or cardiac defibrillator in situ, unstable cardiopulmonary status or a condition that compromised cardiac or respiratory status, distorted oropharyngeal anatomy, additional diagnosis of a progressive neurological disorder, receiving continuous oxygen treatment, or pregnant or nursing mother.
Technique	PES with Phagenyx (Phagenesis, Ltd, Manchester, UK). Electric current at 5 Hz was administered for 10 minutes each day for 3 days. The current of the stimulation was calculated as the threshold current (the current at which the patient can first detect stimulation) plus 75% of the difference between threshold and tolerance current (the current at which the patient does not want the current increased further). The mean treatment stimulation level was 14.5 mA in those randomised to PES.
Follow up	12 weeks
Conflict of interest or source of funding	Conflict of interest: The lead author received honoraria for work as the chief investigator and for consultancy. One author is the co-founder of Phagenesis, the manufacturer of a PES device. One author was an employee of Phagenesis. Source of funding: The trial was sponsored and funded by Phagenesis, the manufacturer of a PES device.

Analysis

Follow up issues: Of 162 people who were randomised, treatment was attempted in 152 (safety population), 141 were treated (with at least 1 session of PES or sham), videofluoroscopy was obtained in 126 at 2 weeks (primary outcome population), and in 95 at 12 weeks.

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Study design issues: This RCT assessed the efficacy and safety of PES to treat post-stroke dysphagia. Patients with recent stroke and confirmed dysphagia were randomised 1:1 to PES or sham. The sample size was based on statistical power calculations such that the trial had 90% power to detect a difference of 1.1 points on the PAS at a 2-sided significance level of 5%. Patients and outcome assessors were blinded to treatment allocation, treating researchers were unblinded. Patients randomised to sham therapy had no stimulation after establishment of threshold and tolerated levels of current. This determination of threshold and tolerated levels of current may have inadvertently exposed sham patients to therapeutic stimulation. As patients could feel the effects of treatment, or the absence of treatment with sham, some patients may have become prematurely unblinded to treatment allocation. The authors also reported that there was evidence of suboptimal treatment, with 58% of PES-treated patients had a treatment level less than 10.2 mA (a figure chosen from earlier research), identical treatment and threshold levels, or a treatment level less than threshold.

The outcomes included:

- Primary: PAS at 2 weeks
- Secondary: PAS at 12 weeks, DSRS, modified Rankin Scale, Barthel Index, NIHSS, HRQoL, and nutritional measures.

The primary outcome was analysed using multiple linear regression. Secondary outcomes were analysed using multiple linear regression (for continuous outcomes), ordinal logistic regression (ordered categorical data), binary logistic regression (dichotomous data), and Kaplan–Meier and Cox regression models (time to event). There was no adjustment for multiple comparisons reported.

Study population issues: No statistical analysis was performed, but the authors reported that the PES and sham groups were ‘well balanced at baseline’. Some select baseline characteristics follow. Most people were white (85.8%), with smaller numbers of Asian (9.3%), black (2.5%), and ‘other’ (2.5%) people. Stroke types were ischaemic/normal (88.8%) and intracerebral haemorrhage (10.6%). The mean time from stroke to randomisation was 13 days.

Key efficacy findings

PAS

Number of people analysed: 126

- There were no statistically significant differences in the change from baseline to 2 weeks in PAS scores between the PES and sham groups (mean difference=0.14; 95% CI -0.37 to 0.64; p=0.60).
  - There was also no statistically significant difference in the proportion of people who had any PAS score above 3 between the PES and sham groups (85.7% vs. 80.4%, p=0.79).
- At 12 weeks, there was no statistically significant difference in the mean PAS scores between the PES and sham groups (mean difference=0.29; 95% CI −0.04 to 0.99; p=0.41).
- There were no statistically significant interactions observed in subgroup analysis.

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PAS outcomes

-	All (N=126)	PES (N=70)	Sham (N=56)	OR/MD (95% CI), Adjusted	p	OR/MD (95% CI), Unadjusted	p
Baseline	-	-	-	-	-	-	-
PAS (scored out of 8)	4.8 (2.0)	4.8 (2.1)	4.7 (1.9)	-	-	-	-
2-week primary outcome	-	-	-	-	-	-	-
Mean of all boluses (scored out of 8)	3.6 (2.0)	3.7 (2.0)	3.6 (1.9)	0.14 (−0.37 to 0.64)	0.60	0.06 (−0.62 to 0.74)	0.86
Change from baseline	−1.2 (1.8)	−1.2 (1.8)	−1.2 (1.8)	0.14 (−0.37 to 0.64)	0.60	0.00 (−0.62 to 0.61)	1.00
Any PAS more than 3 (%)	105 (83.3)	60 (85.7)	45 (80.4)	1.22 (0.29 to 5.15)	0.79	1.47 (0.57 to 3.75)	0.42
12 week	-	-	-	-	-	-	-
Mean of all boluses (scored out of 8)	3.2 (2.1)	3.3 (2.2)	3.0 (2.1)	0.29 (−0.04 to 0.99)	0.41	0.24 (−0.6 to 1.08)	0.57
Any PAS more than 3 (%)	69 (72.6)	36 (70.6)	33 (75.0)	0.62 (0.20 to 1.90)	0.41	0.80 (0.32 to 1.99)	0.63
Repeated measures	-	-	-	-	-	-	-
Mean PAS (scored out of 9 Which includes death: PAS=9.	-	4.1 (2.3)	3.9 (2.3)	0.51 (−0.23 to 1.25)	0.18	0.19 (−0.67 to 1.04)	0.67

All patients had diagnostic videofluoroscopy at both baseline and 2 weeks and received at least 1 treatment session. Data are number (%), median (interquartile range), or mean (SD), with comparisons using unadjusted and adjusted multiple linear, ordinal logistic, or binary logistic regression.

Secondary outcomes

Number of people analysed: various, see table below.

- There were no statistically significant differences between the PES and sham groups in any of the secondary outcomes assessed.

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Secondary outcomes

-	N	All	PES	Sham	OR/HR/MD (95% CI), Unadjusted	p	OR/HR/MD (95% CI), Unadjusted	p
2 week	-	-	-	-	-	-	-	-
DSRS (scored out of 13 where 13=death)	133	5.1 (3.8)	5.2 (4.1)	4.9 (3.6)	0.31 (−0.56 to 1.18)	0.49	0.23 (−1.07 to 1.54)	0.72
NIHSS (scored out of 42) Includes death: NIHSS=43	134	9.6 (7.2)	9.0 (7.4)	10.2 (7.1)	−0.05 (−1.42 to 1.32)	0.94	−1.19 (−3.64 to 1.26)	0.34
mRS (scored out of 6)	134	3.9 (1.1)	3.7 (1.2)	4.1 (1.0)	0.53 (0.23 to 1.22)	0.14	0.49 (0.26 to 0.92)	0.028
BI (scored out of 100) Includes death: BI= -5	134	36.2 (34.9)	41.3 (37.2)	29.8 (31.0)	1.57 (−3.60 to 6.73)	0.55	11.45 (−0.22 to 23.13)	0.055
Death (%)	141	2 (1.4)	1 (1.3)	1 (1.6)	-	-	0.81 (0.05 to 13.13)	0.88
12 week	-	-	-	-	-	-	-	-
DSRS (scored out of 12) Includes death: DSRS=13	124	4.2 (5.1)	4.4 (5.2)	3.9 (5.1)	1.01 (−0.44 to 2.46)	0.17	0.58 (−1.23 to 2.39)	0.53
EQ-5D as HUS scored from -1 to 1 Includes death: HUS=0	113	0.02 (0.40)	0.08 (0.41)	−0.04 (0.39)	0.13 (0.00 to 0.27)	0.054	0.12 (−0.03 to 0.27)	0.11
EQ-VAS	105	50.3 (30.7)	51.6 (30.1)	48.6 (31.7)	−4.17 (−15.22 to 6.88)	0.46	3.03 (−8.70 to 14.76)	0.61

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-	N	All	PES	Sham	OR/HR/MD (95% CI), Unadjusted	p	OR/HR/MD (95% CI), Unadjusted	p
Disposition (%)	141	-	-	-	0.66 (0.30 to 1.49)	0.32	0.63 (0.31 to 1.26)	0.19
Home	30 (21.3)	20 (25.6)	10 (15.9)	-	-	-	-	-
Institution	93 (66.0)	49 (62.8)	44 (69.8)	-	-	-	-	-
Died	18 (12.8)	9 (11.5)	9 (14.3)	-	-	-	-	-
Time to event	-	-	-	-	-	-	-	-
Discharge (days)	141	28.2 (22.8)	27.7 (22.7)	28.7 (23.0)	−0.33 (−7.79 to 7.12)	0.93	−0.97 (−9.72 to 7.78)	0.83
Death (%)	141	18 (12.8)	9 (11.5)	9 (14.3)	1.11 (0.34 to 3.59)	0.86	0.79 (0.32 to 2.00)	0.62

BI, Barthel Index; DSRS, dysphagia severity rating scale; EQ-5D, European Quality of Life-5 Dimensions; EQ-VAS, European Quality of Life Visual Analogue Scale; HR, hazard ratio; HUS, health utility status; MD, mean difference; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and PES, pharyngeal electric stimulation.

Key safety findings

Number of people analysed: 152

- There was no statistically significant difference in the rate of SAEs at the end of follow up: Total n=40 (26.3%), PES n=22 (25.9%), sham n=18 (26.9%; p=1.00).
- No SADEs occurred in either group.

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Key safety findings

-	Any	-	-	-	Fatal	-	-	-
-	All	PES	Sham	p	All	PES	Sham	p
Patients	152	85	67	-	152	85	67	-
Cardiac	9 (5.9)	6 (7.1)	3 (4.5)	0.73	4 (2.6)	2 (2.4)	2 (3.0)	1.00
Gastrointestinal	2 (1.3)	2 (2.4)	0 (0)	0.50	0 (0)	0 (0)	0 (0)	-
General	3 (2.0)	0 (0)	3 (4.5)	0.083	3 (2.0)	0 (0)	3 (4.5)	0.083
Hepatobiliary	1 (0.7)	1 (1.2)	0 (0)	1.00	0 (0)	0 (0)	0 (0)	-
Infections	11 (7.2)	6 (7.1)	5 (7.5)	1.00	4 (2.6)	2 (2.4)	2 (3.0)	1.00
Investigations	1 (0.7)	1 (1.2)	0 (0)	1.00	0 (0)	0 (0)	0 (0)	-
Neoplasms	1 (0.7)	1 (1.2)	0 (0)	1.00	1 (0.7)	1 (1.2)	0 (0)	1.00
Nervous system	8 (5.3)	4 (4.7)	4 (6.0)	0.73	4 (2.6)	3 (3.5)	1 (1.5)	0.63
Renal/urinary	2 (1.3)	1 (1.2)	1 (1.5)	1.00	0 (0)	0 (0)	0 (0)	-
Respiratory	8 (5.3)	5 (5.9)	3 (4.5)	1.00	2 (1.3)	1 (1.2)	1 (1.5)	1.00
Surgical/medical	2 (1.3)	2 (2.4)	0 (0)	0.50	0 (0)	0 (0)	0 (0)	-
Total SAEs	40 (26.3)	22 (25.9)	18 (26.9)	1.00	18 (11.8)	9 (10.6)	9 (13.4)	0.62
Total SADEs	0 (0)	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)	-

PES, pharyngeal electrical stimulation; SADE, serious adverse device-related event; SAE, serious adverse event.

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Study 4 Dziewas R (2018)

Study details

Study type	Multicentre, double-blinded (patients, assessors), sham-controlled RCT followed by open-label crossover period
Country	Austria, Germany, Italy
Recruitment period	2015 to 2017
Study population and number	n=69 (35 active treatment) People with recent stroke and dysphagia who required tracheostomy.
Age and sex (or gender, as reported by the study)	Mean 64 years; 64% male
Patient selection criteria	Inclusion criteria: supratentorial stroke (haemorrhagic or ischaemic), mechanically ventilated for at least 48 hours post-stroke, successfully weaned from mechanical ventilation but remained tracheostomised, free of sedation for at least 3 days at the time of first decannulation screening, scored -1 or more points on the Richmond Agitation and Sedation Scale, and could not be decannulated due to severe dysphagia. Exclusion criteria: infratentorial stroke, pre-existing dysphagia, pre-existing disease that typically causes dysphagia (for example Parkinson's disease), participation in any other study potentially influencing the outcome of PES, presence of a cardiac pacemaker or an implantable defibrillator, nasal deformity or previous oesophageal surgery or any other circumstance where placement of a standard nasogastric tube would be deemed unsafe, need for high levels of oxygen supply (more than 2 l/min), required emergency treatment, or had less than 3 months life expectancy.
Technique	PES with Phagenyx (Phagenesis, Ltd, Manchester, UK). Electric current at 5 Hz was administered for 10 minutes each day for 3 days. The current of the stimulation was calculated as the threshold current (the current at which the patient can first detect stimulation) plus 75% of the difference between threshold and tolerance current (the current at which the patient does not want the current increased further). The mean treatment stimulation level was 33.6 mA in those randomised to PES.
Follow up	90 days
Conflict of interest or source of funding	Conflict of interest: One author is the co-founder of Phagenesis, the manufacturer of a PES device. Other authors report fees from Phagenesis for travel, training, and payments per-patient for the study conduct, amongst others. Source of funding: Funded by Phagenesis, the manufacturer of a PES device.

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Analysis

Follow up issues: Of 69 people randomised, 68 had day 2 data, 65 had day 30 or hospital discharge data, and 52 had day 90 data.

Study design issues: This RCT assessed the efficacy and safety of PES for early decannulation of people who had post-stroke dysphagia. Patients were randomised 1:1 to PES or sham and received 3 days of treatment. Readiness for decannulation was assessed 24 to 72 hours after the final stimulation. Those who remained cannulated could then enter an open-label phase. The maximum sample size was set at 140 people to detect an absolute difference between the groups of 25%, assuming that the control rate would be 20%, significance level of 0.05, and power 0.80. Predetermined interim analyses were performed when recruitment reached 50 patients, 70 patients, and every 10 patients after. At the 70-patient interim analysis, the study was stopped for superiority. Patients and outcome assessors were blinded to treatment allocation, treating researchers were unblinded. As patients could feel the effects of treatment, or the absence of treatment with sham, some patients may have become prematurely unblinded to treatment allocation.

The outcomes included:

- Primary: readiness for decannulation 24 to 72 hours after 3 days of PES
  - The presence of massive pooling of saliva, limited spontaneous swallows (less than 1 per minute), and/or no sensation elicited by endoscope contact with the laryngeal vestibule meant that patients were not ready for decannulation.
- Secondary: treatment effect in delayed and retreated patients, necessity of recannulations (at day 2 and during follow-up of 30 days or until discharge, whichever is first), dysphagia scores (DSRS, FOIS), severity of stroke (modified Rankin Scale and National Institutes of Health Stroke Scale scores; at day 2, during follow-up of 30 days or until discharge, whichever was first), length of stay on different levels of care, Speech and Language Therapy management plan, number and type of AEs, including adverse device-related events.

Outcomes were analysed using Fisher's exact test for binary data, Mann-Whitney-U test for ordinal data, and Student's t-test (pooled) for continuous data. Regressions were performed using binary logistic regression, Cox regression and multiple linear regression. $p<0.05$ was considered statistically significant. No adjustment was made for multiple comparisons, and all analyses were by intention to treat.

Study population issues: No statistically significant differences in baseline characteristics were reported between the treatment groups. Overall, 49 (71%) patients had an ischemic stroke, and 20 (29%) an intracerebral haemorrhage. The median time from stroke to randomisation was 28 days.

Key efficacy findings

Decannulation

Number of people analysed: 69

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- In the primary outcome, there was a higher likelihood of readiness for decannulation 24 to 72 hours after treatment with PES compared to sham, OR: 7.00 (95% CI 2.41 to 19.88, p=0.00082).
  - No patients who had decannulation performed required re-cannulation over the next 48 hours, or during their documented follow-up period up to hospital discharge.
  - Based on these outcome data, the study was stopped for superiority by an Independent Data and Safety Monitoring Board.
- In predefined subgroups, statistically significant treatment-by-subgroup interactions were present, these favouring treatment in patients treated earlier after stroke, or with a shorter duration of mechanical ventilation.
- Considering both the randomised and open-label parts of the study, a total of 57% of the patients became ready for decannulation 24 to 72 hours after PES.

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Decannulation outcomes

-	Total	PES	Sham	OR (95% CI)	p
Randomised part 1 of the study	-	-	-	-	-
Patients	69	35	34	-	-
Ready for decannulation after PES/Sham (%; Primary outcome)	-	17 (49)	3 (9)	7.00 (2.41-19.88)	0.00082
Removal of the tracheal tube (%). Statistical comparison within the subgroup of patients reaching the primary endpoint.	-	14 (82)	1 (33)	9.33 (0.62-139.57)	0.1404
Deflation of the tube-cuff (%) Statistical comparison within the subgroup of patients reaching the primary endpoint.	-	3 (18)	1 (33)	0.43 (0.03-6.41)	0.5088
Open-label part 2 of the study	-	-	-	-	-
Patients	45	15	30	-	-
Ready for decannulation" after open-label treatment (%) . Note that this data is related only to the open label part of the study where all non-responders were given PES.	20 (44)	4 (27)	16 (53)	0.32 (0.08-1.23)	0.1185
Removal of the tracheal tube (%) Statistical comparison within the subgroup of patients reaching the primary endpoint.	17 (38)	3 (20)	14 (47)	0.29 (0.07-1.22)	0.1097
Deflation of the tube-cuff (%) Statistical comparison within the subgroup of patients reaching the primary endpoint.	3 (7)	1 (7)	2 (7)	1.00 (0.08-12.00)	1.0000
Re-cannulation within 48 hrs (%)	-	0 (0)	0 (0)	-	-
Re-cannulation within 30 days or hospital discharge (whichever is first; %)	-	0 (0)	0 (0)	-	-

OR, odds ratio; PES: pharyngeal electrical stimulation.

One patient in the PES group had a non-treatment-related adverse event occurring prior to third day of PES which required transfer to another hospital for surgery; as a result, assessment was not possible. Conservatively, the patient was assigned to no decannulation.

Secondary outcomes

Number of people analysed: Various, see table below.

- There were no differences between the groups in secondary outcomes.

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Secondary outcomes

-	Total	PES	Sham	OR/MD (95% CI)	p
DSRS, N, mean (SD)	-	-	-	-	-
Baseline	-	12 (0)	12 (0)	-	-
Day 2	60	30, 10.6 (2.4)	30, 10.4 (2.7)	0.27 (-1.05, 1.59)	0.6873
Day 30 or Hospital Discharge (whichever is first)	50	25, 8.0 (4.6)	25, 8.9 (3.3)	-0.88 (-3.17, 1.41)	0.4437
Day 90	53	27, 4.6 (5.3)	26, 5.7 (5.1)	-1.10 (-3.97, 1.77)	0.4449
FOIS, N, mean (SD)	-	-	-	-	-
Baseline	-	1 (0)	1 (0)	-	-
Day 2	61	31, 1.7 (1.2)	30, 1.9 (1.4)	-0.191 (-0.878, 0.495)	0.5789
Day 30 or Hospital Discharge (whichever is first)	50	25, 3.0 (2.4)	25, 2.5 (1.7)	0.560 (-0.61, 1.73)	0.3407
Day 90	53	27, 4.6 (2.6)	26, 3.9 (2.5)	0.745 (-0.660, 2.150)	0.2922
NIHSS, N, mean (SD)	-	-	-	-	-
Baseline	68	34, 17.6 (5.0)	34, 17.5 (4.3)	0.118 (-2.129, 2.364)	0.9170
Day 2	47	24, 15.6 (4.5)	23, 15.7 (6.4)	-0.027 (-3.287, 3.233)	0.9867
Day 30 or Hospital Discharge (whichever is first)	48	24, 14.0 (5.0)	24, 13.8 (5.9)	0.292 (-2.865, 3.448)	0.8533
Day 90	16	8, 10.1 (9.2)	8, 16.9 (8.6)	-6.750 (-16.281, 2.781)	0.1510
mRS, N, mean (SD)	-	-	-	-	-
Baseline	68	34, 5.0 (0.0)	34, 5.0 (0.2)	0.029 (-0.029, 0.088)	0.3210
Day 2	61	31, 4.6 (1.3)	30, 4.6 (1.3)	0.078 (-0.570, 0.727)	0.8094
Day 30 or Hospital Discharge (whichever is first)	54	28, 4.8 (0.5)	26, 4.7 (0.5)	0.091 (-0.163, 0.345)	0.4769
Day 90	51	26, 4.1 (0.8)	25, 4.3 (1.0)	-0.203 (-0.730, 0.324)	0.4421
Level of care	-	-	-	-	-
Baseline	-	-	-	-	-
Patients	65	32	33		
Intensive Care Unit		8 (25)	7 (21)	1.24 (0.39-3.93)	0.7746
Intermediate Care Unit		21 (66)	23 (70)	0.83 (0.29-2.35)	0.7944
Normal ward		3 (10)	3 (10)	1.03 (0.19-5.55)	1.0000
Day 2	-	-	-	-	-
Patients	50	25	25		
Intensive Care Unit		3 (12)	1 (4)	3.27 (0.32-33.84)	0.6092
Intermediate Care Unit		15 (60)	16 (64)	0.84 (0.27-2.65)	1.0000
Normal ward		7 (28)	8 (32)	0.83 (0.25-2.78)	1.0000
Day 10	-	-	-	-	-

IP overview: Pharyngeal electrical stimulation for neurogenic dysphagia

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-	Total	PES	Sham	OR/MD (95% CI)	p
Patients	24	13	11		
Intensive Care Unit		2 (15)	1 (9)	1.82 (0.14-23.25)	1.0000
Intermediate Care Unit		4 (31)	5 (46)	0.53 (0.10-2.84)	0.6752
Normal ward		7 (54)	5 (46)	1.40 (0.28-7.02)	1.0000
Day 30	-	-	-	-	-
Patients	14	7	7		
Intensive Care Unit		0 (0)	0 (0)	-	-
Intermediate Care Unit		2 (29)	1 (14)	2.40 (0.16-34.93)	1.0000
Normal ward		5 (71)	6 (86)	0.42 (0.03-6.06)	1.0000

DSRS: dysphagia severity rating scale; FOIS: functional oral intake scale; NIHSS: National Institute of Health Stroke Scale; MD, mean difference; mRS: modified Rankin Scale; OR, odds ratio; PES: pharyngeal electrical stimulation.

Key safety findings

Number of people analysed: 69

- A total of 7 people in the PES group (20%), 3 people in the sham group (9%) and 1 person prior to randomisation (8%) died during the study.
  - None of the deaths were judged to be PES-treatment or investigational device- (base station and catheter) related by the Independent Data and Safety Monitoring Board.
- There was no statistically significant difference between the number of people with at least 1 SAE in the treatment groups.
- A total of 12 non-serious device-related adverse events were observed in 8 different people.

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Safety events

Data are number of events (number of patients [%])	PES	Sham	People who were never randomised
SAEs:	-	-	-
From informed consent to randomisation	1 (1 [3%])	1 (1 [3%])	3 (2 [17%])
0-1 month after randomisation	3 (3 [9%])	4 (4 [12%])	-
1-3 months after randomisation	8 (7 [20%])	4 (1 [3%])	-
Total study	12 (10 [29%])	9 (8 [24%])	3 (2 [17%])
Most commonly observed SAEs (3 or more events)	-	-	-
Pneumonia	2 (2 [6%])	1 (1 [3%])	-
Cardiac Arrest	2 (2 [6%])	1 (1 [3%])	-
Sepsis	3 (3 [9%])	4 (4 [12%])	-
Hydrocephalus	2 (2 [6%])	0	1 (1 [8%])
Death	7 (7 [20%])	3 (3 [9%])	1 (1 [8%])
AEs (non-serious)	55 (21 [60%])	50 (21 [62%])	0
Most commonly observed AEs (3 or more events)	-	-	-
Diarrhoea	2 (2 [6%])	4 (4 [12%])	-
Vomiting	6 (4 [11%])	6 (2 [6%])	-
Pneumonia	3 (3 [9%])	6 (5 [15%])	-
Urinary Tract Infection	8 (7 [20%])	3 (3 [9%])	-
Infection (Other)	6 (6 [17%])	4 (3 [9%])	-
Musculoskeletal Pain	3 (2 [6%])	0	-
Hypoxia	2 (2 [6%])	1 (1 [3%])	-
Thrombophlebitis	2 (2 [6%])	1 (1 [3%])	-
Adverse Device-related Events (ADEs)	8 (5 [14%])	4 (3 [9%])	-
Most commonly observed ADEs (3 or more events)	-	-	-
Medical Device Complication	6 (5 [14%])	3 (2 [6%])	-
Serious ADEs (SADEs)	0	0	-

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Study 5 Suntrup S (2015)

Study details

Study type	Single centre crossover RCT
Country	Germany
Recruitment period	June 2013 to August 2014
Study population and number	N=30 (20 active treatment) People with severe dysphagia and tracheostomy after stroke
Age and sex (or gender, as reported by the study)	PES group mean age= 63 (SD=15); 55% female (11 of 20) Sham group mean age= 67 (SD=15); 40% female (4 of 10)
Patient selection criteria	People who were tracheostomised after stroke and suffered from severe persistent dysphagia according to a standardised endoscopic swallowing evaluation for tracheostomy.
Technique	PES with Phagenyx (Phagenesis, Ltd, UK). Electric current at 5 Hz was administered for 10 minutes each day for 3 days. The current of the stimulation was calculated as the threshold current (the current at which the patient can first detect stimulation) plus 75% of the difference between threshold and tolerance current (the current at which the patient does not want the current increased further).
Follow up	Until discharge from hospital.
Conflict of interest or source of funding	R. Dziewas was a member of the clinical advisory board of Phagenesis Ltd. The other authors declared they have no conflict of interest

Analysis

Follow up issues: all participants completed follow up.

Study design issues: This single centre RCT assessed the efficacy and safety of PES to treat post-stroke dysphagia with tracheostomy. People with recent stroke and confirmed severe dysphagia were randomised 2:1 to PES or sham. Based on an assumed effect size of decannulation at 40%, 26 people would have been required to demonstrate statistical power. This was exceeded. A standardised protocol was followed to determine the primary outcome. This was a crossover study so people were unblinded after 24-72 hours meaning some comparative analyses of secondary outcomes (including length of stay) could not be meaningfully interpreted.

Outcomes included:

- Primary: Decannulation after 3 days of PES
- Secondary: FOIS, mRS, length of stay in ICU, length of stay in hospital.

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Study population issues: there were mostly no differences between groups on a range of demographic and clinical characteristics at baseline. The authors reported time to treatment was longer in the PES group and that this group showed more severe neurological impairment.

Key efficacy findings

Primary outcome: decannulation

There was a statistically significantly higher likelihood of decannulation within 72 hours of treatment completion in the PES group (75% [15/20]) compared with sham (20% [2/10]; p<0.01). This was also a crossover trial and 71% (5/8) of patients in sham group that had severe persistent dysphagia and went on to receive PES were ready for decannulation 72 hours after treatment.

Secondary outcomes

Length of stay

Mean overall length of stay was 1,028 hours (SD=409) in the PES arm and 1,017 hours (SD=493) in the sham arm (p=0.95). Mean Length of stay in ICU was 917 hours (SD=357) in the PES arm and 931 hours (SD=472) in the sham arm (p=0.92). Time from study treatment to discharge was 390 hours (SD=293) in the PES arm and 450 (SD=154) in the sham arm (p=0.55).

FOIS at discharge

-	PES (n=20)	Sham (n=10)	p-value
Tube-dependent (1–3), n (%)	8 (40%)	6 (60%)	0.30
Total oral intake (4–7), n (%)	12 (60%)	4 (40%)	-

mRS at discharge

mRS score	PES (n=20)	Sham (n=10)	p-value
3, n (%)	4 (20%)	1 (10%)	0.79
4, n (%)	9 (45%)	5 (50%)	-
5, n (%)	7 (35%)	4 (40%)	-

Key safety findings

No adverse events related to the procedure or device were recorded during the study. Overall rates of adverse events were not reported.

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Study 6 Bath PM (2020)

Study details

Study type	Multicentre, prospective registry analysis (the PHAryngeal electrical stimulation for treatment of neurogenic Dysphagia European Registry [PHADER])
Country	Austria, Germany, UK
Recruitment period	2015 to 2018
Study population and number	n=252 People with dysphagia due to stroke, traumatic brain injury, or any other neurological cause.
Age and sex (or gender, as reported by the study)	Mean 68.2; 70.6% male
Patient selection criteria	Inclusion criteria: oropharyngeal dysphagia with a DSRS score of 6 or higher, and belonged to one of the following diagnostic groups: dysphagia related to (A) stroke not requiring mechanical ventilation; (B) stroke requiring mechanical ventilation and tracheostomy; (C) mechanical ventilation in non-stroke, non-TBI; (D) TBI with or without the need for mechanical ventilation and tracheostomy; and (E) any other neurological cause not needing mechanical ventilation and tracheostomy. Exclusion criteria: non-neurogenic dysphagia (for example, cancer), presence of an implanted cardiac pacemaker or cardioverter defibrillator, pregnancy or a nursing mother.
Technique	PES with Phagenyx (Phagenesis, Ltd, Manchester, UK). Electric current at 5 Hz was administered for 10 minutes each day for 3 days. The current of the stimulation was calculated as the threshold current (the current at which the patient can first detect stimulation) plus 75% of the difference between threshold and tolerance current (the current at which the patient does not want the current increased further). The mean treatment stimulation level was approximately 28 mA across the 3 treatment sessions.
Follow up	3 months
Conflict of interest or source of funding	Conflict of interest: One author is the co-founder of Phagenesis, the manufacturer of a PES device. Two further authors are employees of Phagenesis. Other authors report grants from various government, charity, and industry sources. Source of funding: Funded and sponsored by Phagenesis Ltd., the manufacturer of a PES device. Sites were compensated for data collection.

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Analysis

Follow up issues: Of 252 people enrolled, 245 were included in the analysis (7 excluded due to lack or withdrawal of consent, spontaneous recovery or unavailability of a catheter or death), 232 had day 2 follow-up data, 210 had day 30 data, and 190 had day 92 data.

Study design issues: This multicentre, prospective study analysed the efficacy and safety of PES for neurogenic dysphagia in people enrolled in the PHADER registry. This study was reported to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. Outcomes included:

- Primary: DSRS score at 3 months post-treatment
- Secondary: dysphagia severity assessed using the FOIS and penetration-aspiration assessed with the PAS measured instrumentally (using videofluoroscopy or fibreoptic endoscopic evaluation of swallowing).

Sample size was set at 60 people per diagnostic group so that the presence of a device deficiency in 5% of the population could be ruled out with confidence of 80% (lower recruitment was expected in groups C, D, and E). Statistical analyses were conducted by intention to treat. A variety of statistical tests were used to analyse the data. No imputation was performed for missing data, and no adjustment was made for multiple comparisons. $p<0.05$ was considered statistically significant.

Study population issues: By diagnostic group, 84 people had an index stroke not requiring mechanical ventilation (group A); 99 had an index stroke requiring mechanical ventilation and tracheostomy (group B); 35 had dysphagia related to a non-stroke/non-TBI cause (group C) with 15 of these due to critical illness polyneuropathy; 24 had a TBI (group D); and 3 had another cause for their dysphagia (group E). The median time from onset of dysphagia to treatment was 32.0 days. There were statistically significant differences in the median time from onset of dysphagia to treatment in the subgroups (from stroke, not ventilated=16.0 days; to other neurological causes=169.0 days).

Key efficacy findings

Primary outcome

Number of people analysed: various, see table below.

- There was a statistically significant decrease in DSRS score in the overall population from 11.4 at baseline to 5.1 on day 92 after PES (mean difference=-6.3, $p<0.001$).
  - All subpopulations saw similar statistically significant decreases in DSRS scores after PES.

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DSRS outcomes

-	All	Stroke, not ventilated	Stroke, ventilated	Ventilator-related	TBI	p
DSRS (scored out of 12)	-	-	-	-	-	-
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), p<0.001	-6.7 (-7.8, -5.5), p<0.001	-6.5 (-7.6, -5.5), p<0.001	-6.6 (-8.4, -4.8), p<0.001	-4.5 (-6.6, -2.4), p<0.001	0.31
MD (paired)	174, -6.3 (-7.0, -5.6), p<0.001	46, -6.5 (-7.9, -5.2), p<0.001	78, -6.5 (-7.6, -5.3), p<0.001	30, -6.6 (-8.5, -4.6), p<0.001	20, -4.7 (-6.8, -2.5), p<0.001	0.033

Data are number of participants, mean (standard deviation), difference in means and mean difference

(95% confidence interval); comparison of groups by analysis of variance, and day 92 versus baseline by paired and unpaired t-tests.

Secondary outcomes

Number of people analysed: various, see table below.

- 66% (66/99) of people with tracheostomy could be decannulated after receiving PES. The magnitude of improvement at three months was greater (7.5 vs 2.1 points on the DSRS) in the decannulated compared to non-decannulated group.
- There was a statistically significant increase in FOIS score in the overall population from 1.4 at baseline to 4.3 on day 92 after PES (mean difference=2.9, p<0.001).
  - All subpopulations except TBI saw similar statistically significant increase in FOIS scores after PES.
- There was a statistically significant decrease in PAS score in the overall population from 6.7 at baseline to 3.2 on day 92 after PES (mean difference=-4.1, p<0.001).
  - All subpopulations except TBI saw similar statistically significant decrease in PAS scores after PES.

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Secondary outcomes

-	All	Stroke, not ventilated	Stroke, ventilated	Ventilator-related	TBI	p
FOIS (scored out of 7)	-	-	-	-	-	-
Baseline	220, 1.4 (0.9)	65, 1.7 (1.3)	97, 1.2 (0.6)	34, 1.1 (0.3)	24, 1.4 (0.7)	<0.001
Day 5	214, 1.8 (1.4)	63, 2.2 (1.5)	96, 1.8 (1.3)	32, 1.8 (1.4)	23, 1.5 (1.0)	-
Day 9	213, 2.7 (1.9)	61, 3.2 (1.9)	96, 2.5 (1.9)	34, 3.0 (2.1)	22, 1.9 (1.5)	-
Day 92	172, 4.3 (2.5)	42, 4.5 (2.3)	79, 4.3 (2.6)	31, 4.4 (2.7)	20, 3.4 (2.4)	0.38
DIM (unpaired)	2.9 (2.5, 3.3), p<0.001	2.8 (2.1, 3.5), p<0.001	3.1 (2.5, 3.6), p<0.001	3.3 (2.4, 4.3), p<0.001	2.0 (1.0, 3.0)	0.20
MD (paired)	170, 2.9 (2.5, 3.3), p<0.001	40, 2.8 (2.0, 3.5), p<0.001	79, 3.1 (2.5, 3.7), p<0.001	31, 3.3 (2.3, 4.3), p<0.001	20, 2.0 (0.9, 3.0)	0.042
PAS (scored out of 8)	-	-	-	-	-	-
Baseline	144, 6.7 (1.7)	42, 6.2 (1.7)	53, 7.2 (1.2)	27, 6.8 (1.6)	22, 6.5 (2.4)	0.031
Day 5	89, 5.2 (2.5)	19, 4.3 (2.5)	39, 5.4 (2.4)	18, 4.9 (2.8)	13, 6.1 (2.4)	-
Day 9	100, 4.4 (2.7)	21, 3.8 (2.6)	44, 4.3 (2.7)	20, 3.6 (2.7)	15, 6.7 (1.9)	-
Day 92	68, 3.2 (2.6)	10, 2.8 (2.1)	31, 3.0 (2.6)	15, 2.2 (2.0)	12, 5.3 (2.7)	0.011
DIM (unpaired)	-3.5 (-4.1, -2.9), p<0.001	-3.4 (-4.7, -2.1), p<0.001	-4.2 (-5.0, -3.3), p<0.001	-4.6 (-5.8, -3.5), p<0.001	-1.2 (-3.0, 0.6)	0.003
MD (paired)	68, -4.1 (-4.8, -3.3), p<0.001	10, -3.8 (-6.3, -1.3)	31, -4.5 (-5.5, -3.4), p<0.001	15, -5.3 (-6.5, -4.1), p<0.001	12, -1.7 (-3.6, 0.3)	-
Discharge disposition		-	-	-	-	0.001
Acute care	16 (11.2)	3 (5.0)	10 (18.9)	1 (5.9)	2 (18.2)	-
Sub-acute care	40 (28.0)	9 (15.0)	26 (49.1)	4 (23.5)	1 (9.1)	-
Assisted care	6 (4.2)	5 (8.3)	0 (0.0)	0 (0.0)	1 (9.1)	-
Full-nursing care	11 (7.7)	6 (10.0)	3 (5.7)	1 (5.9)	1 (9.1)	-
Home care	44 (30.8)	22 (36.7)	7 (13.2)	9 (52.9)	4 (36.4)	-
Death	26 (18.2)	15 (25.0)	7 (13.2)	2 (11.8)	2 (18.2)	-

Data are number of participants, mean (standard deviation), difference in means and mean difference

(95% confidence interval); comparison of groups by analysis of variance, and day 92 versus baseline by paired and unpaired t-tests.

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Key safety findings

Number of people analysed: 245

- SAEs: 74 SAEs in 60 people.
- Fatal SAEs: 29
- Most common SAEs were pneumonia (n=27, 11.0%), cardiac arrest (n=5, 2.0%), respiratory failure (n=4, 1.6%) and recurrent stroke (n=3, 1.2%).
- One SAE (0.4%) was considered possibly related to PES: pneumonia related to catheter insertion leading to sepsis.
- There was no difference in the risk of individual SAEs between diagnostic groups.

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Summary of SAEs

System	SAE Term	All, n (%)	Time to event, days (SD)
N	-	245	-
Participants	-	-	-
SAE	-	60 (24.5)	25 (44)
Fatal SAE	-	29 (11.8)	34 (33)
Events	-	-	-
SAE	-	74	-
Fatal SAE		30 (40.5)	-
Cardiac	Cardiac Atrial fibrillation	2 (0.8)	36 (45)
	Cardiac arrest	5 (2.0)	38 (43)
	Cardiac failure	1 (0.4)	74 (0)
Gastrointestinal	Gastrointestinal Liver cancer	1 (0.4)	51 (0)
	Liver insufficiency	1 (0.4)	16 (0)
	Parotitis	1 (0.4)	-9 (0)
	Peritonitis	1 (0.4)	22 (0)
Neurological	Neurological Brain Abscess	1 (0.4)	4 (0)
	Encephalomyelitis	1 (0.4)	93 (0)
	Hydrocephalus	1 (0.4)	64 (0)
	PRES	1 (0.4)	41 (0)
	Reduced consciousness	1 (0.4)	7 (0)
	Seizures	2 (0.8)	103 (39)
	Stroke	3 (1.2)	18 (30)
Other	Death, cause unknown	2 (0.8)	68 (97)
	Dehydration	1 (0.4)	66 (0)
	Infection/sepsis, other	3 (1.2)	21 (11)
	Multiple organ failure	1 (0.4)	60 (0)
	Wound healing disorder	1 (0.4)	51 (0)
Renal	Renal Acute kidney injury	1 (0.4)	38 (0)
	Haematuria	1 (0.4)	78 (0)
	Urosepsis	2 (0.8)	54 (44)
Respiratory	Respiratory Lung cancer	1 (0.4)	37 (0)
	Pneumonia/RTI	26 (10.6)	22 (35)
	Pneumonia/RTI (1 case of chest sepsis “possibly related” to catheter insertion)	1 (0.4)	2 (0)
	Respiratory failure	4 (1.6)	12 (33)

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System	SAE Term	All, n (%)	Time to event, days (SD)
	Severe bronchitis	1 (0.4)	30 (0)
-	Tracheal stenosis	1 (0.4)	34 (0)
Vascular	Fainting	1 (0.4)	87 (0)
	Peripheral vascular disease	1 (0.4)	15 (0)
	Pulmonary embolism	2 (0.8)	16 (2)

PRES: posterior reversible encephalopathy syndrome; RTI: respiratory tract infection/chest infection; SAE: serious adverse event.

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Study 7 Restivo DA (2013)

Study details

Study type	Double-blinded (patient, assessor), sham-controlled pilot RCT
Country	Italy
Recruitment period	Not reported
Study population and number	n=20 (10 active treatment) People with dysphagia related to MS
Age and sex (or gender, as reported by the study)	Mean 39.7; 65% female
Patient selection criteria	Inclusion criteria: Expanded Disability Status Scale (EDSS) score of 7.5 or less (scored out of 10, higher numbers indicate worse disability), subjects in a stable phase of the disease, without relapses or a worsening major than 1 point at the EDSS in the previous 3 months; swallowing difficulty for liquids, solids or both, present for at least 2 consecutive months. Exclusion criteria: neurologic disease other than MS, older than 60 (because nonspecific swallowing abnormalities may occur around and especially above the age of 60), concomitant illness or upper gastrointestinal disease, inability to give informed consent because of cognitive impairment.
Technique	PES. bipolar platinum pharyngeal ring electrodes built into a 3 mm-diameter intraluminal catheter connected to a constant/current electrical simulator Electric current at 5 Hz was administered for 10 minutes each day for 5 days. A stimulation intensity of 75% maximum tolerated was used (calculated as the 75% of the current between sensory threshold and pain threshold). The mean treatment stimulation level was 14.2 mA.
Follow up	4 weeks
Conflict of interest or source of funding	Conflict of interest: Not reported Source of funding: supported by a Grant FISM (Fondazione Italiana Sclerosi Multipla onlus)

Analysis

Study design issues: This RCT was a pilot study to assess the efficacy and safety of PES for the treatment of dysphagia in people with MS. Patients were randomised 1:1 to PES or sham using a computer-generated list. In people assigned to sham, the same electrode was used, but no current was applied. Patients and outcome assessors were blinded to treatment allocation, treating researchers were unblinded. As patients could feel the effects of treatment, or the absence of treatment with sham, some patients may have become prematurely unblinded to treatment allocation.

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The outcomes included:

- Primary: PAS
- Secondary: variation in the electromyographic (EMG) measures: 1) duration of laryngeal transductor excursion (A-0 interval). 2) duration of the EMG activity of suprahyoid/submental (SHEMG-D) muscles. 3) interval between onset of EMG activity of suprahyoid/submental muscles and the onset of the laryngeal elevation (AeC interval). 4) duration of the inhibition (pause) of the cricopharyngeal (CP) muscle (CPEMG-P). 5) cortical motor thresholds (MT) recorded from the left CP muscle after TMS of the contralateral pharyngeal motor area.

Various statistical tests were used to compare pre-post and between-group outcomes. Wilcoxon signed ranks tests and analysis of variance (ANOVA) were used to evaluate differences in outcomes between PES and sham arms. Post-hoc testing with Bonferroni correction for multiple comparisons was used. $p<0.05$ was considered statistically significant.

Study population issues: There were no significant differences in baseline outcome measures between the PES and sham groups. Baseline demographic data were not provided.

Key efficacy findings

Primary outcome

Number of people analysed: 20

- In the PES group, there was a statistically significant decrease in PAS score from baseline to each post-stimulation period ($p<0.001$). A similar decrease was not observed in the sham group.

Outcome	**PES**	**-**	**-**	**-**	**Sham**	**-**	**-**	**-**
-	**Baseline**	**T1**	**T2**	**T3**	**Baseline**	**T1**	**T2**	**T3**
PAS (Mean (SD))	6.4 (0.9)	3.1 (0.8)	3.3 (1.0)	4.4 (1.1)	6.5 (0.8)	6.2 (1.4)	6.3 (1.0)	6.4 (0.9)

PAS, penetration-aspiration scale; PES, pharyngeal electrical stimulation; T1, immediately after final treatment session; T2, 2 weeks after final treatment session; T3, 4 weeks after final treatment session.

Secondary outcomes

Number of people analysed: 20

- In the secondary outcomes, ANOVA showed a statistically significant main effect of groups ($p<0.05$ for A–0 interval, A–C interval, SHEMG-D; $p<0.01$ for CPEMG-P; $p<0.05$ for cortical MT), treatment ($p<0.0001$) and a statistically significant interaction between group and treatment ($p<0.0001$). This statistical significance was confirmed by post-hoc testing ($p<0.0001$).

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Secondary outcomes

Outcome	PES	-	-	-	Sham	-	-	-
-	Baseline	T1	T2	T3	Baseline	T1	T2	T3
A–0 interval (mean (SD))	767.7 (181.4)	595.6 (75.5)	594.9 (67.7)	631.8 (83.8)	771.5 (181.0)	768.2 (169.5)	767.1 (179.0)	770.4 (180.0)
SHEMG-D (mean (SD))	1085.2 (151.4)	922.4 (106.2)	929.6 (106.8)	952.5 (124.8)	1076.3 (154.2)	1073.3 (156.4)	1075.2 (156.0)	1078.2 (153.8)
A–C interval (mean (SD))	579.0 (244.1)	456.8 (164.6)	315 (166.9)	361.5 (216.5)	584.6 (241.1)	582.8 (241.7)	584 (241.4)	585.6 (241.3)
CPEMG-P (mean (SD))	216.8 (113.5)	456.8 (164.6)	455.1 (158.3)	387.4 (120.2)	215.1 (112.7)	216.6 (111.1)	216.4 (111.2)	216.8 (111.3)
MT (mean % (SD))	55.7 (5.8)	48.9 (4.5)	48.8 (4.6)	52 (5.0)	55.4 (5.4)	55.6 (4.5)	55.7 (5.5)	55.7 (5.5)

Key safety findings

Safety findings were not reported.

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Study 8 Herrmann C (2022)

Study details

Study type	Single centre, open-label, active comparator controlled pilot RCT
Country	Germany
Recruitment period	2018 to 2020
Study population and number	n=20 (10 active treatment) People with dysphagia related to ALS.
Age and sex (or gender, as reported by the study)	PES group: mean 76.0; 50% female
Patient selection criteria	Inclusion criteria: Patients with possible, probable or definitive ALS with combined upper motor neurone/lower motor neurone bulbar involvement with moderate to severe dysphagia (as defined as a PAS value of at least 4 in thin liquid as assessed by fibreoptic endoscopic evaluation of swallowing at baseline). Exclusion criteria: atypical diagnoses (including primary lateral sclerosis, progressive muscular atrophy, and progressive bulbar palsy), tracheostomy, severe psychiatric disorders or dementia, implanted pacemaker or cardiac defibrillator and severe cardiopulmonary diseases.
Technique	PES with Phagenyx (Phagenesis, Ltd, Manchester, UK) in addition to standard logopaedic therapy (SLT). Electric current at 5 Hz was administered for 10 minutes each day for 3 days. The current of the stimulation was calculated as the threshold current (the current at which the patient can first detect stimulation) plus 75% of the difference between threshold and tolerance current (the current at which the patient does not want the current increased further). The median treatment stimulation level was approximately 12.7 mA. SLT was given over 45 minutes each day for 3 days and involved restitutional procedures (for example, passive manual treatment, tactile and thermal stimulation and moderate movement exercises), compensatory procedures (for example, changes in posture or specific swallowing techniques), and adaptive procedures (for example, an adaption of patients' eating and drinking habits).
Follow up	3 months
Conflict of interest or source of funding	Conflict of interest: The authors declared no potential conflicts of interest. Source of funding: Phagenesis, the manufacturer of a PES device, supplied the catheters and stimulation device for free. Data collection, analysis, interpretation and publication were performed by the research team without involvement of Phagenesis.

Analysis

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Follow up issues: In the PES group, 1 patient did not complete treatment after 1 day due to pneumonia and dislocation of the gastric tube. Over the entire duration of the study, there were 6 (60%) dropouts in the PES group compared with 1 (10%) dropouts in the control group. Dropouts in both groups were mainly caused by the patients' request to not perform subsequent study visits at the hospital due to further disease progression and severe disability. Two patients in the PES group died during the study due to disease progression.

Study design issues: This RCT was a pilot study to assess the efficacy and safety of PES for the treatment of dysphagia in people with ALS. The sample size was determined by practicality, not statistical power. People were randomised 1:1 to PES plus SLT or to SLT alone. Treatments were open label, with patients, treatment administrators, and assessors were unblinded to treatment assignment.

The outcomes included:

- Primary: PAS
- Secondary: Swallowing-specific QoL, DSRS, classification of leaking and residues (Residues are parts of the bolus that remain in the pharynx after swallowing and put the patient at risk of aspiration, while leaking describes that solid or fluid food enter the pharynx before triggering swallowing reflex), Clinical Evaluation of Swallowing (a description of this scale was not provided), and the ALSFRS-R.

All statistical tests were performed at a 2-sided level of alpha of 0.05 and interpreted as exploratory. An adjustment for multiple comparisons was not done.

Study population issues: Patients in the PES group were statistically significantly older than patients in the control group (76.0 versus 57.5 years). There were no other statistically significant differences between the groups.

Key efficacy findings

Primary outcome

Number of people analysed: 20

- There were no statistically significant differences in PAS score improvement between the treatment groups at any of the follow up visits.

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Primary outcome

Outcome	Treatment group	Day 1	Day 4	Week 3	Month 3
PAS	PES	−0.8 (−1.5 to −0.3)	−0.2 (−1.9 to 0.5)	−1.1 (−2.0 to 0.5)	−0.02 (−2.0 to 2.2)
-	Control	−1.8 (−2.2 to −0.2)	−1.5 (−1.8 to −1.2)	−1.4 (−1.7 to 0.5)	−0.7 (−1.0 to 0.5)
-	p-value	0.32	0.74	0.69	0.71

Data are median (IQR).

IQR, interquartile range; PAS, penetration-aspiration scale; PES, pharyngeal electrical stimulation.

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Secondary outcomes

Number of people analysed: 20

- There were no statistically significant differences in any of the secondary outcome measures between the treatment groups at any of the follow up visits.

Outcome	Treatment group	Day 1	Day 4	Week 3	Month 3
ALSFRS-R	PES	Not analysed	0.0 (−3.0 to 2.0)	−1.5 (−6.8 to 1.5)	−0.5 (−1.0 to 1.5)
-	Control	Not analysed	0.0 (−1.0 to 2.0)	−1.0 (−4.0 to 0.0)	−1.0 (−7.5 to 0.5)
-	p-value	-	0.37	0.99	0.54
SWAL-QOL	PES	9.5 (−3.8 to 24.0)	0.5 (−17.0 to 16.0)	−6.0 (−12.0 to 8.5)	4.0 (4.0 to 9.0)
-	Control	−2.0 (−11.0 to 13.0)	3.0 (−17.0 to 21.0)	0.0 (−17.0 to 11.0)	−4.0 (−36.0 to 3.3)
-	p-value	0.29	0.52	0.93	0.07
DSRS	PES	−1.0 (−2.0 to −0.3)	−1.0 (−1.0 to 0.0)	−0.5 (−2.0 to 0.3)	−2.0 (−2.0 to 1.0)
-	Control	−1.0 (−1.0 to −1.0)	−1.0 (−2.0 to −1.0)	0.0 (−1.0 to 0.0)	0.0 (−1.0 to 0.5)
-	p-value	0.90	0.09	0.79	0.46
Leaking	PES	−0.2 (−0.32 to 0.06)	−0.1 (−0.18 to −0.03)	−0.09 (−0.31 to 0.09)	−0.05 (−0.4 to 0.21)
-	Control	0.0 (−0.16 to 0.21)	0.06 (−0.19 to 0.42)	−0.21 (−0.25 to 0.14)	−0.02 (−0.45 to 0.16)
-	p-value	0.08	0.12	0.73	0.95
Residues	PES	0.0 (−0.57 to 0.03)	−0.15 (−0.37 to 0.19)	−0.34 (−1.1 to 0.17)	0.0 (−0.12 to 0.11)
-	Control	−0.24 (−0.66 to 0.07)	−0.32 (−0.55 to −0.25)	−0.2 (−0.41 to 0.0)	−0.51 (−0.67 to 0.01)
-	p-value	0.95	0.09	0.58	0.28
CES	PES	0.0 (−2.0 to 1.5)	1.0 (−3.0 to 4.0)	1.0 (−1.5 to 3.0)	0.5 (−1.0 to 3.5)
-	Control	−1.5 (−2.0 to 0.2)	0.0 (−4.0 to 1.0)	−1.0 (−1.8 to 0.8)	1.5 (0.0 to 4.0)
-	p-value	0.73	0.10	0.19	0.57

Data are median (IQR).

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; CES, Clinical Evaluation of Swallowing; DSRS, Dysphagia Severity Rating Scale; IQR, interquartile range; PAS, Penetration-spiration scale; PES, pharyngeal electrical stimulation; SWAL-QOL, Swallowing Quality of Life.

Key safety findings

Number of people analysed: 10

- Two minor adverse events were observed:

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- Uncomfortable feeling in the pharynx while using non-invasive ventilation after PES, n=1
- Mild burning pain in the nasopharynx after PES due to an erythema, n=1.

Validity and generalisability of the studies

- The studies recruited people with various causes of dysphagia, including stroke, ventilator-related, TBI, MS, and ALS. The severity of dysphagia and the interval between onset of dysphagia/injury to treatment varied between the studies.
- The treatment protocol for PES was similar between studies, though there were differences in the strength of current used. The undertreatment of patients in the Bath (2016) RCT may have contributed to the findings of this trial.
- Two meta-analyses were included in the key evidence (several others are listed in the appendix). The studies included in the meta-analyses were exclusively RCTs, most of which enrolled fewer than 50 patients. The findings of the meta-analyses were contradictory and seemed to differ based on different inclusion criteria used to select studies. Notably, Dziewas (2018) was excluded from Speyer (2022) but included in Cheng (2021). The 'overall treatment effect' presented by Cheng (2021) was also a combination of different outcomes (decannulation, PAS and DSRS) making interpretation of the effect difficult.
- In sham-controlled RCTs, as patients could feel the effects of treatment, or the absence of treatment with sham, some patients may have become prematurely unblinded to treatment allocation. Furthermore, in the Bath (2016) RCT, patients randomised to sham may have inadvertently been exposed to a therapeutic dose of PES when establishing threshold and tolerance stimulation levels.
- Two pilot RCTs were included in the key evidence (Restivo, 2013 and Herrmann, 2022). These studies were not powered to demonstrate non-inferiority/superiority and were included to show the use of PES in different patient populations. These are progressive diseases, and their findings may not extend to post-stroke, traumatic brain injury and other non-progressive disease populations.
- Most studies did not conduct an adjustment for multiple comparisons during statistical analysis. Testing many hypotheses without adjustment for multiple comparisons increases the likelihood of a Type 1 error (false positive).
- Studies were conducted in countries across Europe, including the UK.

Existing assessments of this procedure

In 2021, the European Stroke Organisation and European Society for Swallowing Disorders published guidelines for the diagnosis and treatment of post-stroke dysphagia (Dziewas, 2021a). The recommendations were informed by a literature review, meta-analysis, and expert consensus. The following recommendations were made:

- Recommendation 20: In patients with post-stroke dysphagia, we suggest treatment with rTMS, TES, tDCS and PES as adjunct to conventional dysphagia treatments to improve swallowing function.

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  - Quality of evidence: Moderate
  - Strength of recommendation: Weak for intervention

- Recommendation 21: In tracheostomised stroke patients with severe dysphagia, we suggest treatment with pharyngeal electrical stimulation to accelerate decannulation.
  - Quality of evidence: High
  - Strength of recommendation: Weak for intervention

In 2021, the German Society of Neurology published S1 guidelines on the diagnosis and treatment of neurogenic dysphagia (Dziewas, 2021b). The recommendations were informed by a systematic literature review and expert consensus. The following recommendations were made:

- Recommendation 46: Due to limited data, neurostimulation methods in principle should be used in clinical trials or registries.
- Recommendation 47: Pharyngeal electrical stimulation should be used to treat dysphagia in tracheostomised stroke patients with supratentorial lesion. Participation in prospective clinical registries is recommended.

The National Clinical Guideline for Stroke 2023 highlights pharyngeal electrical stimulation treatment:

- Recommendation 4.26: Patients with tracheostomy and severe dysphagia after stroke may be considered for pharyngeal electrical stimulation to aid decannulation where the device is available and it can be delivered by a trained healthcare professional.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Transcutaneous neuromuscular electrical stimulation for oropharyngeal dysphagia in adults (2018) NICE interventional procedures guidance 634: special arrangements for patients with stroke, research for dysphagia associated with conditions other than stroke.
- Endoscopic carbon dioxide laser cricopharyngeal myotomy for relief of oropharyngeal dysphagia (2016) NICE interventional procedures guidance 550: special arrangements

NICE guidelines

- Stroke and transient ischaemic attack in over 16s: diagnosis and initial management (2019) NICE guideline 128
- Stroke rehabilitation in adults (2023) NICE guideline 236

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NICE advice

- IQoro for stroke-related dysphagia (2019) NICE medtech innovation briefing 175

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, when comments are considered voluminous, or publication would be unlawful or inappropriate.

Four professional expert questionnaires for pharyngeal electrical stimulation for neurogenic dysphagia were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE received 6 completed questionnaires from people who had the procedure. Additionally, 3 people who had been treated at 2 separate centres with pharyngeal electrical stimulation for neurogenic dysphagia shared their experiences through NICE's public involvement programme. Commentary from 1 person who had the procedure was submitted to NICE by the company.

Company engagement

A structured information request was sent to 1 company who manufactures a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- The PhINEST Study (https://clinicaltrials.gov/ct2/show/NCT03840395) is currently ongoing. This is a prospective, multicentre, randomised, sham-controlled, single-blind (outcome assessor) study of PES for the treatment of oropharyngeal dysphagia after invasive mechanical ventilation in an ICU population. Expected recruitment is 360 people, estimated study end date is December 2025.

- The PhEAST study (https://www.isrctn.com/ISRCTNISRCTN98886991) is currently ongoing. This is a prospective, multicentre, randomised, sham-controlled, open label study of PES for the treatment of post-stroke oropharyngeal dysphagia. Expected recruitment is 800 people, estimated study end date is July 2025.

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References

1. Speyer R, Sutt AL, Bergstrom L et al. (2022) Neurostimulation in People with Oropharyngeal Dysphagia: A Systematic Review and Meta-Analyses of Randomised Controlled Trials-Part I: Pharyngeal and Neuromuscular Electrical Stimulation. Journal of Clinical Medicine 11(3):776.
2. Cheng I, Sasegbon A, and Hamdy S. (2021) Effects of Neurostimulation on Poststroke Dysphagia: A Synthesis of Current Evidence From Randomized Controlled Trials. Neuromodulation: Journal of the International Neuromodulation Society 24(8):1388-1401.
3. Bath PM, Scutt P, Love J et al. (2016) Pharyngeal Electrical Stimulation for Treatment of Dysphagia in Subacute Stroke: A Randomized Controlled Trial. Stroke 47(6):1562-70.
4. Dziewas R, Stellato R, van der Tweel I et al. (2018) Pharyngeal electrical stimulation for early decannulation in tracheotomised patients with neurogenic dysphagia after stroke (PHAST-TRAC): a prospective, single-blinded, randomised trial. The Lancet Neurology 17(10):849-59.
5. Suntrup S, Marian T, Schroder JB et al. (2015) Electrical pharyngeal stimulation for dysphagia treatment in tracheotomized stroke patients: a randomized controlled trial. Intensive care medicine 41(9):1629-37
6. Bath PM, Woodhouse LJ, Suntrup-Krueger S et al. (2020) Pharyngeal electrical stimulation for neurogenic dysphagia following stroke, traumatic brain injury or other causes: Main results from the PHADER cohort study. EClinicalMedicine 28:100608.
7. Restivo DA, Casabona A, Centonze D et al. (2013) Pharyngeal electrical stimulation for dysphagia associated with multiple sclerosis: a pilot study. Brain stimulation 6(3):418-23.
8. Herrmann C, Schradt F, Lindner-Pfleghar B et al. (2022) Pharyngeal electrical stimulation in amyotrophic lateral sclerosis: a pilot study. Therapeutic Advances in Neurological Disorders 15.
9. Dziewas R, Michou E, Trapl-Grundschober M et al. (2021) European Stroke Organisation and European Society for Swallowing Disorders guideline for the diagnosis and treatment of post-stroke dysphagia. European Stroke Journal 6(3):lxxxix-cxv.
10. Dziewas R, Allescher HD, Aroyo I et al. (2021) Diagnosis and treatment of neurogenic dysphagia - S1 guideline of the German Society of Neurology. Neurological Research and Practice 3(1):23.

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Literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	18/10/2022	1946 to October 17, 2022
MEDLINE In-Process (Ovid)	18/10/2022	1946 to October 17, 2022
MEDLINE Epubs ahead of print (Ovid)	18/10/2022	October 17, 2022
EMBASE (Ovid)	18/10/2022	1974 to October 17, 2022
EMBASE Conference (Ovid)	18/10/2022	1974 to October 17, 2022
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	18/10/2022	Issue 10 of 12, October 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	18/10/2022	Issue 10 of 12, October 2022
International HTA database (INAHTA)	18/10/2022	-

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

MEDLINE search strategy

The MEDLINE search strategy was translated for use in the other sources.

1 Deglutition Disorders/ 22326
2 ((Deglutition or swallow*) adj4 (difficult* or problem* or disorder*)).tw. 5801

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3	dysphagia.tw.	26227
4	or/1-3	38685
5	Electric Stimulation/	115702
6	Electric Stimulation Therapy/	21575
7	((electr* adj4 stimul*) or EPS).tw.	92893
8	(electrostimul* or electro-stimul* or galvanostimul* or (galvan* adj4 stimul*)).tw.	4341
9	electrotherap*.tw.	1345
10	(neurostimul* or neuro-stimul* or neuromodulat* or neuro-modulat*).tw.	18941
11	(Peripheral adj4 sens* adj4 stimul*).tw.	363
12	PES.tw.	7632
13	or/5-12	207712
14	Phagenyx*.tw.	0
15	4 and 13	423
16	14 or 15	423
17	Animals/ not Humans/	4944921
18	16 not 17	399

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Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Balcerak P, Corbiere S, Zubal R and Kagi G. (2022) Post-stroke Dysphagia: Prognosis and Treatment–A Systematic Review of RCT on Interventional Treatments for Dysphagia Following Subacute Stroke. Front. Neurol; 13	Systematic review n=4 studies	Of the four studies in this review, two reached the study goal and showed a positive effect on post-stroke dysphagia. One study included was in a further specified study population with stroke survivors needing tracheostomy.	Systematic Reviews with more studies are included in the key evidence - Speyer R (2022) and Cheng I (2021).
Bath PM, Lee HS and Everton LF. (2018) Swallowing therapy for dysphagia in acute and subacute stroke. The Cochrane database of systematic reviews 10:cd000323	Systematic review and meta-analysis n=4 studies	Moderate- and low-quality evidence suggests that swallowing therapy did not have a significant effect on the outcomes of death or dependency/disability, case fatality at the end of the trial, or penetration-aspiration score. However, swallowing therapy may have reduced length of hospital stay, dysphagia, and chest infections, and may have improved swallowing ability.	More recent systematic reviews included.

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Article	Number of patients/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
		However, these results are based on evidence of variable quality, involving a variety of interventions. Further high-quality trials are needed to test whether specific interventions are effective.	
Beirer S, Grisold W and Dreisbach J. (2020) Therapy-resistant dysphagia successfully treated using pharyngeal electrical stimulation in a patient with the pharyngeal-cervical-brachial variant of the Guillain-Barre syndrome. eNeurologicalSci 20:100255	Case report n=1 FU=18 days	PES was safe and may be beneficial in other neurologic disorders, where traditional dysphagia therapies have proved unsuccessful.	Studies with more people or longer follow up included.
Blakemore C, Hunter J, Bhaskar B. (2021) Rapid swallow improvement following pharyngeal electrical stimulation in a covid-19 patient with long-term severe neurogenic dysphagia: a case report. JRM-CC; 4	Case report n = 1	We present a 62-year-old male with COVID-19 pneumonitis, prolonged intubation- and stroke-related severe neurogenic dysphagia, who was given novel PES treatment for 5 days. PES was safe and appeared to facilitate faster recovery	Studies with more people or longer follow up included.
Cheng I, Sasegbon A, Hamdy S. (2022) Dysphagia treatment in Parkinson's disease: A systematic review and meta-analysis. Neurogastroenterology & Motility, 00:e14517	Systematic review and meta-analysis	Dysphagia treatments, particularly stimulation treatments, can potentially benefit Parkinson's disease	Systematic reviews with broader population in line with the topic are included

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Article	Number of patients/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
	n=9 studies (sample size of 286)	patients. However, given the limited number of small RCTs for each type of treatment, the evidence remains weak and uncertain. Further large-scale, multicentre RCTs are warranted to fully explore their clinical efficacy in the Parkinson's disease population.	
Chiang CF, Lin MT, Hsiao MY et al. (2019) Comparative Efficacy of Noninvasive Neurostimulation Therapies for Acute and Subacute Poststroke Dysphagia: A Systematic Review and Network Meta-analysis. Archives of Physical Medicine and Rehabilitation 100(4):739-50e4	Systematic review and meta-analysis n=3 studies	Among the 4 non-invasive neurostimulation therapies, rTMS, tDCS, and sNMES were effective for treating poststroke dysphagia; furthermore, rTMS may be the most effective therapy according to probability ranking.	More recent systematic reviews included.
Ebihara S and Naito T. (2022) A Systematic Review of Reported Methods of Stimulating Swallowing Function and their Classification. The Tohoku journal of experimental medicine 256(1):1-17	Systematic review n=15 studies	PES with a catheter electrode has been shown to be useful in early recovery from post-stroke dysphagia and other various conditions of dysphagia including post-tracheal intubation.	Meta-analyses included.
Essa H, Vasant DH, Raginis-Zborowska A et al. (2017) The BDNF polymorphism Val66Met may be predictive	RCT post hoc analysis	Our findings suggest an association between BDNF and stimulation induced	RCT (Vasant, 2016) included.

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Article	Number of patients/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
of swallowing improvement post pharyngeal electrical stimulation in dysphagic stroke patients. Neurogastroenterology and motility: the official journal of the European Gastrointestinal Motility Society 29(8)	n=36 (18 active treatment) FU=3 months	swallowing recovery. Further work will be required to validate these observations and demonstrate clinical utility in patients.	
Everton LF, Benfield JK, Michou E et al. (2022) Reliability of the Penetration-Aspiration Scale and Temporal and Clearance Measures in Poststroke Dysphagia: Videofluoroscopic Analysis From the Swallowing Treatment using Electrical Pharyngeal Stimulation Trial. Journal of speech, language, and hearing research: JSLHR 65(3):858-68	RCT post hoc analysis n=18	Analysis of interrater reliability for analysis of penetration-aspiration scale scores. Interrater reliability for PAS is acceptable but depends on how the PAS scores are handled in the analysis. Interrater reliability for most temporal measures was high, although some measures required additional training. No clearance measures had excellent reliability.	RCT (Bath, 2016) included.
Everton LF, Benfield JK, Michou E et al. (2021) Effects of Pharyngeal Electrical Stimulation on Swallow Timings, Clearance and Safety in Post-Stroke Dysphagia: Analysis from the Swallowing Treatment Using Electrical Pharyngeal Stimulation (STEPS) Trial. Stroke Research and Treatment: 5520657	RCT post hoc analysis n=81 (43 active treatment)	This study, which conducted additional measurements of kinematic and residue analysis on the STEPS data did not detect "missed" improvements in swallowing function that the PAS is not designed to measure. However, more	RCT (Bath, 2016) included.

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Article	Number of patients/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
		studies with greater numbers are required.	
Florea C, Braumann C, Mussger C et al. (2020) Therapy of dysphagia by prolonged pharyngeal electrical stimulation (Phagenyx) in a patient with brainstem infarction. Brain Sciences 10(5):256	Case report n=1	We present a case of brainstem infarction with severe dysphagia in a 53-year-old woman with preserved cognitive functions. Though the swallowing improved, she stayed tube-dependent with minimal attempts with puréed food during therapy, and could not be decannulated.	Studies with more people or longer follow up included.
Jayasekeran V, Singh S, Tyrrell P et al. (2010) Adjunctive functional pharyngeal electrical stimulation reverses swallowing disability after brain lesions. Gastroenterology 138(5):1737-46	RCT n=28 (16 active treatment) FU=2 weeks	This pilot study of PES confirms that it is a safe neurostimulation intervention that reverses swallowing disability after virtual lesion or stroke.	Studies with more people or longer follow up included. Included in systematic reviews and meta-analyses.
Kesik G and Ozdemir L. (2021) Non-pharmacologic approaches to dysphagia in patients with multiple sclerosis: A systematic review. Turk Noroloji Dergisi 27(2):111-6	Systematic review n=1 study	One study was identified that used PES to treat dysphagia associated with multiple sclerosis.	The study identified (Restivo, 2013) was included in the key evidence.
Koestenberger M, Neuwersch S, Hoefner E et al. (2020) A Pilot Study of Pharyngeal Electrical Stimulation for Orally Intubated ICU Patients with	Cohort study n=40 (15 active treatment)	This study demonstrated the benefits of PES in ICU patients still orally intubated, thus offering a potential new method to reduce morbidity,	Studies with more people or longer follow up included.

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Article	Number of patients/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Dysphagia. Neurocritical care 32(2):532-8		mortality, and economic burden in a mixed ICU population.	
Michou E, Mistry S, Jefferson S et al. (2014) Characterizing the mechanisms of central and peripheral forms of neurostimulation in chronic dysphagic stroke patients. Brain stimulation 7(1):66-73	RCT n=6 (had both active and sham) FU=30 days	The 2 neurostimulation paradigms, PES and PAS, which mainly employ peripheral stimulation, showed associated increases in cortical excitability of the affected hemisphere.	Studies with more people or longer follow up included. Included in systematic reviews and meta-analyses.
Muhle P, Suntrup-Krueger S, Bittner S et al. (2017) Increase of Substance P Concentration in Saliva after Pharyngeal Electrical Stimulation in Severely Dysphagic Stroke Patients - an Indicator of Decannulation Success? Neuro-Signals 25(1):74-87	Before-and-after study n=23 FU=35 days	The physiological mechanism of PES may consist in restoration of sensory feedback, which is known to be crucial for the execution of a safe swallow. Substance P possibly acts as a biomarker for indicating response to PES.	Studies with more people or longer follow up included.
Scutt P, Lee HS, Hamdy S, and Bath PM. (2015) Pharyngeal Electrical Stimulation for Treatment of Poststroke Dysphagia: Individual Patient Data Meta-Analysis of Randomised Controlled Trials. Stroke Research and Treatment 429053	Systematic review and meta-analysis n=3 studies	PES was associated with less radiological aspiration and clinical dysphagia and possibly reduced length of stay in hospital across three small trials.	More recent systematic reviews included.
Traugott M, Hoepler W, Kitzberger R et al. (2021) Successful treatment of intubation-induced severe neurogenic post-extubation dysphagia using pharyngeal	Case report n=1	PES treatment contributed to the restoration of a safe swallowing function in this critically ill patient with COVID-19 and	Studies with more people or longer follow up included.

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Article	Number of patients/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
electrical stimulation in a COVID-19 survivor: a case report. Journal of medical case reports 15(1):148		ICU-acquired swallowing dysfunction.	
Traugott MT, Hoepler W, Kelani H, Schatzl M, Friese E and Neuhold S. (2022) Pharyngeal Electrical Stimulation Treatment of Critically Ill Intensive Care Tracheostomized Patients Presenting with Severe Neurogenic Dysphagia: A Case Series	Case series n = 19	In this mixed population, PES led to improved swallowing function resulting in successful decannulation of 15/19 patients and return to normal oral intake at hospital discharge in 11/15 patients with severe neurogenic swallowing disorders and tracheostomy	Studies with more people or longer follow up included.
Vasant DH, Michou E, O'Leary N et al. (2016) Pharyngeal Electrical Stimulation in Dysphagia Poststroke: A Prospective, Randomized Single-Blinded Interventional Study. Neurorehabilitation and neural repair 30(9):866-75	RCT n=36 (18 active treatment) FU=3 months	Although the direction of observed differences were consistent with PES accelerating swallowing recovery over the first 2 weeks postintervention, suboptimal recruitment prevents definitive conclusions.	Studies with more people or longer follow up included. Included in systematic reviews and meta-analyses.
Wang T, Dong L, Cong X et al. (2021) Comparative efficacy of non-invasive neurostimulation therapies for poststroke dysphagia: A systematic review and meta-analysis. Neurophysiologie Clinique, Clinical neurophysiology 51 (6):493-506	Systematic review and meta-analysis n=2 studies	Non-invasive neurostimulation therapies can effectively promote the recovery of dysphagia after stroke.	More recent systematic reviews included. Included in systematic reviews and meta-analyses.

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Article	Number of patients/ follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Youssef, G., El-Banna, M. (2015). The outcome of intraluminal electrical stimulation (EPS) on oropharyngeal dysphagic stroke patients, Al-Azhar Assiut Medical Journal, 13(1), 67-72.	Pilot non-randomised study n=18 2 weeks	All participants of this study had severe dysphagia after stroke. Findings show a positive, significant outcome for PES compared to sham on 2 measures that relate to swallow function (Penetration-Aspiration Scale; Functional Oral Intake Scale).	Studies with more people and longer follow-up were included.
Zhang X, Liang Y, Wang X, Shan Y et al. (2022) Effect of Modified Pharyngeal Electrical Stimulation on Patients with Severe Chronic Neurogenic Dysphagia: A Single-Arm Prospective Study, Dysphagia	A single-arm prospective study n=30 FU=3 months	mPES likely has long-term effects of improving the capability of oral feeding, pharyngeal contractility, swallowing safety, and decannulation in patients with SCND	Studies with more people or longer follow up included.
Zhang X, Wang X, Dou Z, Wen H (2023) A novel approach to severe chronic neurogenic dysphagia using pharyngeal sensory electrical stimulation. American Journal of Physical Medicine & Rehabilitation 102 (3):e32-e35	Case report n=1	Pharyngeal sensory electrical stimulation might be a potential therapeutic option for severe chronic neurogenic dysphagia with hypopharyngeal weakness.	Studies with more people or longer follow up included.

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