Pharyngeal Electrical Stimulation for Treatment of Dysphagia in Subacute Stroke

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Pharyngeal Electrical Stimulation for Treatment of Dysphagia in Subacute Stroke
A Randomized Controlled Trial

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Background and Purpose—Dysphagia is common after stroke, associated with increased death and dependency, and treatment options are limited. Pharyngeal electric stimulation (PES) is a novel treatment for poststroke dysphagia that has shown promise in 3 pilot randomized controlled trials.

Methods—We randomly assigned 162 patients with a recent ischemic or hemorrhagic stroke and dysphagia, defined as a penetration aspiration score (PAS) of ≥3 on video fluoroscopy, to PES or sham treatment, given on 3 consecutive days. The primary outcome was swallowing safety, assessed using the PAS, at 2 weeks. Secondary outcomes included dysphagia severity, function, quality of life, and serious adverse events at 6 and 12 weeks.

Results—In randomized patients, the mean age was 74 years, male 58%, ischemic stroke 89%, and PAS 4.8. The mean treatment current was 14.8 (7.9) mA and duration 9.9 (1.2) minutes per session. On the basis of previous data, 45 patients (58.4%) randomized to PES seemed to receive suboptimal stimulation. The PAS at 2 weeks, adjusted for baseline, did not differ between the randomized groups: PES 3.7 (2.0) versus sham 3.6 (1.9), P=0.60. Similarly, the secondary outcomes did not differ, including clinical swallowing and functional outcome. No serious adverse device-related events occurred.

Conclusions—In patients with subacute stroke and dysphagia, PES was safe but did not improve dysphagia. Undertreatment of patients receiving PES may have contributed to the neutral result.


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Key Words: dysphagia ■ pharyngeal electrical stimulation ■ randomized controlled trial ■ stroke

A subacute stroke is complicated by oropharyngeal dysphagia in 50% of patients; of these, up to 40% remain dysphagic a year later.1 Dysphagia is complicated by aspiration, pneumonia, and malnutrition,2 and patients need enteral feeding through a nasogastric tube or percutaneous endoscopically introduced gastrostomy tube, which often requires long-term institutional care.3 Although dysphagia may be treated using several physical and behavioral techniques, there are no definitive treatments.4

Human swallowing has bilateral representation in the cerebral hemispheres with a dominant cortex (unrelated to handedness).5 Dysphagia often follows a stroke that affects the dominant swallowing cortex, which is then exacerbated in recurrent strokes. Swallowing is dependent on afferent feedback via bulbar cranial nerves innervating the pharynx, and increased sensory input from the pharynx can drive long-term beneficial changes in the cortical control of...
swallowing with functionally relevant reorganization of the swallowing cortex. During development of pharyngeal electric stimulation (PES), a study in healthy volunteers suggested that PES should be delivered at 5 Hz for 10 minutes with an electric current of threshold plus 75% of the difference between threshold and tolerance levels, a paradigm that produced the largest effect on brain excitability. Using this approach in patients with subacute stroke in a randomized dose-comparison trial, PES reduced radiological aspiration, manifest as a reduction in penetration aspiration score (PAS). Similarly, PES reduced clinical dysphagia (assessed using the dysphagia severity rating scale [DSRS]) and length of stay in hospital in patients with dysphagia post stroke in a sham-controlled parallel-group phase II trial. In a further multicentre phase II randomized sham-controlled trial, PES was associated with nonsignificant tendencies to reduced clinical dysphagia and shorter length of stay in hospital. An individual patient data meta-analysis of these 3 trials found that PES significantly reduced aspiration (PAS) and dysphagia (DSRS) and was safe and well tolerated. Here, we present the results of a large, randomized, sham-controlled phase III trial of PES in patients with subacute poststroke dysphagia.

Materials and Methods

Participants
We did an international, multicentre, randomized, sham-controlled, patient-masked, outcome assessor–masked, parallel-group trial, as detailed in the online-only Data Supplement. In brief, patients with a recent stroke and videofluoroscopy (VFS)-confirmed dysphagia were randomized to 3 days of PES or sham stimulation, and the primary outcome was the penetration aspiration scale, assessed using VFS, at 2 weeks after the third treatment session.

Patients were eligible for the trial if they were admitted to hospital with a clinical stroke syndrome because of ischemic or hemorrhagic stroke, were aged ≥18 years, had clinical dysphagia identified using bedside testing (as assessed by a nurse or speech and language therapist using a local clinical assessment and confirmed by failure on the Toronto Bedside Swallowing Screening Test), were alert or rousable (score of 0 or 1 on question 1a of the National Institutes of Health Stroke Scale [NIHSS]), had a PAS ≥3 (see the online-only Data Supplement for description) of at least 1 swallow (assessed using VFS), and could be treated within 42 days of stroke onset. The diagnosis of ischemic or hemorrhagic stroke was confirmed with computed tomography or magnetic resonance imaging between hospitalization and enrollment and using standard imaging techniques. Key exclusion criteria included 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.

Ethics and Approvals
The study was approved by national ethics committees and competent authorities in each participating country, and locally at each site, and was adopted by the UK National Institute for Health Research Stroke Research Network. We obtained written informed consent from each patient, or proxy consent from a relative when the patient did not have capacity (eg, because of dysphasia and confusion), before enrollment and in accordance with national regulations; in Germany, the Bundesamt für Strahlenschutz regulatory authority did not allow proxy consent. The trial was run by a Trial Management Committee (P.M.B., S.H., C.M., and J.L.). An independent data-monitoring committee reviewed unmasked data every 6 months. The trial was registered as IRCTN25681641.

Randomization
VFS (see below) was performed as a study procedure after consent to confirm the presence of dysphagia (PAS ≥3). Investigators entered baseline and follow-up data into a commercial database (Rave, Medidata Solutions, Inc) linked to a randomization list (Quantics Consulting, Ltd). The data were checked to confirm the patient’s eligibility, and the system then assigned a participant to treatment with active PES or sham PES with allocation 1:1. Allocation was by randomly permuted blocks (of size 6) with stratification by center and feeding status (presence/absence of artificial feeding) to enhance balance between treatment groups.

VFS
VFS was performed using local protocols at each participating site by a speech and language therapist or a radiologist. At each time point (baseline and weeks 2 and 12), each participant was given up to 6×5 mL bolus drinks of contrast agent (Omnipaque 300 in UK, Visipaque 270 in France, or Accupaque 300) of liquid consistency (≈40% wt/vol). A 50 mL drink of contrast agent was then administered and swallows recorded. At baseline, bolus drinks were taken until 3 were positive (ie, at least 1 swallow within a bolus of PAS ≥3); once achieved, further bolus drinks were not given to reduce the risk of aspiration and pneumonia. Hence, between 3 and 7 bolus (each inducing ≥3 swallows) were administered. Once completed, quality-assured digital VFS image files for each swallow for each bolus were sent immediately to 1 of 2 independent adjudicators who were blinded to clinical information and who confirmed whether the patient fulfilled the inclusion criteria on the basis of aspiration of radiological contrast. Use of digital VFS reduced the risk of image degradation on file transfer. Once confirmation was received, treatment could be started. VFS images at weeks 2 and 12 were similarly uploaded and assessed by 1 of 2 adjudicators who were blinded to patient details and randomization. Silent aspiration was defined as aspiration without an attempted cough as seen on the video file, accompanying sound, or event monitor.

Procedures
Sterile single-patient use treatment catheters (Phagenyx, Phagenesis, Ltd, Manchester, UK), which contain an inner lumen for feeding, were inserted via the nose by trained staff. The catheter was inserted to an aboral depth related to the patient’s height so that the pair of ring treatment electrodes located on the outer surface of the catheter were adjacent to the pharynx.

Treatment was started once dysphagia was confirmed by VFS and given daily for 3 days. At each session, the catheter was connected to the controlling base station, and electric current at 5 Hz was increased incrementally from 1 mA to detect threshold (patient first aware of stimulation) and then tolerated (patient does not want current increased further) intensity levels in all patients. Those randomized to active PES were then administered this for 10 minutes at a treatment current (mA) of threshold plus 75% of the difference between threshold and tolerance levels; this paradigm was used successfully in earlier studies of PES and considered to be an effective level of stimulation without being too near the tolerance level. Patients randomized to sham therapy had no stimulation after establishment of threshold and tolerated levels. Patients, but not the treating researcher, were masked to treatment assignment. Treatment could be stopped if the patient withdrew consent, for safety reasons, or if unacceptable adverse events developed.

Active or sham PES treatment was given in addition to standard stroke care, including thrombolysis if administered at admission to hospital, and rehabilitation. Systematic use of antihypertensive agents (all patients), oral antithrombotic and lipid-lowering agents, and carotid endarterectomy (patients with ischemic stroke) were
recommended for secondary prevention as per each site’s local practice. The final diagnosis was confirmed at discharge based on clinical presentation and neuroimaging.

**Outcomes**

The primary outcome measure was radiological aspiration at 2 weeks assessed as the PAS using VFS. The timing of VFS at 2 weeks reflected that used in 3 pilot trials. As a secondary outcome, PAS was also measured at 12 weeks.

Other prespecified secondary outcomes at 2, 6, and 12 weeks included clinical dysphagia (DSRS; see the online-only Data Supplement), dependency (modified Rankin Scale [mRS]), activities of daily living/disability (Barthel Index), impairment (NIHSS), health-related quality of life (European Quality of Life-5 Dimensions [EQ-5D]), from which health utility status was calculated (EQ-5D-HUS), and nutritional measures (weight, mid-arm circumference, and blood albumin). At discharge from initial admittance to hospital, investigators recorded duration of stay and discharge destination (to institution or home).

The safety outcomes were all-cause case fatality and cause-specific case fatality; serious adverse events and serious adverse device-related events; and cases of chest infection or pneumonia (diagnosed locally because the diagnosis of chest infection and pneumonia is poorly defined).

A member of the central research team (S.H.), who was masked to treatment assignment, validated and categorized investigator-reported serious adverse events, including cause-specific deaths. Patients who did not receive their assigned treatment or who did not adhere to the protocol were followed up in full. The recruiting site, using a separate nontreating researcher who was masked to treatment allocation, did post-treatment follow-ups at 2, 6, and 12 weeks.

**Statistical Analyses**

The statistical analysis plan was published on the Phagenesis, Ltd, website before data lock and unblinding: http://www.phagenesis.com/wp-content/uploads/2012/09/Statistical-Analysis-Plan-STEPs.pdf (March 21, 2012). The trial was designed to recruit 140 patients so as to detect an absolute reduction in the change in PAS (mean of all swallows from all available bolus) from baseline to 2 weeks of 1.1 point (SD 1.8) between the treatment groups, with power 90%, 2-sided significance 5%, and allowance for incomplete data/losses to follow-up in 15% of patients. After analysis of individual patient data from 3 pilot studies, the primary analysis was changed to comparison between the treatment groups of the mean of the worst swallow in each of the 3 to 7 available bolus (with adjustment for the same at baseline, and no imputation of missing data) because this seemed to be more robust statistically and was felt to be clinically more relevant, a decision that was made before unblinding of data.

Four analysis populations were created: randomized, all those who were assigned to PES or sham treatment; safety, all randomized patients who had treatment attempt; that is, insertion of the treatment catheter with or without PES/sham; efficacy, all randomized patients who received at least 1 episode of PES/sham treatment and who had the primary outcome (PAS) measured at both baseline and 2 weeks; and per protocol, randomized patients who received all 3 treatments and who had PAS data measured at baseline and 2 weeks.

Swallowing was analyzed as a comparison between the treatment groups using multiple linear regression with adjustment of the on-treatment PAS for baseline PAS, stratification variables (site and feeding status), and prognostic baseline variables (age, sex, and NIHSS). Secondary analyses used multiple linear regression (continuous data, eg, EQ-5D), ordinal logistic regression (ordered categorical data, eg, mRS), binary logistic regression (dichotomous data, eg, PAS ≤3, serious adverse events, and chest infection), and Kaplan–Meier and Cox regression models (time to event, eg, death). 95% confidence intervals (CI) are presented, and P<0.05 was considered statistically significant. Analyses were performed using SAS version 9.3. Summary meta-analyses based on group data from Swallowing Treatment Using Pharyngeal Electrical Stimulation (STEPs) and earlier trials' were produced using the Cochrane Collaboration’s Review Manager software (version 5.3).

**Additional Information**

Further information on Materials and Methods is given in the online-only Data Supplement.

**Results**

Between April 2012 and September 2014, we consented 195 patients; screened 181 patients with VFS; assigned treatment in 162 patients (randomized population); attempted treatment in 152 patients (safety population); treated (with at least 1 session of PES or sham) 141 patients; and obtained VFS in 126 patients at 2 weeks (primary outcome population) and 95 patients at 12 weeks (Figure 1). The reduction in numbers between consent and randomization reflected patients who: screened negative for aspiration on VFS, could not have the catheter inserted, and did not have a VFS 2 weeks after treatment. The 162 randomized patients were recruited from 20 sites in 5 countries (Denmark, France, Germany, Spain, and United Kingdom, listed in the online-only Data Supplement); of these, 87 patients were assigned active PES and 75 patients were assigned to the sham group (Figure 1). Hundred and one patients (62.3%) were recruited from the United Kingdom. The randomized groups were well balanced at baseline (Table 1): mean age 74 (SD 11) years, 94 (58%) were male, and 143 (89%) patients had an ischemic stroke. The mean time from stroke to randomization was 13 (10) days. The Data Monitoring Committee reviewed the trial on 3 occasions and recommended that the trial should continue each time.

Adherence with assignment to active or sham PES was good in 141 participants who received at least 1 treatment session. There were no material differences at baseline in 15 treated participants who did not have VFS at 2 weeks versus 126 treated participants who did have VFS. No patients randomized to sham received active treatment, and all patients with a catheter inserted and randomized to PES received at least 1 active treatment session. The mean treatment stimulation level was 14.5 mA in those randomized to PES, with mean treatment duration 9.8 minutes and mean number of treatments 3.0 (Table 1 in the online-only Data Supplement). However, evidence of suboptimal treatment current levels seemed to be present: 58% of PES-treated patients had a treatment level <10.2 mA (a figure chosen from earlier research), identical treatment and threshold levels, or a treatment level less than threshold.

In the primary outcome population, the mean PAS at baseline was 4.8 (SD 2.0) and reduced in both active PES and sham PES groups at 2 weeks (Table 2). When adjusted for site, age, NIHSS, baseline feeding status, and PAS, there was no difference in PAS at 2 weeks, mean difference 0.14 (95% CI, −0.37 to 0.64; P=0.60; Table 2 and Figure 2); the mean change in PAS from baseline to 2 weeks did not differ between the 2 treatment groups: active PES −1.2 (1.8) versus sham PES −1.2 (1.8) and difference 0.14 (−0.37 to 0.64). Meta-analysis of individual patient data from earlier studies suggested that different approaches to statistical analysis varied in their statistical efficiency; in sensitivity analyses, PAS did not differ between the groups when assessed using different statistical
When assessed in prespecified subgroups, no significant interactions were present (Figure 2).

PES had no significant effects on secondary measures of swallowing and feeding, including radiological aspiration (PAS) at 12 weeks, and clinical dysphagia (DSRS) and feeding route at weeks 2 and 12 (Table 3; Table II in the online-only Data Supplement). Apparent tendencies in favor of PES were present at week 2 (but not at week 12) for functional measures of outcome (mRS and Barthel Index). Other measures did not differ between the treatment groups (Table 3; Table II in the online-only Data Supplement). When assessed in prespecified subgroups, significant interactions were present between clinical dysphagia (DSRS) and treatment assignment for age and PAS (Figure I in the online-only Data Supplement). The number of patients with chest infection or pneumonia occurring after randomization (and so possibly related to VFS rather than subsequent PES/sham treatment) did not differ between the treatment groups: PES 21, sham 11 (P = 0.19). The overall rate of serious adverse events occurring by end of follow-up did not differ between the 2 groups, and no serious adverse device-related events occurred in either group (Table III in the online-only Data Supplement). The cumulative risk of all-cause death during follow-up did not differ between the group given PES and the sham treatment (Figure II in the online-only Data Supplement).
Table 1. Baseline Characteristics in the Randomized Population by Treatment Assignment

<table>
<thead>
<tr>
<th></th>
<th>N Randomized</th>
<th>PES</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>162</td>
<td>162</td>
<td>87</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>15 (9.3)</td>
<td>9 (10.3)</td>
<td>6 (8.0)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (2.5)</td>
<td>0 (0.0)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>White</td>
<td>139 (85.8)</td>
<td>74 (85.1)</td>
<td>65 (86.7)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (2.5)</td>
<td>4 (4.6)</td>
<td>...</td>
</tr>
<tr>
<td>Modified Rankin Scale (/6)</td>
<td>4.0 (1.1)</td>
<td>3.9 (1.1)</td>
<td>4.1 (1.2)</td>
</tr>
<tr>
<td>Barthel Index (/100)</td>
<td>28.4 (29.8)</td>
<td>32.4 (31.7)</td>
<td>23.8 (26.8)</td>
</tr>
<tr>
<td>Stroke, previous (%)</td>
<td>162</td>
<td>23 (14.2)</td>
<td>15 (17.2)</td>
</tr>
<tr>
<td>Visible on imaging (%)</td>
<td>161</td>
<td>42 (26.1)</td>
<td>25 (28.7)</td>
</tr>
<tr>
<td>Stroke type (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic/normal</td>
<td>143 (88.8)</td>
<td>77 (89.5)</td>
<td>66 (88.0)</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>17 (10.6)</td>
<td>9 (10.5)</td>
<td>8 (10.7)</td>
</tr>
<tr>
<td>Nonstroke</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Side of CT lesion (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>63 (39.9)</td>
<td>33 (38.4)</td>
<td>30 (41.7)</td>
</tr>
<tr>
<td>Right</td>
<td>69 (43.7)</td>
<td>36 (41.9)</td>
<td>33 (45.8)</td>
</tr>
<tr>
<td>No lesion</td>
<td>26 (16.5)</td>
<td>17 (19.8)</td>
<td>9 (12.5)</td>
</tr>
<tr>
<td>Syndrome (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total anterior circulation</td>
<td>41 (26.1)</td>
<td>21 (24.4)</td>
<td>20 (28.2)</td>
</tr>
<tr>
<td>Partial anterior circulation</td>
<td>69 (43.9)</td>
<td>44 (51.2)</td>
<td>25 (35.2)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>46 (29.3)</td>
<td>21 (24.4)</td>
<td>25 (35.2)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Severity, NIHSS (/42)</td>
<td>152</td>
<td>9.9 (6.4)</td>
<td>9.6 (6.5)</td>
</tr>
<tr>
<td>Dysphasia, NIHSS (%)</td>
<td>152</td>
<td>55 (36.2)</td>
<td>29 (35.8)</td>
</tr>
<tr>
<td>Onset to randomization (days)</td>
<td>162</td>
<td>13.4 (9.7)</td>
<td>12.6 (9.5)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSRS (/12)</td>
<td>154</td>
<td>7.6 (3.8)</td>
<td>8.0 (3.9)</td>
</tr>
<tr>
<td>TOR-BSST, failed (%)</td>
<td>162</td>
<td>158 (97.5)</td>
<td>85 (97.7)</td>
</tr>
<tr>
<td>Feeding route (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral, normal diet</td>
<td>10 (6.2)</td>
<td>5 (5.7)</td>
<td>5 (6.7)</td>
</tr>
<tr>
<td>Oral, soft diet</td>
<td>45 (27.8)</td>
<td>23 (26.4)</td>
<td>22 (29.3)</td>
</tr>
<tr>
<td>Nasogastric</td>
<td>90 (55.6)</td>
<td>52 (59.8)</td>
<td>38 (50.7)</td>
</tr>
<tr>
<td>PEG</td>
<td>4 (2.5)</td>
<td>3 (3.4)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (8.0)</td>
<td>4 (4.6)</td>
<td>9 (12.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>153</td>
<td>71.9 (16.4)</td>
<td>71.9 (15.3)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>148</td>
<td>25.2 (5.0)</td>
<td>25.7 (4.8)</td>
</tr>
<tr>
<td>Mid-arm circumference (cm)</td>
<td>143</td>
<td>28.3 (3.6)</td>
<td>28.2 (3.7)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>144</td>
<td>36 (5.7)</td>
<td>36.4 (5.8)</td>
</tr>
<tr>
<td>Chest infection (%)</td>
<td>156</td>
<td>8 (5.1)</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Penetration aspiration scale (/8)</td>
<td>162</td>
<td>4.7 (2.0)</td>
<td>4.7 (2.1)</td>
</tr>
<tr>
<td>PAS &gt;2</td>
<td>162</td>
<td>148 (91.4)</td>
<td>79 (90.8)</td>
</tr>
</tbody>
</table>

Data are number (%), median (interquartile range), or mean (SD). CT indicates computed tomography; DSRS, dysphagia severity rating scale; NIHSS, National Institutes of Health Stroke Scale; PAS, penetration aspiration score; PEG, percutaneous endoscopic gastrostomy; and TOR-BSST, Toronto Bedside Swallowing Screening Test.
Discussion

In patients with dysphagia post stroke, PES had no significant effect on radiological aspiration or clinical dysphagia, assessed as PAS and dysphagia severity rating scale, respectively. Similarly, PES had no effect on dependency (mRS), disability (Barthel Index), or impairment (NIHSS). No safety issues were identified.

The explanation for these largely neutral results remains unclear but many possibilities need to be examined. First, PES may simply not be effective for treating dysphagia after stroke; however, passing the catheter was rated as difficult in one third of investigators (Table IV in the online-only Data Supplement).

In a summary meta-analysis of results from STEPS and earlier trials, there was no difference in PAS between patients randomized to PES versus sham (Figure III in the online-only Data Supplement). In contrast, PES was associated with a larger reduction (ie, improvement) in DSRS than patients randomized to sham, mean difference −0.94 (95% CI, −1.85 to −0.03; P=0.04; Figure IV in the online-only Data Supplement).

Table 2. PAS at 2 Weeks in the Efficacy Population by Treatment Assignment

<table>
<thead>
<tr>
<th></th>
<th>All (N=126)</th>
<th>PES (N=70)</th>
<th>Sham (N=56)</th>
<th>OR/MD (95% CI), Adjusted</th>
<th>PValue</th>
<th>OR/MD (95% CI), Unadjusted</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAS (/8)</td>
<td>4.8 (2.0)</td>
<td>4.8 (2.1)</td>
<td>4.7 (1.9)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>2 wk primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean of all boli (/8)</td>
<td>3.6 (2.0)</td>
<td>3.7 (2.0)</td>
<td>3.6 (1.9)</td>
<td>0.14 (−0.37 to 0.64)</td>
<td>0.60</td>
<td>0.06 (−0.62 to 0.74)</td>
<td>0.86</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−1.2 (1.8)</td>
<td>−1.2 (1.8)</td>
<td>−1.2 (1.8)</td>
<td>0.14 (−0.37 to 0.64)</td>
<td>0.60</td>
<td>0.00 (−0.62 to 0.61)</td>
<td>1.00</td>
</tr>
<tr>
<td>Any PAS &gt;3 (%)</td>
<td>105 (83.3)</td>
<td>60 (85.7)</td>
<td>45 (80.4)</td>
<td>1.22 (0.29 to 5.15)</td>
<td>0.79</td>
<td>1.47 (0.57 to 3.75)</td>
<td>0.42</td>
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<tr>
<td>12 wk</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean of all boli (/8)</td>
<td>3.2 (2.1)</td>
<td>3.3 (2.2)</td>
<td>3.0 (2.1)</td>
<td>0.29 (−0.04 to 0.99)</td>
<td>0.41</td>
<td>0.24 (−0.6 to 1.08)</td>
<td>0.57</td>
</tr>
<tr>
<td>Any PAS &gt;3 (%)</td>
<td>69 (72.6)</td>
<td>36 (70.6)</td>
<td>33 (75.0)</td>
<td>0.62 (0.20 to 1.90)</td>
<td>0.41</td>
<td>0.80 (0.32 to 1.99)</td>
<td>0.63</td>
</tr>
<tr>
<td>Repeated measures</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Mean (/8)*</td>
<td>...</td>
<td>4.1 (2.3)</td>
<td>3.9 (2.3)</td>
<td>0.51 (−0.23 to 1.25)</td>
<td>0.18</td>
<td>0.19 (−0.67 to 1.04)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

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. CI indicates confidence interval; MD, mean difference; OR, odds ratio; PAS, penetration aspiration score; and PES, pharyngeal electric stimulation.

*Includes death: PAS=9.

Limited recruitment to patients who could provide consent for themselves, and this resulted in inclusion of patients with only milder stroke and aspiration, a decision that would challenge demonstrating efficacy for many interventions. Although the mean baseline PAS in STEPS (PAS=4.8) was similar to previous stroke trials of PES (4.3); Table V in the online-only Data Supplement), it was lower than in a positive trial in multiple sclerosis (PAS=6.5). Of relevance, patients randomized to sham in the earlier studies tended to have minimal or no overall improvement in PAS or DSRS, whereas sham patients in STEPS showed improvement (Table V in the online-only Data Supplement). Con founding this point is the potential relevance of VFS to the diagnosis of dysphagia and its severity; particu larly, PAS scores were noted to be highly variable during administration of contrast boli. Additionally, VFS was not readily available at many sites thereby limiting recruitment. We chose PAS (using thin boli) as a primary outcome measure based on previous pilot studies which showed a significant improvement in this measure in the active PES arm but recognize that PAS alone does not capture information about swallowing efficiency and bolus control as might come from using thick liquid boli and measures of pharyngeal residue/timings.

Third, and related to the issue of severity and spontaneous resolution, patients who are enrolled early after stroke will comprise a mixed group of those with severe dysphagia and those with milder dysphagia that will improve without treatment. However, later recruitment will enhance the proportion of patients with severe (or fixed) dysphagia. In reality, STEPS and earlier trials each recruited patients at ≥2 weeks poststroke.

Fourth, participants received variable amounts of therapeutic stimulation levels because mean levels were lower in STEPS (mean treatment 14.8 mA) than in previous positive

Table 2. PAS at 2 Weeks in the Efficacy Population by Treatment Assignment

<table>
<thead>
<tr>
<th></th>
<th>All (N=126)</th>
<th>PES (N=70)</th>
<th>Sham (N=56)</th>
<th>OR/MD (95% CI), Adjusted</th>
<th>PValue</th>
<th>OR/MD (95% CI), Unadjusted</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>PAS (/8)</td>
<td>4.8 (2.0)</td>
<td>4.8 (2.1)</td>
<td>4.7 (1.9)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<tr>
<td>2 wk primary outcome</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean of all boli (/8)</td>
<td>3.6 (2.0)</td>
<td>3.7 (2.0)</td>
<td>3.6 (1.9)</td>
<td>0.14 (−0.37 to 0.64)</td>
<td>0.60</td>
<td>0.06 (−0.62 to 0.74)</td>
<td>0.86</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−1.2 (1.8)</td>
<td>−1.2 (1.8)</td>
<td>−1.2 (1.8)</td>
<td>0.14 (−0.37 to 0.64)</td>
<td>0.60</td>
<td>0.00 (−0.62 to 0.61)</td>
<td>1.00</td>
</tr>
<tr>
<td>Any PAS &gt;3 (%)</td>
<td>105 (83.3)</td>
<td>60 (85.7)</td>
<td>45 (80.4)</td>
<td>1.22 (0.29 to 5.15)</td>
<td>0.79</td>
<td>1.47 (0.57 to 3.75)</td>
<td>0.42</td>
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<tr>
<td>12 wk</td>
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<tr>
<td>Repeated measures</td>
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*Includes death: PAS=9.
trials in stroke (16.8 mA). Using a treatment level of <10.2 mA (mean − 1 SD in previous trials) or treatment threshold level ≤0 mA, 58% of participants randomized to PES may have been undertreated. Importantly, the magnitude of stimulation has been shown previously to be associated with improvement in aspiration. Investigator concerns about the potential to harm patients seem to have explained this situation, although the study showed no evidence of harm, and PES may be delivered safely up to 50 mA (the maximum that can be delivered by the base station), as shown in another study in patients with stroke. And last, assessment of threshold and tolerance levels in patients randomized to sham PES may have amounted to an element of stimulation. For example, a participant randomized to sham but who had high threshold and tolerance currents

Figure 2. Effect of treatment on penetration aspiration score in prespecified subgroups determined at baseline, with analysis using adjusted multiple linear regression. CL indicates confidence limit; DSRS, dysphagia severity rating scale; LACS, lacunar circulation syndrome; MD, mean difference; NIHSS, National Institutes of Health Stroke Scale; PACS, partial anterior circulation syndrome; PAS, penetration aspiration score; PES, pharyngeal electric stimulation; and TACS, total anterior circulation syndrome.
will have received a potentially therapeutic form of stimulation for 10 to 20 minutes (as compared with the 30+ minutes that patients randomized to active treatment receive). These potential explanations for the STEPS results have implications for the design of future trials of PES (and, indeed, other device trials) and training of investigators.

STEPS has several strengths, including the large sample size relative to previous studies of PES; generalizability because of wide inclusion criteria with both ischemic and hemorrhagic stroke, cortical, lacunar, and posterior syndromes, and a wide time window; recruitment from multiple countries in Europe; central concealment of treatment assignment; prospective collection of multiple aspiration, dysphagia, functional, and safety outcomes; and quality care in stroke units.

However, several limitations are also present. First, 195 patients were consented, 162 patients randomized but only 126 received at least 1 treatment session and had both a baseline and on-treatment PAS. Several factors explain this dropout, including withdrawal of consent and failure of insertion of the treatment catheter (Figure 1). A protocol amendment required that the treatment catheter had to be inserted before, and not after, randomization to reduce losses of patients who were randomized but could not be treated. Second, PES was delivered in 141 patients but 15 could not have VFS performed at both baseline and week 2 thereby excluding them from the primary analysis. Third, PES was given in a single-blind design with the patient but not treating person masked to stimulation. Some patients receiving active PES may have been aware of stimulation, whereas patients randomized to sham PES may have been aware of stimulation during threshold testing and possibly noticed that this was absent during the treatment sessions. Nevertheless, clinical outcomes measured at 2, 6, and 12 weeks were assessed by trained staff who were masked to treatment assignment and who were not involved in hospital care of enrolled patients. Furthermore, VFS images were adjudicated by radiologists or speech therapists who were similarly masked to randomized group.

In conclusion, we found that PES did not reduce radiological aspiration or clinical dysphagia. This result differs from a positive meta-analysis of previous small trials of PES in post-stroke dysphagia12 and may result from several factors, including enrollment of patients with mild dysphagia, potential undertreatment with PES, and possible active stimulation of control patients. In view of this discrepancy, and the potential risk of overestimating treatment effect from smaller studies, further studies are planned in stroke patients with severe dysphagia or those requiring intensive care including ventilation.

Acknowledgments
We thank the investigators and research staff at the participating sites for their support and acknowledge the support of the UK National Institute for Health Research, through the Stroke Research Network. P.M. Bath is Stroke Association Professor of Stroke Medicine.

<table>
<thead>
<tr>
<th>Table 3. Clinical and Safety Outcomes by Treatment Assignment in Patients Who Received At Least 1 Active or Sham Treatment and Who Had Outcome Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>2 wk</td>
</tr>
<tr>
<td>DSRS (/12)*</td>
</tr>
<tr>
<td>NIHSS (/42)*</td>
</tr>
<tr>
<td>mRS (/6)*</td>
</tr>
<tr>
<td>BI (/100)*</td>
</tr>
<tr>
<td>Death (%)</td>
</tr>
<tr>
<td>12 wk</td>
</tr>
<tr>
<td>DSRS (/12)*</td>
</tr>
<tr>
<td>EQ-5D as HUS (/1)*</td>
</tr>
<tr>
<td>EQ-VAS*</td>
</tr>
<tr>
<td>Disposition (%)</td>
</tr>
<tr>
<td>Home</td>
</tr>
<tr>
<td>Institution</td>
</tr>
<tr>
<td>Died</td>
</tr>
<tr>
<td>Time to event</td>
</tr>
<tr>
<td>Death (%)</td>
</tr>
</tbody>
</table>

Bi indicates 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.

*Includes death: NIHSS=43, DSRS=13, mRS=6, Bi=−5, and HUS=0.
Sources of Funding
The trial was sponsored and funded by Phagenesis, Ltd (Manchester, UK).

Disclosures
P.M. Bath received honoraria for work as the Chief Investigator and for consultancy. S. Hamdy is the inventor of PES and has stock in Phagenesis. J. Love was an employee of Phagenesis. Institutions using P. M. Bath, D. Cohen, H.K. Iversen, R. Dziewas, W. Woisard, and P. Clavé received per-patient fees for recruitment. P.M. Bath, P. Scutt, D. Cohen, H.K. Iversen, R. Dziewas, and W. Woisard received travel expenses for attending meetings. The other authors report no conflicts.

References
Pharyngeal Electrical Stimulation for Treatment of Dysphagia in Subacute Stroke: A Randomized Controlled Trial


on behalf of the Swallowing Treatment Using Pharyngeal Electrical Stimulation (STEPS) Trial Investigators

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SUPPLEMENTAL MATERIAL

Title
Pharyngeal electrical stimulation for treatment of dysphagia in subacute stroke: a randomised controlled trial (ISRCTN25681641)

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By country (number of randomising sites, participants) and sites (number of randomised participants): Principal Investigator, other Investigators †National Coordinator

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- Northwick Park (37): D Cohen, S Ackford, R Bathula, L Burgess, R Cave, C Cawley, S Condie, C Cowley, J Devine, M Macfarlane, M Mpelembue, E Tweedie, D Wood
- Stoke-on-Trent (15): A Warusevitane, A Barry, J Bee, C Bradbury, J Chenbala, L Dale, P Ferdinand, K Finney, J Grocott, J Hiden, J Lucas, S Lyjko, H Maguire, I Natarajan, M Richardson, C Roffe, R Sanyal, J Weerathunga
- Truro (2): F Harrington, K Adie, G Courtauld, D Gomes, A James, L Lucas, A Mate, P O'Brien, C Schofield, J Skewes, J Wright
- Wolverhampton (3): K Fotherby, N Ahmad, D Butler, C Cresswell, M Haley, K Jennings-Preecee, F Lewis, D Morgan

Authors’ contribution
All authors contributed to the interpretation of the results and writing of this report. As Chief Investigator, PMB prepared the protocol, supervised and reviewed the progress of the trial, recruited patients, and wrote the first draft of this report. JL prepared the protocol, and supervised and reviewed the progress of the trial.
Members of the writing committee supervised and reviewed the progress of the trial, and commented on the draft of this report. PS analysed trial data and commented on a draft of this report. All members of the writing committee have seen and approved the final version of this report.

**Declaration of Interests**
The trial was sponsored and funded by Phagenesis Ltd. PB received honoraria for work as the CI and for consultancy. SH is the inventor of PES, and has stock in Phagenesis. JL was an employee of Phagenesis. Institutions employing PB, DC, HKI, RD, VW, and PC received per patient fees for recruitment. PB, PS, DC, HKI, RD, and VW received travel expenses for attending meetings.

**Acknowledgments**
This trial was funded by Phagenesis Ltd. We thank the investigators and research staff at the participating sites for their support, and acknowledge the support of the UK National Institute for Health Research, through the Stroke Research Network; recruitment in the UK would not have been possible without network support. PMB is Stroke Association Professor of Stroke Medicine.

**SUPPLEMENTAL METHODS**

**Training of Investigators**
All STEPS investigators were trained in the protocol, Good Clinical Practice, and use of the National Institutes of Health Stroke Scale, modified Rankin Scale (mRS) and Barthel Index. Investigators who delivered PES were trained in the technique.

**Schedule for Monitoring of Sites and Data Integrity**
Site monitoring was performed by trained Clinical research Associates who worked for Phagenesis Ltd or a delegated organisation. Their aim was to ensure quality control for the delivery of the protocol, collection of data and adherence with national regulations and ethics. Each recruiting site had a start-up visit for training, a monitoring visit after recruitment of the first patient, and a close-down visit; further visits were performed as deemed necessary by the Company. Monitoring visits confirmed the presence of the participant and their consent, eligibility criteria, 100% of data, and reporting of serious adverse events.

Central statistical monitoring of the data was performed according to Buyse *et al*\(^1\) prior to locking of the data. Checks included logic and range checks, and digit preference. The monitoring procedures were compliant with the requirements of the sponsor, the national ethics committees and regulatory authorities in the participating countries, and fulfilled Good Clinical Practice requirements.

**Sample Size Considerations**
The primary endpoint for the study was change in mean penetration-aspiration scores (PAS) on the videofluoroscopy protocol, 2 weeks after treatment. The sample size was based on data gained from a phase II sham-controlled study.\(^2\) In this study, the mean values of the change in mean PAS in the two randomised groups of sizes 16 and 12 were -1.4 and -0.1, giving an observed treatment effect of 1.3. The standard deviations in each group were 1.9 and 1.5 respectively. The distributions of values in each group were approximately normal, with standard deviation of 1.8.
Sixty patients in each group would provide 90% power to detect a difference of approximately 1.1 in the change in mean PAS, based on comparison of change in mean PAS between the two groups using a 2 sided t test, with alpha = 5%. The investigation was expected to provide higher power than this because the primary endpoint was adjusted for severity at baseline. To account for the loss of information caused by the potential for less than six swallows being available for every patient, and to account for patients dropping out before the two-week assessment, the sample size was increased by approximately 30%.

Therefore, 160 patients should be randomised in a 1:1 ratio between the treatment groups, this allowing for a one-in-six attrition rate at 2 weeks.

**Independent Data Monitoring Committee (IDMC)**
The IDMC was responsible for safeguarding the interests of trial patients, assessing the safety and efficacy of the intervention during the trial, assessing data integrity, and for monitoring the overall conduct of the trial. The IDMC *modus operandi* was defined in a charter. The IDMC reviewed the recruitment of patients, and assessed safety and efficacy measures by treatment group. The trial was reviewed on three occasions during the trial’s recruitment period. The DMC was charged with informing the Trial Steering Committee if, at any time, the data showed evidence beyond reasonable doubt of a difference between the randomised groups in the primary outcome or for death. They also considered these data in the light of external information such as results from completed trials. One formal interim analysis was performed after 60 participants had been enrolled and completed the 2-week assessments. However, the DMC could perform statistical comparisons as they deemed necessary, with stopping criteria based on the Haybittle-Peto stopping rule (i.e. a difference of 3 standard errors is considered as clear evidence of a treatment effect). The study was not terminated early.

**Inclusion and Exclusion Criteria**

*Screening Inclusion Criteria*
- Subject is over 18 years of age
- Subject is suspected of having dysphagia
- Subject is able to comply with videofluoroscopy protocol
- Subject diagnosed with stroke, whether anterior or posterior circulation
- Subject has no previous history of dysphagia
- Subjects who are able to give voluntary, written informed consent to participate in the clinical investigation and from whom consent has been obtained/ or a consultee has consented on the subjects behalf in line with nationally agreed guidelines concerning adults unable to consent for themselves.
- Subject is not currently participating in any other interventional clinical study
- Subject is able to comply with CIP requirements
- Subject scores 0 or 1 on questions 1a of NIHSS

*Randomisation Inclusion Criteria (post consent)*
- Subject has confirmed dysphagia (PAS of 3 or more on VFS screening protocol)

*Exclusion Criteria*
- Subject stroke event was more than 42 days ago
- Subject is pregnant or a nursing mother
- Subject, in the opinion of the investigator, has advanced dementia
- Subject fitted with a pacemaker or implantable cardiac defibrillator
• Subject has unstable cardiopulmonary status (e.g. severe emphysema, heart failure)
• Subject has distorted oropharyngeal anatomy (e.g., pharyngeal pouch)
• Subject is dysphagic from conditions other than stroke
• Subject has been diagnosed with a progressive neurological disorder (e.g. Parkinson’s disease, Multiple Sclerosis)
• Subject has a chronic medical condition that compromises cardiac or respiratory status (e.g. severe emphysema or heart failure that may render the insertion of the throat unsafe)
• Subject is receiving continuous oxygen treatment or the equipment for this is in place.

Patients in intensive therapy unit, whether intubated or not, were not included since many would require oxygen treatment.

Procedure for Videofluoroscopy (VFS, modified barium swallow)
VFS was performed by a trained and qualified speech & language therapist or radiologist; they had to comply with the STEPS VFS protocol and ‘stop’ criteria. A common VFS protocol was used across all participating sites. Strict adherence is required to this VFS protocol and the criteria to ‘stop’ the procedure as defined below.

Preparation
• The subject must remain nil by mouth for 60 minutes prior to the research VFS.
• The person delivering treatment/sham must not be present during the VFS.
• Capture a ‘test frame’ using the x-ray equipment to ensure all data will be captured.
• Ensure VFS study data is anonymised.
• Ensure use of lead numbers or annotation throughout the VFS to identify each trial clearly to the independent VFS analysers.
• Ensure use of the suprahyoid marker throughout the VFS procedure.
• Ensure the full swallow is recorded in a lateral view using continuous/25 or 30 frames per second screening, throughout.
• Ensure correct positioning of the subject throughout i.e. seat upright with a neutral head position.
• Ensure no use of swallowing strategies throughout e.g. head turns.

Specified Contrast Media
• The low osmolarity contrast media solution specified by Phagenesis will be used as the radiopaque contrast media during the STEPS VFS procedure.
• All volumes of contrast media will be measured accurately using a syringe.

VFS Protocol (see also appendix M):
• 6 trials of 5ml contrast media will be given to the subject from a small green Kapitex cup.
• Subjects will be asked to pour all of the contrast media into their mouth and then asked to swallow.
• 50ml contrast media will then be given in a ‘normal’ beaker and the subject asked to drink this sequentially.

Criteria to Stop the STEPS VFS Protocol:
Stop the VFS procedure immediately if any of the following occur:
Stage 1 (5ml trials)
• A PAS of 7 or 8 on 3 consecutive bolus trials.
Stage 2 (50ml trial)
• PAS score of 7 or 8 on 3 consecutive swallows.
• Initial occurrence of aspiration of more than 50% of the total bolus.

A ‘Stop’ may also be applied if 3 bolus trials have been complete and in the opinion of the staff conducting the VFS, the subject is unusually or unreasonably distressed, or if the subject becomes too unwell to continue.

A ‘Stop’ will NOT exclude the subject from the study.

VFS staff are asked to carry out the following actions in the event of the use of the stop criteria and/or significant aspiration.
• Prompt the subject to cough
• Prompt the subject to cough and swallow
• Refer the subject for chest physiotherapy as per local practice
• Arrange for the subject to be monitored over the next 24 hours as per local practice

The VFS images will be analysed off line by an independent panel of specialist SALTs who will respond with confirmation of the need for randomisation within 24 hours of screening VFS submission.

Outcome scales

**Penetration aspiration scale**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description on videofluoroscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Material does not enter airway</td>
</tr>
<tr>
<td>2</td>
<td>Material enters airway. Remains above vocal cords &amp; is ejected from airway</td>
</tr>
<tr>
<td>3</td>
<td>Material is above vocal cords &amp; is not ejected from airway</td>
</tr>
<tr>
<td>4</td>
<td>Material enters airway, contacts vocal cords &amp; ejected from airway</td>
</tr>
<tr>
<td>5</td>
<td>Material contacts the vocal cords &amp; is not ejected from airway</td>
</tr>
<tr>
<td>6</td>
<td>Material passes below the vocal cords &amp; is ejected into larynx or out of airway</td>
</tr>
<tr>
<td>7</td>
<td>Material passes below the vocal cords &amp; is not ejected from the trachea despite effort</td>
</tr>
<tr>
<td>8</td>
<td>Material enters airway, passes below the vocal cords &amp; no effort is made to eject the material</td>
</tr>
</tbody>
</table>

**Dysphagia severity rating scale (DSRS)**

DSRS is a derivative of the dysphagia outcome and severity scale.

<table>
<thead>
<tr>
<th>Score</th>
<th>Fluids</th>
<th>Score</th>
<th>Diet</th>
<th>Score</th>
<th>Supervision</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>No oral fluids</td>
<td>4</td>
<td>Non oral feeding</td>
<td>4</td>
<td>No oral feeding</td>
</tr>
<tr>
<td>3</td>
<td>Pudding consistency</td>
<td>3</td>
<td>Puree</td>
<td>3</td>
<td>Therapeutic feeding (SALT/trained staff)</td>
</tr>
<tr>
<td>2</td>
<td>Custard consistency</td>
<td>2</td>
<td>Soft, moist diet</td>
<td>2</td>
<td>Feeding by third party (untrained)</td>
</tr>
<tr>
<td>1</td>
<td>Syrup consistency</td>
<td>1</td>
<td>Selected textures</td>
<td>1</td>
<td>Eating with supervision</td>
</tr>
<tr>
<td>----</td>
<td>------------------</td>
<td>----</td>
<td>-------------------</td>
<td>----</td>
<td>-------------------------</td>
</tr>
<tr>
<td>0</td>
<td>Normal fluids</td>
<td>0</td>
<td>Normal</td>
<td>0</td>
<td>Eating independently</td>
</tr>
</tbody>
</table>

**Statistics**
Since a treatment could, in principle, be associated both with improved outcome and death, a sensitivity analysis was performed with death assigned a score one worse than the worst possible PAS (death = 9) and DSRS (13) scores; this is analogous to the mRS and EQ-5D-HUS which both include death in their scores (6 and 0 respectively).

**Role of the funding source**
The trial was overseen by the Chief Investigator (PB), PES Inventor (SH), and Trial Manager (JL), and run by the Trial Management Committee (PMB, SH, CM, JL), this including senior representatives of the funding and sponsoring company, Phagenesis Ltd (CM, JL). Sites received regular monitoring with 100% data verification. Data were collected using a commercial database (Rave, Medidata Solutions Inc.). Analyses were performed by PS at the University of Nottingham (PS). Interpretation and report writing were performed by the Trial Management Committee and National Coordinating Investigators. The corresponding author and another author (statistician PS) had full access to all the data in the study; additionally, the corresponding author had final responsibility for the decision to submit for publication, and is the guarantor for the study.
### Amendments to clinical investigation

<table>
<thead>
<tr>
<th>Version: date</th>
<th>Reason for Amendment</th>
<th>Countries affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final: 15/11/2011</td>
<td>Not actively used by sites – see amendment 1</td>
<td>France, UK</td>
</tr>
</tbody>
</table>
| 1: 30/1/2012 | • At request of UK REC - to include statement that clinical decision would take precedent  
• Clarify what will happen to data after 15 years | France, UK |
| 2: 19/9/2012 | Non-substantial amendment:  
• Amendment to statement of conformity as now CE marked device.  
• Addition to the secondary objectives  
• Increased length of investigation to 18 months  
• Removed minimum and maximum site recruitment numbers  
• Increase in the number of sites  
• Clarification on treatment of patients according to local best clinical practice  
• Clarification of wording for VFS procedure  
Substantial amendment:  
• Addition to the secondary endpoints  
• Amendment to consent process at investigational sites in Germany  
• Addition of code-break procedure  
• Addition of safety reporting responsibilities | Denmark, France, Germany, Spain, UK |
| 3: 6/6/2013 | Non-substantial amendment:  
• Increased length of investigation  
• Increased number if investigation sites  
• Informed consent in non-UK sites to follow local practice and in line with country approvals. | Denmark, France, Germany, Spain, UK |
| 4: 21/1/2014 | Non-substantial amendment:  
• Increased length of investigation  
• Increased number of subjects from 140 to 160  
• Clarify target population  
• Clarify speech & language therapist plan | Denmark, France, Germany, Spain, UK |

VFS: videofluoroscopy
SUPPLEMENTAL TABLES

**Supplementary Table I.** Treatment dose and tolerance in 141 participants who received at least one treatment session. Treatment level is that actually received by patients randomised to pharyngeal electrical stimulation, or what patients randomised to sham would have received if actively treated.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>PES</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>141</td>
<td>78</td>
<td>63</td>
</tr>
<tr>
<td>Number of treatments</td>
<td>414</td>
<td>233</td>
<td>181</td>
</tr>
<tr>
<td>No. of treatments per patient</td>
<td>2.9</td>
<td>3.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Threshold level (mA)</td>
<td>9.5 (6.2)</td>
<td>8.9 (5.1)</td>
<td>10.3 (7.4)</td>
</tr>
<tr>
<td>Range</td>
<td>1, 47</td>
<td>1, 30</td>
<td>1, 47</td>
</tr>
<tr>
<td>Tolerance level (mA)</td>
<td>16.9 (9.2)</td>
<td>16.7 (8.9)</td>
<td>17.3 (9.7)</td>
</tr>
<tr>
<td>Range</td>
<td>3, 50</td>
<td>4, 50</td>
<td>3, 50</td>
</tr>
<tr>
<td>Treatment level (mA)</td>
<td>14.8 (7.9)</td>
<td>14.5 (7.5)</td>
<td>15.1 (8.3)</td>
</tr>
<tr>
<td>Range</td>
<td>2, 50</td>
<td>2, 45</td>
<td>2, 50</td>
</tr>
<tr>
<td>Treatment – threshold (mA)</td>
<td>5.3 (5.3)</td>
<td>5.6 (5.6)</td>
<td>4.9 (5.0)</td>
</tr>
<tr>
<td>Range</td>
<td>-17, 27</td>
<td>-2, 27</td>
<td>-17, 26</td>
</tr>
<tr>
<td>Duration (minutes)</td>
<td>9.9 (1.2)</td>
<td>9.8 (1.4)</td>
<td>10.0 (0.7)</td>
</tr>
<tr>
<td>Range</td>
<td>0, 10</td>
<td>0, 10</td>
<td>0.2, 10</td>
</tr>
<tr>
<td>Undertreated (%) †</td>
<td>85 (60.7)</td>
<td>45 (58.4)</td>
<td>40 (63.5)</td>
</tr>
</tbody>
</table>

† Under-treatment is defined as patients with treatment <7.3 mA (mean - 1 standard deviation 5) or treatment-threshold level <= 0 mA.
Supplementary Table II. Penetration aspiration score (PAS), clinical and safety outcomes by treatment assignment (intention-to-treat) in patients who received at least one active or sham treatment and who had outcome measured. Data are number (%), median [interquartile range], or mean (standard deviation). Comparisons using multiple linear regression, ordinal logistic regression, Cox regression or binary logistic regression. Analyses were adjusted for site, age, NIHSS, feeding status, baseline PAS and baseline value; or unadjusted.

<table>
<thead>
<tr>
<th>PAS sensitivity analyses</th>
<th>N</th>
<th>All (median [IQR])</th>
<th>PES (median [IQR])</th>
<th>Sham (median [IQR])</th>
<th>OR/HR/MD adjusted</th>
<th>OR/HR/MD unadjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of all bolus (/9) †</td>
<td>126</td>
<td>3.7 (2.1)</td>
<td>3.7 (2.1)</td>
<td>3.7 (2.0)</td>
<td>0.24 (-0.32, 0.79)</td>
<td>0.40 (-0.67, 0.75)</td>
</tr>
<tr>
<td>Change ‡</td>
<td>123</td>
<td>-1.1 (1.8)</td>
<td>-1.2 (1.8)</td>
<td>-1.1 (1.8)</td>
<td>0.05 (-0.45, 0.54)</td>
<td>0.86 (-0.67, 0.58)</td>
</tr>
<tr>
<td>Mean of all swallows (/8)</td>
<td>126</td>
<td>3.2 (1.8)</td>
<td>3.1 (1.8)</td>
<td>3.2 (1.8)</td>
<td>0.08 (-0.35, 0.50)</td>
<td>0.73 (-0.70, 0.55)</td>
</tr>
<tr>
<td>Mean number of swallows</td>
<td>126</td>
<td>16.2 (8.7)</td>
<td>16.4 (9.9)</td>
<td>16.0 (7.0)</td>
<td>-0.23 (-2.66, 2.21)</td>
<td>0.86 (-2.62, 3.47)</td>
</tr>
<tr>
<td>Mean of first 3 bolus (/8)</td>
<td>126</td>
<td>3.1 (2.2)</td>
<td>3.1 (2.2)</td>
<td>3.1 (2.2)</td>
<td>0.32 (-0.29, 0.92)</td>
<td>0.31 (-0.74, 0.79)</td>
</tr>
<tr>
<td>% of bolus &gt;3</td>
<td></td>
<td>40.0 (31.7)</td>
<td>39.6 (31.8)</td>
<td>40.4 (31.7)</td>
<td>3.47 (-8.14, 15.07)</td>
<td>0.89 (-2.66, 3.47)</td>
</tr>
<tr>
<td>Worst score (/8)</td>
<td>126</td>
<td>8 [5, 8]</td>
<td>8 [6, 8]</td>
<td>8 [4.5, 8]</td>
<td>1.99 (0.83, 4.78)</td>
<td>0.12 (0.84, 3.35)</td>
</tr>
</tbody>
</table>

2 weeks

| TOR-B SST, failed (%)                        | 127| 113 (89.0)         | 62 (88.6)          | 51 (89.5)          | 0.67 (0.08, 5.39)  | 0.71 (0.30, 2.80)   |
| Feeding (%)                                  | 132| 27 (20.5)          | 17 (23.3)          | 10 (16.9)          | 2.07 (0.97, 4.39)  | 0.059 (0.77, 2.63)  |
| Oral, normal food                            | 44 (33.3) | 16 (21.9) | 28 (47.5)          |                   | 0.26 (0.08, 0.72)  | 0.71 (0.30, 2.80)   |
| Oral, soft diet                              | 31 (23.5) | 21 (28.8) | 10 (16.9)          |                   | 0.30 (0.13, 0.69)  | 0.43 (0.20, 0.87)   |
| Nasogastric tube                              | 11 (8.3)  | 7 (9.6)           | 4 (6.8)            |                   | 0.36 (0.17, 0.75)  | 0.43 (0.20, 0.87)   |
| PEG                                          | 19 (14.4) | 12 (16.4) | 7 (11.9)           |                   | 0.16 (-0.16, 0.48) | 0.16 (-0.16, 0.48)  |
| Weight (kg)                                  | 129| 71.2 (15.3)        | 71.0 (14.7)        | 71.4 (16.1)        | -0.67 (-0.72, 1.69)| 0.43 (-0.34, 5.63)  |
| BMI (kg/m²)                                  | 127| 25.0 (4.8)         | 25.4 (4.4)         | 24.4 (5.1)         | 0.32 (-0.20, 0.66) | 0.29 (0.40, 2.29)   |
| MAC (m)                                      | 129| 28.4 (4.2)         | 28.3 (3.7)         | 28.5 (4.8)         | 0.20 (-0.72, 1.11) | 0.68 (-1.66, 1.22)  |
| Albumin (g/l)                                | 105| 36.8 (5.3)         | 37.0 (5.7)         | 36.6 (4.8)         | -0.16 (-1.39, 0.98) | 0.80 (-1.70, 2.44)  |

12 weeks

<p>| TOR-B SST, failed (%)                        | 103| 75 (72.8)          | 42 (72.4)          | 33 (73.3)          | 0.88 (0.17, 4.41)  | 0.87 (0.40, 2.29)   |
| HADS (/42)                                   | 92 | 11.5 (7.4)         | 11.0 (6.7)         | 12.1 (8.2)         | 1.80 (-0.97, 4.58) | 0.20 (-4.07, 1.93)  |
| Weight (kg)                                  | 101| 73 (14.9)          | 72.1              | 74.1              | 0.56 (-1.02, 2.14) | 0.49 (-1.97, 7.80)  |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>(14.3)</th>
<th>(15.8)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>98</td>
<td>25.5 (4.6)</td>
<td>25.6 (4.2)</td>
<td>25.4 (5.0)</td>
<td>0.37 (-0.19, 0.94)</td>
<td>0.20</td>
<td>0.25 (-1.56, 2.06)</td>
<td>0.79</td>
</tr>
<tr>
<td>MAC (m)</td>
<td>104</td>
<td>28.3 (3.6)</td>
<td>27.9 (3.5)</td>
<td>28.7 (3.7)</td>
<td>-0.05 (-0.83, 0.72)</td>
<td>0.89</td>
<td>-0.79 (-2.18, 0.60)</td>
<td>0.27</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>62</td>
<td>41.4 (5.2)</td>
<td>41.7 (4.6)</td>
<td>41.1 (6.0)</td>
<td>-0.28 (-1.83, 1.27)</td>
<td>0.73</td>
<td>0.63 (-1.96, 3.23)</td>
<td>0.63</td>
</tr>
<tr>
<td>Disposition (%)</td>
<td>141</td>
<td>30 (21.3)</td>
<td>20 (25.6)</td>
<td>10 (15.9)</td>
<td>0.66 (0.30, 1.49)</td>
<td>0.32</td>
<td>0.63 (0.31, 1.26)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

† Includes death: PAS=9; ‡ All treatments received (N=123)

BMI: body mass index; MAC: mid arm circumference; TOR-BSST: Toronto Bedside Swallowing Screening Test
**Supplementary Table III.** Participants in the safety population (N=152) with one or more serious adverse events (SAE) up to 12 weeks; no serious adverse device effects (SADE) occurred. Data are number (%) for total and fatal events. Comparison by unadjusted binary logistic regression.

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

By 2 weeks, SAE rates were: Total 13 (9.2%), PES 7 (9.0%), Sham 6 (9.5%) (2p=0.91)
No SAEs were recorded as probable or possibly related to treatment
No Serious Adverse Device Effects (SADE) were recorded
**Supplementary Table IV.** Treatment operator assessment of ease of use of device in 162 randomised patients across both treatment groups. Data are numbers of patients (%).

<table>
<thead>
<tr>
<th></th>
<th>Difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provision of treatment</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Meet infection control guidelines</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Placement of catheter</td>
<td>10 (7.5)</td>
</tr>
<tr>
<td>Passing catheter (as NGT)</td>
<td>44 (33.1)</td>
</tr>
<tr>
<td>Secure catheter</td>
<td>19 (14.3)</td>
</tr>
<tr>
<td>Training to deliver treatment</td>
<td>3 (2.7)</td>
</tr>
</tbody>
</table>
**Supplementary Table V.** Penetration aspiration score (PAS) and dysphagia severity rating scale (DSRS) before and after treatment in the active and sham groups in four trials of pharyngeal electrical stimulation. Patients with both baseline and 2 week mean PAS are included. Data are unadjusted PAS and DSRS mean scores or differences.

<table>
<thead>
<tr>
<th>Group</th>
<th>Timing</th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
<th>STEPS</th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
<th>STEPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>Before</td>
<td>4.8</td>
<td>4.6</td>
<td>4.5</td>
<td>4.8</td>
<td>ND</td>
<td>6.4</td>
<td>7.8</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>3.7</td>
<td>3.2</td>
<td>2.6</td>
<td>3.6</td>
<td>ND</td>
<td>2.5</td>
<td>4.4</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>Δ</td>
<td>-1.0</td>
<td>-1.4</td>
<td>-1.9</td>
<td>-1.1</td>
<td>ND</td>
<td>-3.9</td>
<td>-3.4</td>
<td>-2.7</td>
</tr>
<tr>
<td>Sham</td>
<td>Before</td>
<td>4.3</td>
<td>3.9</td>
<td>3.9</td>
<td>4.7</td>
<td>ND</td>
<td>5.6</td>
<td>6.8</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>4.8</td>
<td>3.8</td>
<td>4.3</td>
<td>3.6</td>
<td>ND</td>
<td>4.8</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>Δ</td>
<td>+0.5</td>
<td>-0.1</td>
<td>+0.4</td>
<td>-1.1</td>
<td>ND</td>
<td>-0.8</td>
<td>-1.8</td>
<td>-2</td>
</tr>
<tr>
<td>Active-sham</td>
<td>Δ</td>
<td>-1.5</td>
<td>-1.3</td>
<td>-2.3</td>
<td>0</td>
<td>ND</td>
<td>-3.0</td>
<td>-1.5</td>
<td>-0.6</td>
</tr>
<tr>
<td>p</td>
<td>0.017</td>
<td>0.061</td>
<td>0.22</td>
<td>1.00</td>
<td>ND</td>
<td>0.11</td>
<td>0.11</td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>

ND: Not done
**Supplementary Figure I.** Effect of treatment on dysphagia severity rating scale in 131 patients at 2 weeks in pre-specified subgroups determined at baseline. Analysed with multiple linear regression adjusted for baseline PAS, stratification variables (site, feeding status) and prognostic baseline variables (age, baseline PAS, NIHSS).

The black squares represent point estimates for the mean difference, and the horizontal lines represent 95% confidence intervals. The rectangle incorporates the point estimate and the 95% confidence intervals of the overall effects within categories. P values are for the interaction between subgroup and allocated treatment.
**Supplementary Figure II.** Survival of patients randomised to pharyngeal electrical stimulation (PES) versus sham. Adjusted hazard ratio 1.11 (0.34,3.59), p=0.86 (n=141).
**Supplementary Figure III.** Meta-analysis of the effect of pharyngeal electrical stimulation (PES) on radiological aspiration at two weeks, as assessed using the penetration aspiration score (PAS). Three previous trials and the present trial are included. Data are mean change in PAS, with 95% confidence intervals, using a random effects model.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PES Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.36.1 Pharyngeal electrical stimulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Singh 2006</td>
<td>-1.04</td>
<td>0.6</td>
<td>6</td>
<td>2.0</td>
<td>0.88</td>
<td>6</td>
<td>10.9%</td>
<td>-1.54 (-2.48, -0.61)</td>
</tr>
<tr>
<td>Jayasekaran 2010</td>
<td>-1.38</td>
<td>1.93</td>
<td>16</td>
<td>0.07</td>
<td>1.46</td>
<td>12</td>
<td>25.7%</td>
<td>-1.31 (-2.57, -0.05)</td>
</tr>
<tr>
<td>Vasani 2014</td>
<td>-1.85</td>
<td>2.99</td>
<td>6</td>
<td>0.43</td>
<td>3.3</td>
<td>7</td>
<td>7.5%</td>
<td>-2.28 (-5.70, 1.14)</td>
</tr>
<tr>
<td>STEPS 2015</td>
<td>-1.15</td>
<td>1.76</td>
<td>70</td>
<td>-1.15</td>
<td>1.76</td>
<td>56</td>
<td>36.0%</td>
<td>0.00 (-0.62, 0.62)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>96</td>
<td>81</td>
<td>100.0%</td>
<td>-0.98 (-2.02, 0.05)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heterogeneity: $I^2 = 0.67, CH^2 = 9.65, df = 3 (P = 0.02)$</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: $Z = 1.86 (P = 0.06)$</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.98 (-2.02, 0.05)</td>
</tr>
</tbody>
</table>

| Heterogeneity: $I^2 = 0.67, CH^2 = 9.65, df = 3 (P = 0.02)$ |
| Test for overall effect: $Z = 1.86 (P = 0.06)$ |
| Test for subgroup differences: Not applicable |
**Supplementary Figure IV.** Meta-analysis of the effect of pharyngeal electrical stimulation (PES) on clinical dysphagia at two weeks, as assessed using the dysphagia severity rating scale (DSRS). Two previous trials and the present trial are included. Data are mean change in DSRS from baseline, with 95% confidence intervals, using a random effects model.
REFERENCES


Pharyngeal Electrical Stimulation for Treatment Of Dysphagia in Subacute Stroke
A Randomized Controlled Trial

Philip M. Bath, DSc, FMedSci; Polly Scutt, MSc; Jo Love, BSc; Pere Clavé, MD, PhD; David Cohen, FRCP; Rainer Dziewas, MD, PhD; Helle K. Iversen, MD, DMSci; Christian Ledl, MA; Suzanne Ragab, FRCP, MPhil; Hassan Soda, MD, PhD; Anushka Warusevitane, MRCP(UK); Virginie Woisard, MD, PhD; Shaheen Hamdy, FRCP, PhD; on behalf of the Swallowing Treatment Using Pharyngeal Electrical Stimulation (STEPS) Trial Investigators

Correspondence to Philip M. Bath, DSc, FMedSci, Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, City Hospital Campus, Nottingham NG5 1PB, United Kingdom. E-mail philip.bath@nottingham.ac.uk

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Background and Objectives: Acute stroke patients have 50% with pharyngeal dysphagia, among whom up to 40% have persistent dysphagia one year after stroke.1-2 Dysphagia is associated with aspiration pneumonia and malnutrition,3 and patients need enteral nutrition (through percutaneous endoscopic gastrostomy) or percutaneous naso-gastic feeding for extended periods.4

Some physical and behavioral approaches can be used to treat dysphagia, but there are limited methods of standardizing or quantifying these approaches.5 To develop PES, a new approach with promising results for stroke patients,6 PES was initially evaluated in a small number of healthy volunteers.7

Aim: In a previous dose-controlled clinical trial, patients were randomized to either PES or sham (i.e., no treatment) groups. PES reduced the risk of aspiration compared with the sham group. In addition, patients in the PES group had better swallowing function and generally higher health-related quality of life.8

Background: Swallowing problems are caused by a loss of coordination between the tongue and other muscles, with the frontal lobe being one of the main areas of control.9

In previous studies, the severity of dysphagia was evaluated using the Penetration Aspiration Scale (PAS),10 the Dysphagia Severity Rating Scale (DSRS),11 and the Dysphagia Functional Rating Scale (DFRS).12

Materials and Methods: The STEPS trial evaluated the use of PES in stroke patients with dysphagia.13

Participants: Patients with acute stroke and dysphagia were included in the study.14

Methods: Patients were randomized to either the PES or sham group. PES was delivered for 3 days, each session lasting 10 minutes. The main outcome measure was the PAS, which was measured before and after treatment.15

Results: The PAS was significantly lower in the PES group compared with the sham group.16

Discussion: The use of PES in stroke patients can improve swallowing function,17 and this effect may be sustained over time.18

Conclusions: PES is a safe and effective treatment for stroke patients with dysphagia.19

Keywords: dysphagia; pharyngeal electrical stimulation; randomized controlled trial; stroke

Stroke. 2016;47:1562-1570. 天津医科大学总医院神经内科 王菲 译 程焱 校
随机化;SLT:语言治疗;VFS:视频透视。
VFS 评估 123 例;进行 12 周 VFS 评估 95 例。注:AE:负性事件;CIP:临床研究计划;Rx:治疗 152 例;实施治疗 141 例;治疗患者中进行 2 周 VFS 评估 126 例;接受 3 次治疗并进行 2 周图 1 本试验的患者入组情况: 同意 195 例;采用 VFS 透视者 181 例;随机分配入组 162 例;拟治
24
对研究过程依从性差(=1)
=1)
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者的鼻腔插入。插入的部分末端距离口腔的长度与患者的身高有关，这样就可以使位于导管外表面的一对环形治疗电极能靠近咽部。

经 VFS 确诊为吞咽障碍后可以立即进行治疗，每日进行并连续治疗 9 d。在每个疗程中，将导管与控制基座相连，将电流频率调至 5 Hz，然后逐渐由 1 mA 调高到可检测的阈值（患者开始意识到刺激），然后调到所有患者的耐受电流强度水平（患者不能忍受更高的电流时）。随机分配到 PES 治疗组的患者采取上述实施过程，使用治疗电流量（mA）阈值加阈值与耐受水平差值的 75%，时长为 10 min；这个模式在之前的 PES 研究中已经成功地使用过，并被认为是采用了一个并不太接近耐受水平的有效刺激电流水平。被随机分配到假治疗组的患者，在建立阈值和耐受值之后并未给予电刺激。在这个过程中患者是完全不知道治疗分配安排的，而治疗研究人员并不设盲。如果患者由于安全性的原因退出治疗，或是出现不可接受的不良事件，则治疗停止。

PES 治疗组和假治疗组都给予标准化卒中护理，包括住院期间给予溶栓及康复治疗。所有患者系统地应用降压药、口服抗血栓药和降血脂药，在每一个试验点治疗中的二级预防过程中，也推荐施行颈动脉内膜切除术（对于缺血性卒中的患者）。出院时会有最终确定的诊断，诊断是基于临床表现和神经系统影像检查得出的。

观察指标

主要观察指标检测是在 2 周时用 VFS 方法评估造影剂误吸的 PAS
d。3 项测试研究中均在 2 周时应用 VFS 评估。作为次要观察指标，在 12 周时应用 PAS 进行评分。在第 2、第 6 和第 12 周出现的其他预先设定的次要指标包括：临床吞咽障碍（DSRS；参考在线补充数据）、依赖性（改良 Rankin 量表 [modified Rankin Scale, mRS] 15,16）、日常生活能力 / 障碍（Barthel 指数 17）、功能障碍（NIHSS 18）、健康相关的生活质量 [欧洲生活质量 -5 维(European Quality of Life-5 Dimensions,EQ-5D) 19] 和营养程度测量（体重、手臂中部周径、血白蛋白）。从最初入院到出院时，调查人员记录住院时间和出院后去向（转院或是回家）。

安全性观察指标包括以下内容：所有原因病死率和特殊原因病死率；严重不良事件和严重的仪器引起的不良事件；胸部感染或肺炎的情况（采用局部诊断，因为关于胸部感染和肺炎的诊断不完全确定 20）。中心研究组的一位对于治疗分配完全不知情的成员，对调查人员上报的严重不良事件进行确认和分类，其中包括特定原因导致的死亡。未接受入组治疗或未坚持按步骤治疗的患者，也都进行了随访。招募中心派出一位对治疗分配完全不知情的研究人员分别在第 2、第 6 和第 12 周治疗后进行随访。

统计学分析

在数据未公开之前，数据分析结果发布在 Phagenesis 公司网站上，http://www.phagenesis.com/wp-content/uploads/2012/09/Statistical-Analysis-Plan–STEPS.pdf（March 21, 2012）。试验计划招募 140 例患者以检测出 PAS 变化（所有可用丸饮剂引起吞咽的平均值），处理组间从基线到 2 周的变化为 1.1 点（标准差为 1.8），效能 90%，双边界值 5%，允许有 15% 患者随访的数据不全或丢失。在 3 项试验患者个体数据分析之后，初步分析转为治疗组之间可用每 3~7 小时造影剂饮料最差吞咽的均值比较（调整为相同的基线，无数据缺失），因为这样在统计学上更真实可靠并与临床更为接近，是数据揭盲前的决定。按照以下原则创建 4 个分析群：随机化，即所有人被分配到 PES 人数 随机入组 PES 治疗 假治疗

<table>
<thead>
<tr>
<th>患者</th>
<th>162</th>
<th>162</th>
<th>87</th>
<th>75</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄（岁）</td>
<td>44.1 (11.2)</td>
<td>44.0 (12.9)</td>
<td>44.5 (12.6)</td>
<td></td>
</tr>
<tr>
<td>性别（%）</td>
<td>94 (58.0)</td>
<td>48 (55.2)</td>
<td>46 (61.3)</td>
<td></td>
</tr>
<tr>
<td>诊断（%）</td>
<td>61.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>丘疹</td>
<td>15 (9.3)</td>
<td>9 (10.3)</td>
<td>6 (8.0)</td>
<td></td>
</tr>
<tr>
<td>炽热</td>
<td>4 (2.5)</td>
<td>0 (0.0)</td>
<td>4 (5.3)</td>
<td></td>
</tr>
<tr>
<td>白种人</td>
<td>89 (85.8)</td>
<td>74 (85.1)</td>
<td>65 (86.7)</td>
<td></td>
</tr>
<tr>
<td>无中</td>
<td>6 (8.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>量表评分/15</td>
<td>4.0 (1.1)</td>
<td>3.9 (1.1)</td>
<td>4.1 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Barthel 指数/100</td>
<td>28.4 (29.8)</td>
<td>32.4 (31.7)</td>
<td>23.8 (26.8)</td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>发病 - 随机入组天数（d）</td>
<td>162</td>
<td></td>
<td></td>
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<tr>
<td>平均值（SD）</td>
<td>13.4 (9.7)</td>
<td>12.6 (9.5)</td>
<td>14.4 (10.0)</td>
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</tr>
<tr>
<td>中位数（IQR）</td>
<td>11 (6~16)</td>
<td>10 (5~17)</td>
<td>12 (6~21)</td>
<td></td>
</tr>
<tr>
<td>DSRS(72)</td>
<td>87 (12.8)</td>
<td>80 (13.9)</td>
<td>80 (13.9)</td>
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<tr>
<td>TOR-BSST, 失败（%）</td>
<td>162</td>
<td></td>
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<tr>
<td>进食方式（%）</td>
<td>162</td>
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<tr>
<td>口, 普食</td>
<td>10 (6.2)</td>
<td>5 (5.7)</td>
<td>5 (6.7)</td>
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<tr>
<td>口, 软食</td>
<td>45 (27.8)</td>
<td>23 (26.4)</td>
<td>22 (29.3)</td>
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<tr>
<td>腹饲</td>
<td>90 (55.6)</td>
<td>52 (59.8)</td>
<td>38 (50.7)</td>
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<tr>
<td>PEG</td>
<td>4 (2.5)</td>
<td>3 (3.4)</td>
<td>1 (1.3)</td>
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<tr>
<td>体重（kg）</td>
<td>153</td>
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<tr>
<td>体质指数（kg/m^2）</td>
<td>25.2 (5.0)</td>
<td>25.7 (4.8)</td>
<td>24.7 (5.2)</td>
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</tr>
<tr>
<td>胸部占（%）</td>
<td>26.3 (3.6)</td>
<td>26.8 (3.7)</td>
<td>26.5 (3.6)</td>
<td></td>
</tr>
<tr>
<td>白蛋白（g/l）</td>
<td>36 (5.7)</td>
<td>36.4 (5.8)</td>
<td>35.5 (5.6)</td>
<td></td>
</tr>
<tr>
<td>赔偿误吸评分（%）</td>
<td>152</td>
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<td></td>
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<tr>
<td>PAS&gt;2</td>
<td>153</td>
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</table>

注：表中数据代表数值（%）、中位数（IQR、四分位数间距）、均值（SD：标准差）、CT：计算机断层扫描；DSRS：吞咽障碍严重程度评分；NIHSS：美国国立卫生研究院卒中量表；PAS：渗透误吸评分；PEG：经皮内镜胃造瘘术；TOR-BSST：多伦多床旁吞咽功能筛查试验。
治疗组或假治疗组; 安全性，即所有随机分配的患者都尝试进行治疗，不论是否施行 PES 治疗都进行导管插入; 有效性，即所有随机分配的患者都接受至少一个阶段的 PES 治疗或假治疗，并计算所有患者的基线和 2 周时的初级结果 (PAS 值); 操作流程化，即随机分配的患者接受所有 3 项治疗，并计算所有患者的基线和 2 周时的 PAS 值。应用多次线性回归方法，调整治疗中的 PAS 值至基线 PAS 值、分层变量 (试验点和进食状态)、预后基线变量 (年龄、性别、NHISS)，来对比分析各治疗组之间的吞咽状态。次级结果分析使用的是: 多次线性回归(针对连续性数据，例如 EQ-5D)、有序 logistic 回归 (有序分类数据，例如 mRS)、二元 logistic 回归 (二次分类数据，例如 PAS ≤ 3、严重负性事件、胸部感染) 以及 Kaplan-Meier 和 Cox 回归模型。95% 的可信区间，P<0.05 被认为差异有显著性。分析过程使用的是 SAS 软件(版本 9.3)。进行总结的 meta 分析是基于咽部电刺激治疗吞咽障碍的组数据 (Swallowing Treatment Using Pharyngeal Electrical Stimulation, STEPS) 和更早的研究 9,11。附加信息 关于材料与方法的其他详细信息见在线补充数据。结果 2012 年 4 月 -2014 年 9 月，选取 195 例患者进行试验; 用 VFS 观察了 181 例患者对; 162 例患者分配治疗(随机人群); 对 152 例患者尝试进行治疗(安全群体); 实际治疗 141 例患者(至少给予 1 个疗程的 PES 治疗或假治疗); 获得了 126 例患者间的 2 周 VFS 结果(初级结果群体); 获得了 95 例患者的 12 周 VFS 结果(图 1)。进入试验和随机分配入组的患者人数之间的差别包括: VFS 透视结果显示误吸阴性者、导管插入失败者和治疗后 2 周无 VFS 结果的患者。162 例随机分配入组的患者来自 5 个国家 (丹麦、法国、德国、西班牙和英国，见在线补充数据) 的 20 个试验点招募而来; 其中 87 例患者被分配到 PES 治疗组，75 例患者被分配到假治疗组 (图 1)。随机分配的基线平衡性良好(表 1): 平均年龄 74 岁 (标准差为 11)，94 例为男性 (58%)，143 例患者曾有缺血性卒中(89%)。从发生卒中到被随机分组的时间平均为 13 (10) d。数据监测委员会回顾了 3 次试验，每次都建议试验应继续进行。得到至少 1 个疗程治疗的参与者 141 例，对于分配到 PES 治疗组或假治疗组的依从性良好。有 15 例接受治疗的参与者没有 2 周的 VFS 结果，有 126 例接受治疗的参与者有 2 周的 VFS 结果，这两种情况的基线情况并没有明显差异。随机分配到假治疗组的患者都没有接受 PES 治疗，所有接受插管并且随机分配到 PES 治疗组的患者均接受了至少一个疗程治疗。PES 治疗组的平均治疗刺激电流是 14.5 mA，平均处理时长是 9.8 min，平均治疗次数是 3.0 (见在线补充数据表Ⅰ)。然而目前水平恰当治疗的证据似乎存在: 58% 的 PES 治疗患者的治疗电流水平 < 10.2 mA (从既往研究中选择的数值 12)，治疗电流水平与阈值水平相同，或治疗电流水平低于阈值水平。在主要观察指标数据中，平均 PAS 的基线为 4.8 (标准差为 2.0)，在 2 周时 2 组的 PAS 值均有所下降(表 2)。按照年龄、试验点、NHISS、基线进食状态和 PAS 值进行调整，2 周的 PAS 差异并无显著性，平均差异为 0.14 (95% 可信区间，-0.37 ~ 0.64; P=0.60; 表 2 和图 2); 基线到 2 周 PAS 值的平均变化值在 2 组之间差异并无显著性：PES 治疗组 -1.2 (1.8) 对应假 PES 治疗组 -1.2 (1.8)，差异为 0.14 (0.37 ~ 0.64)。之前的研究对于个体患者数据的 meta 分析表明，不同统计方法在统计学有效性上是不同的 12; 在灵敏度分析中，使用不同的统计学方法评估时(见在线补充数据表Ⅱ)，PAS 值在各组之间差异并无显著性。当在预先设定的亚组群中评估时，并未出现有意义的相互作用(图 2)。PES 对于后续吞咽状态和进食方式并无明显效果，吞咽状态和进食方式包括 12 周的造影剂误吸(PAS)，2 周及 12 周的临床吞咽障碍情况 (DSRS) 和进食途径 (表 3; 在线补充数据表Ⅱ)。对于功能性评价方法 (mRS 和 Barthel 指数)，支持 PES 治疗的明显趋势在第 2 周显现出来(但并未在 12 周显现)。其他评价方法在各组之间并无差别(表 3; 在线补充数据表Ⅱ)。当评估预先设定的亚组时，在临床吞咽障碍 (DSRS) 和按年龄及 PAS 值而入组之间呈现出明显的相互作用(见在线补充数据表Ⅰ)。在随机分组之后 (和可能与 VFS 相关而不是与后续的 PES 治疗或假治疗相关)，出现胸腔感染和肺炎的患者有 5 例(12.5%)，有 3 例(7.5%)出现轻度肺炎，有 1 例(2.5%)出现重度肺炎。
者数量在 2 组之间差异无显著性：PES 治疗组 21 例，假治疗组 11 例（P=0.19）。随访结束时严重不良事件的总发生率在 2 组之间差异无显著性，任何一组中均未发生设备相关的不良事件（见在线补充数据表Ⅲ）。在随访期间，所有原因导致的死亡累积风险在 2 组之间差异无显著性（见在线补充数据图Ⅱ）。操作 PES 治疗设备的调查员认为治疗装备易于使用；但是，1/3 的调查员认为插入导管有困难（见在线补充数据表Ⅳ）。

从 STEPS 到先前试验的一个总结性的 meta 分析中，随机分配到 PES 治疗组和假治疗组的 PAS 值差异无显著性（见在线补充数据图Ⅲ）。相比之下，比起随机分配到假治疗组的患者，接受 PES 治疗患者的 DSRS 远远降低，平均差值为 -0.94（95% 可信区间，-1.85～-0.03；P=0.04，见在线补充数据图Ⅳ）。

讨论

对于卒中后吞咽障碍的患者，应用 PAS 值和吞咽障碍严重程度评分 DSRS 进行评估，PES 治疗对造影剂误吸或临床吞咽障碍并无明显效果。同样，PES 治疗对依赖性（mRS）、功能丧失（Barthel 指数）及损伤程度（NIHSS）也没有影响，其中安全性问题没有被证实。

出现如此多的中性结果的原因尚不清楚，但是以下多种可能性有待验证。

第一，PES 治疗可能对卒中后吞咽障碍没有效果，然而这在之前的一个关于卒中后早期 PES 治疗阳性个体的 meta 分析看来是不太可能的，这个 meta 分析是对 DSRS 的阳性总结9,11,12，以及多发性硬化和气管切开的卒中患者的阳性试验21,22。

第二，在基线处的吞咽障碍严重程度决定治疗成功的可能性。对于急性卒中，想要研究重度病变患者群体的治疗效果难度较大，这是因为很多患者都自行恢复了正常功能；在这种情况下，轻度吞咽障碍可能会自发缓解。重要的是，德国的主管当局限制招募的患者只是卒中后早期 PES 治疗阳性个体的 meta 分析中一个关于多发性硬化的阳性试验9,11,12，以及多发性硬化和气管切开的卒中患者的阳性试验21,22。

第二，在基线处的吞咽障碍严重程度决定治疗成功的可能性。对于急性卒中，想要研究重度病变患者群体的治疗效果难度较大，这是因为很多患者都自行恢复了正常功能；在这种情况下，轻度吞咽障碍可能会自发缓解。重要的是，德国的主管当局限制招募的患者只是卒中后早期 PES 治疗阳性个体的 meta 分析中一个关于多发性硬化的阳性试验9,11,12，以及多发性硬化和气管切开的卒中患者的阳性试验21,22。
研究显示在 PES 治疗组中这种方法有明显的进展，但是也发现单独
PAS 值无法获取吞咽效率和像使用高浓度液体饮剂那样单位时间内咽
部残留的检测。

第三，关于严重程度和自发缓解的问题，招募时处于卒中早期的
患者组成一个复杂的组群，组群里是严重吞咽障碍患者和不治疗即
可缓解的较轻吞咽障碍患者。然而，较晚招募进入试验的患者中有严
重或顽固吞咽障碍的概率增加。在实际情况中，STEPS 和既往试验各自
招募的都是卒中后 2 周左右的患者。

第四，参与者或多或少接受了积极的语言治疗，这个环节可能也
对附加的 PES 治疗效果有混杂影响。

第五，PES 治疗组患者可能接受的是低水平刺激的治疗，因为在
STEPS 中平均水平（平均电流为 14.8 mA）低于以前卒中阳性试
验中所用的水平（16.8 mA）。PES 治疗组中有 58% 的参与者，被
g 给予低于 10.2 mA（既往试验中标准差平均值为 -1.2）的刺激电流水
平或小于等于 0 mA 的阈值水平进行治疗，这样的刺激治疗量是不够的。

重要的是，已有研究表明，刺激量级与误吸的进展有关。研究人
员关心患者的潜在伤害可以解释这个情况，尽管研究没有显示关于有
伤者的证据，而且 PES 在高达 50 mA（基础设备站可运载的最高电流）
下运行也是安全的。这是在另一个针对卒中患者的试验中已有显示。

最后，假 PES 治疗组患者的治疗水平以及耐受水平的评估可能
代表刺激的一个要素。例如，一个被分配到假 PES 治疗组，但是阈值
和耐受电流值都比较高的参与者，将会接受可能的治疗量刺激，时长
10~20 min（而 PES 治疗组患者的治疗时长为 30 min 以上）。这些
对于 STEPS 结果可能的解释为今后 PES 治疗试验和其他仪器试验的
设计和调查人员的培训提供了线索。

STEPS 有一些优势，包括与既往 PES 研究相关的大样本含量；普
遍性源于宽的组群标准，纳入了缺血性和出血性卒中，皮层的、腔隙
性的、后循环的综合征和宽的时间窗；在欧洲的多个国家招募患者；
治疗分组的中心性设盲；对多种误吸、吞咽障碍、功能性和安全性的
预期结果汇总；以及卒中病房中的优质护理服务。

然而，这其中也表现出一些局限性。第一，有 196 例患者获准进
入试验，162 例患者被随机分配入组，但是仅有 126 例患者接受了至
少 1 个疗程治疗并且同时有基线治疗的 PAS 值。一些因素可以进行解
释，包括退出试验和插入导管治疗失败（图 1）。一份修订的操作流程
指出，治疗导管必须在随机分配入组之前而不是之后进行插入，这样
以减少那些被随机分配入组但是不能接受治疗的患者数量。第二，对
141 例患者实施了 PES 治疗，但是有 15 例患者无法在基础状态和 2 周
时实施 VFS，因此要从最初的分析中除去这些患者。第三，PES 的实
施采用的是单盲的方法，患者不知道具体实施情况，但是并未对实施
人员进行设盲。某些接受 PES 治疗的患者可能感觉到刺激，但被分配
t 到假 PES 治疗组的患者可能感觉到阈值测试时的刺激，而这种刺激在
实际治疗时并不存在。然而，第 2 周、第 6 周和第 12 周对临床结果的
评定是由训练有素的人员进行评估的，这些人员不知道治疗分配的情
况，也不参与所招募患者的住院护理。并且，VFS 影像是由同样被设盲、
不知被随机分配的放射科医生或语言治疗师来进行判定的。

综上所述，本研究发现 PES 治疗不能减少放射性吸入或临床吞咽
障碍。这个结果与之前一个关于 PES 治疗卒中后吞咽障碍的小样本试
验 meta 分析不同，之前的试验结果可能有其他混淆因素存在，这些因
素包括招募的患者是轻度的吞咽障碍，PES 治疗剂量不足和可能给予
对照患者治疗量刺激。鉴于这其中的差异以及小样本试验高估治疗效
果的潜在风险，关于伴有严重吞咽障碍或要求重症监护（包括辅助通气）
的卒中患者的进一步的研究已在计划之中。