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Post-stroke dysphagia: A review and design considerations for future trials

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Abstract

Post-stroke dysphagia (a difficulty in swallowing after a stroke) is a common and expensive complication of acute stroke and is associated with increased mortality, morbidity, and institutionalization due in part to aspiration, pneumonia, and malnutrition. Although most patients recover swallowing spontaneously, a significant minority still have dysphagia at six months. Although multiple advances have been made in the hyperacute treatment of stroke and secondary prevention, the management of dysphagia post-stroke remains a neglected area of research, and its optimal management, including diagnosis, investigation and treatment, have still to be defined.

Keywords

Stroke, dysphagia, treatment, randomized controlled trial, design, pneumonia, aspiration, rehabilitation

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Background

Stroke is recognized as a leading cause of death and disability worldwide and is associated with multiple medical complications leading to prolonged hospital admissions and significant health care costs.¹ Post-stroke dysphagia (PSD), defined here as difficulty in swallowing after a stroke, is a common complication affecting many patients in the first few hours and days after ictus. PSD is associated with increased mortality and morbidity due in part to aspiration, pneumonia, and malnutrition. Although many stroke patients recover swallowing spontaneously, 11–50% still have dysphagia at six months.^{2,3} Persistent dysphagia independently predicts poor outcome and institutionalization.⁴ Dysphagia leading to aspiration of ingested foods, liquids, or oral secretions, is thought to be the primary risk factor for pneumonia after stroke.⁵ Dysphagic patients are three times, and those with confirmed aspiration eleven times, more likely to develop pneumonia.^{1,6} A recent large retrospective US study of stroke patients quantified the individual cost of pneumonia and associated mortality as \$21,338. The relative risk of hospital death in stroke patients with pneumonia is 5.7 (95% CI, 5.4–6.0).⁵

Although multiple advances have been made in the hyper acute treatment of stroke (e.g. with thrombolysis,

mechanical thrombectomy, and hemicraniectomy), and secondary prevention (antithrombotics, blood pressure lowering, lipid lowering), the management of PSD remains a neglected area of research. As such, the optimal management of PSD, including diagnosis, investigation and treatment, remains to be defined.

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Epidemiology of PSD

Globally, 15 million people suffer a stroke annually⁷ and up to 65% have swallowing problems of whom half will be symptomatic.⁸ Some early studies included people with diagnosed dysphagia who were referred for further assessment and this increased artificially the rate of aspiration.^{9,10} The true prevalence of dysphagia can only be established by studying an unselected stroke population^{3,11} and there have been no such recent studies.

In acute stroke, the prevalence of dysphagia has been reported as between 28 and 65%,^{3,11–13} a variation that reflects differences in the assessment of dysphagia, setting, and timing of the test used. Dysphagia improves significantly during the early days and after two weeks 90% of patients swallow safely,^{3,8} although a small proportion will have problems for longer.² Further, some patients who appear to have a safe swallow at three months are found to have difficulties again at six.^{3,11} In general, if the swallow does not show any signs of recovery in the first 10 days after stroke, the return of a safe swallow may take up two or three months to show signs of recovery.¹⁴

Aspiration in dysphagic patients is often not associated with a cough response or outward signs of difficulty in swallowing. This absence of any outward sign or distress is known as silent aspiration and has been reported as occurring in over 40% of patients.¹⁵ Since there is an association between aspiration and abnormal pharyngeal sensation, with 8% of patients silently aspirating,¹⁶ silent aspiration is considered to be related to sensory loss or gradual desensitization if aspiration is chronic.¹⁷ Since 100% of dysphagic patients showed either unilateral or bilateral sensory loss in one study,

and a sensory deficit exists in the pharynx and larynx in stroke patients with dysphagia, it has been concluded that the severity of laryngeal sensory deficits determines a predisposition to aspiration.¹⁸

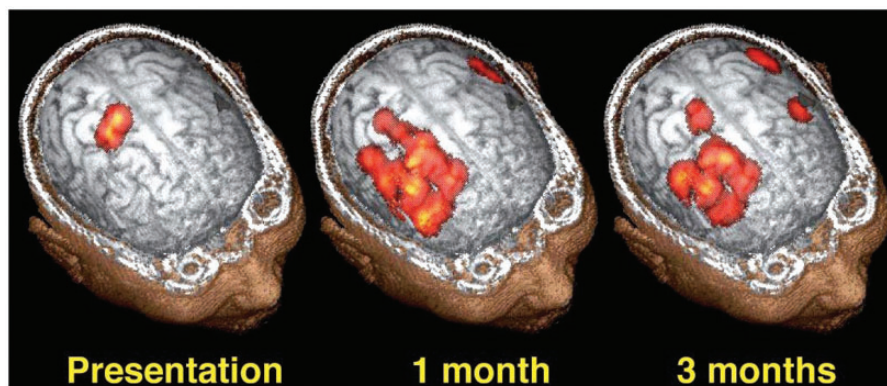
Mechanisms of PSD

PSD is thought to be due to damage to the cortex and subcortical structures. Cortical re-organization then leads to swallowing recovery. Studies using transcranial magnetic stimulation (TMS) have shown that pharyngeal musculature is represented bilaterally, but asymmetrically, in the cerebral cortex of healthy volunteers.¹⁹ A stroke lesion affecting the “dominant swallowing hemisphere” may therefore be responsible for dysphagia following unilateral hemispheric stroke.¹⁵

In an attempt to understand the mechanism for recovery of swallowing after stroke, swallowing was studied by videofluoroscopy (VFS) and TMS mapping over time in 28 hemispheric stroke patients. Subjects who were non-dysphagic after hemispheric stroke had greater pharyngeal cortical representation in the contralesional hemisphere as compared to dysphagic subjects. TMS follow-up data at one and three months indicated that subjects who recovered swallowing function had significantly greater pharyngeal representation in the unaffected hemisphere as compared to baseline. These findings suggest that re-organization in the contralesional hemisphere is key in swallowing recovery,²⁰ as illustrated in Figure 1.

A recent functional magnetic resonance imaging study comparing cortical activations during swallowing between dysphagic hemispheric stroke patients and healthy subjects confirmed compensatory recruitment and activation of regions of the cerebral cortex in the intact hemisphere, supporting the theory that changes

Figure 1. Expansion of pharyngeal motor cortex on unlesioned hemisphere during swallowing recovery after stroke. Magnetic resonance image with co-registered topographic data from transcranial magnetic stimulation at baseline, one month, and three months after enrolment.²⁰



in the unaffected hemisphere are crucial in swallowing recovery.²¹ Moreover, a magnetoencephalography (MEG) study imaged swallowing activations in sub-acute stroke patients with and without dysphagia compared with healthy controls described similar evidence for increased contralesional activity being predictive of no dysphagia.²² Thus, neuroplasticity is likely to play a significant role in the recovery of swallowing function.²³

In addition to the neuropathophysiological changes described above, dysphagia will also occur when level of consciousness is reduced, either acutely due to a large stroke lesion with associated edema, or later due to delirium in which case the size and location of stroke will be less important.

Complications of PSD

Complications of dysphagia include the consequences of aspiration: pneumonia, recurrent cough, and choking, and those of modifications to dietary and fluid intake: compromised nutrition and hydration, reduced quality of life, and social isolation.

Pneumonia is a frequent complication of stroke, occurring in around 10% of hospitalized patients.²⁴ In those at greatest risk because of advanced age, severe stroke, and PSD, the incidence of pneumonia may be as high as 40%.²⁵ Confirmed aspiration is strongly associated with pneumonia (relative risk 11.56; 95% CI 3.36 to 39.77).⁸ Current thinking recognizes the potential interplay between poor oral health, aspiration, and immune suppression in determining susceptibility to pneumonia.²⁶ Pneumonia most often presents in the first week after a stroke, probably because of the high prevalence of dysphagia and the extent of immune suppression during the acute phase. Nevertheless, the diagnosis of pneumonia complicating stroke remains challenging as its presentation may be non-specific and investigations such as chest radiography and microbiological specimens are of limited value.²⁷ This has significant implications for clinical care and research that considers pneumonia as a trial endpoint and recent consensus diagnostic criteria have been proposed to address this.²⁸

Patients developing pneumonia are more likely to die or survive dependent on others,^{24,29,30} and have a longer stay in hospital. As compared to alternative settings, care on a stroke unit compared to alternative settings reduces the frequency of pneumonia (odds ratio 0.60; 95% CI 0.42 to 0.87).³¹ Little is known about the impact of particular care processes such as positioning, early swallow screening, and oral care practices. The time trend in pneumonia prevalence in stroke units is unclear, for example, one registry study suggested no significant change in pneumonia

prevalence between 1998 and 2007.³² Pneumonia remains an important and modifiable complication of stroke, and strategies to prevent it such as reducing aspiration could significantly improve outcomes.

Compromised nutrition, hydration, and poor quality of life caused by PSD have attracted less clinical and research attention than pneumonia. In a systematic review from 2009, the chance of malnutrition increased in patients with dysphagia particularly in the post-acute phase.³³ The conclusions were limited by widely varying definitions and prevalence of both dysphagia and malnutrition. The validity and utility of the available methods for assessing nutritional status in patients with stroke such as the Demiquet Index, anthropometry, and those for hydration status, are unclear and need further evaluation. Dysphagia-related quality of life tools such as SWAL-QUAL and SWAL-CARE are available³⁴ but these were not derived in patients with stroke and require evaluation in this setting.

Diagnosis: Clinical and instrumental

Dysphagia can be diagnosed by clinical bedside assessment (CBA), or instrumentally by VFS, or by fiberoptic endoscopic evaluation of swallowing (FEES). CBA consists of a detailed oral examination and an assessment with food and liquid to ascertain oral and pharyngeal competency. Several methodological variations have been reported.³⁵ CBA predicts pharyngeal dysphagia poorly and has been criticized for its inaccuracy in identifying aspiration,^{36,37} missing up to 40% of people who aspirate.³⁶

In hyperacute stroke studies, swallowing has been assessed using a water swallow test, a screening test rather than full assessment.³⁸ Many subsequent swallow screens have been based on this with or without a scoring mechanism.^{39–42} Some tests require specialist training or are copyrighted (e.g. TOR-BSST).³⁹ Assessment later after the stroke is more comprehensive but will detect fewer cases as swallowing improves or recovers.^{11,43} It is difficult to estimate how many patients simply have difficulty swallowing and how many are also aspirating as few studies have performed routine VFS in the first few days.

It is important to decide which aspect of swallowing, for example, clinical dysphagia or radiological aspiration, is the focus of study. This will determine the type of assessment required and the relevance to clinical practice. For example, it remains unclear whether a finding of asymptomatic aspiration on FEES is relevant or whether a minor tongue movement abnormality on clinical examination is important if it does not cause symptoms.

VFS is an instrumental assessment of swallowing and involves swallowing a radiological contrast agent

such as barium. It is expensive as it needs a radiology suite and often a number of different staff. Many patients are too ill to travel to radiology and sit up for long enough to be assessed. It involves radiation exposure (although this is of less relevance to stroke patients) and is not readily repeatable. Hence, it is impractical to perform VFS in every case.

In FEES a laryngoscope is passed transnasally to the hypopharynx to view the larynx and pharynx. Food and drinks are dyed to aid visualization of the bolus. FEES allows an assessment of the anatomy, secretions and of food and drink management. Information is obtained on the ability to protect the airway, timing of the bolus through the hypopharynx and ability to clear the bolus during the swallow. It also allows the clinician to see pooling and residue in the hypopharynx and detect aspiration.^{44,45} The equipment is portable, sitting is not essential, and the procedure can be performed at the bedside. It is a repeatable, and safe allowing more swallows to be tested. Patients can be assessed while eating a full meal rather than with the limited number of spoonfuls of contrast given during VFS. However, FEES is not routinely available in many hospitals worldwide which, like VFS, limits the number of centers which could participate in research using it as an assessment.

VFS and FEES are considered interchangeable in clinical practice, especially when examining aspiration or penetration,^{45–50} and they are the only two assessments that can diagnose aspiration reliably.⁵¹ VFS has been considered the gold standard for the diagnosis of dysphagia, but FEES is increasingly seen as a cost-effective, portable, and reliable alternative.⁵¹ Validation of FEES against VFS showed high sensitivity and specificity.^{45,52,53} In one study FEES was shown to detect aspiration more reliably than VFS.⁵⁰ Other assessments, such as cervical auscultation or pulse oximetry are other potential approaches.

In conclusion, instrumental assessment is considered the gold standard in the diagnosis of dysphagia, but requires specialist staff and equipment and therefore cannot readily be conducted within a few hours of stroke onset, as would be needed in a study of early intervention. CBA is the only option in this situation but is not as reliable.

Dysphagia management

The primary aim of dysphagia management has been to reduce aspiration and to manage swallowing difficulties rather than rehabilitate the swallow. This is partly due to the heterogeneity of swallowing difficulties and developing knowledge of the normal and disordered swallow. Management includes modifying food and fluid, altering posture and changing swallowing strategies with some rehabilitative techniques. These may be

used independently but are mostly used together. Management depends on whether the focus is on risk of aspiration or level of swallow breakdown and can be individualized.

Compensatory techniques support management of food and drink within a person's current situation and reduce aspiration risk. They are short-term adjustments and may not improve the physiology of the swallow or promote neural network swallow recovery. Postural techniques (e.g. chin tuck) redirect the bolus and change pharyngeal dimensions. Compensatory swallow techniques such as the effortful swallow aim to increase the efficacy and safety of swallowing. There is some evidence of a reduction in aspiration with these techniques.^{54,55}

Thickening liquids slow the bolus and increase bolus cohesion leading to a reduction in penetration and aspiration.⁵⁶ The quality and extent of modification of food and fluids are inconsistent and subjective as thickness of fluids depends on the base fluid, temperature, the individual making the drink, and the type of thickener, resulting in variability within and between patients.⁵⁷

Rehabilitation techniques such as oral and lingual exercises tend to focus on strength and endurance.⁵⁸ They result in an increase in isometric pressure, but are aimed at specific parts of the swallow so it is not clear how they generalize to the dynamic swallow. Other approaches report a more explicit focus on motor learning principles and the functional swallowing process. One of these with some evidence of effectiveness is the McNeill Dysphagia Therapy program.⁵⁹ More recently, neurostimulation techniques for rehabilitation have been employed, such as TMS, pharyngeal electrical stimulation (PES), and neuromuscular electrical stimulation; there is some evidence that these may reduce aspiration, pharyngeal residue, length of stay in hospital, and improved swallowing performance.⁶⁰ Recent reviews of dysphagia management report limited consistency of evidence for interventions, but with some evidence of effectiveness for behavioral interventions and PES on aspects of swallow and functional outcomes.^{55,61}

Although there is little evidence for postural and compensatory techniques, these are widely but variably used leading to difficulties in establishing what "usual care" is in a research context. This could be addressed by cluster rather than patient level randomization. Issues around subjectivity of fluid modification can be addressed by using pre-thickened bolus which has been shown to be more consistent.⁵⁸

Medical treatment of dysphagia

There is no established medical treatment for PSD, although multiple studies have investigated a variety

Table 1. Potential treatments for post-stroke dysphagia and their effects on important outcomes

Intervention	Trials	Patients	Dysphagia	Case fatality	Pneumonia
Acupuncture	5	321	0.24 (0.13–0.45)		
Behavioural	5	423	0.52 (0.30–0.88)	0.83 (0.46–1.51)	0.50 (0.24–1.04)
Drug therapy	2	75	0.48 (0.07–3.35)	1.14 (0.06–21.87)	0.08 (0.02–0.24)
Pharyngeal electrical stimulation	3	66	0.55 (0.15–2.11)	3.75 (0.39–36.18)	0.43 (0.06–3.09)
Neuromuscular electrical stimulation	1	22	0.51 (0.18–1.49)	–	–
Transcranial direct current stimulation	1	14	0.29 (0.01–8.39)	–	–
Transcranial magnetic stimulation	4	78	–	0.28 (0.03–2.93)	–

Note: Summary results from Cochrane Collaboration review,⁶¹ currently being updated.⁶² Data are odds ratio (95% confidence intervals); odds ratio less than 1.00 are compatible with benefit – significant results highlighted in bold.

of interventions, including therapist-delivered, behavioral, acupuncture, electrical or magnetic stimulation, and drugs. Completed randomized controlled trials are summarized in a Cochrane Collaboration review⁶¹ that is currently being updated.⁶² Table 1 summarizes the main effects of a variety of treatments used in these trials on a number of different outcomes. Overall, there were few studies when considered by type of treatment, most were single-center, and all were small. Interpretation of them is further confounded as many involved mixed populations of patients with different types of dysphagia, not just PSD, and many trials recruited patients over a wide time range after stroke. Overall, the quality of most trials judged using Cochrane Collaboration criteria was low to moderate although a few were high quality. The existing evidence demonstrates the necessity for large high quality dysphagia-treatment trials.

Prevention of post-stroke pneumonia

Post-stroke pneumonia is due to a combination of dysphagia, aspiration,⁸ and stroke-induced immunosuppression.⁶³ It can be caused by bacteria aspirated from the oropharynx or by the chemical effects of the gastric acid on the bronchial mucosa.⁶⁴ Prevention of pneumonia therefore includes early identification of dysphagia, interventions to reduce the volume and frequency of aspiration and the pathogenicity of the aspirate, enhancement of laryngeal sensation and protective mechanisms such as cough, and promotion of cortical plasticity to enhance recovery of the swallow.

Stroke unit care is associated with significant reductions in the incidence of pneumonia.³¹ This is likely to be due to timely screening for dysphagia, modification of the consistency of diet and fluids and/or provision of enteral feeding^{65,66}, and early mobilization.^{67,68}

Pharmacologic approaches could further decrease the risk of pneumonia. Selective oral decontamination lowers oropharyngeal colonization with pathogenic Gram negative bacteria and was associated with a significant reduction in pneumonia in a study of 203 patients with acute stroke.⁶⁹ Prevention of vomiting and regurgitation is another promising approach, as stroke does not only cause dysphagia, but is also associated with lower esophageal sphincter dysfunction, gastro-paresis, increased gastric residual volume and gastro-esophageal reflux.⁷⁰ A recent randomized controlled study of the antiemetic agent metoclopramide in 60 patients with acute stroke fed via nasogastric tubes showed a 69% reduction in pneumonia with regular treatment.⁷¹

Pneumonia after stroke could potentially be prevented by the use of prophylactic antibiotics. A Cochrane review of five studies including 506 patients demonstrated that prophylactic antibiotics significantly reduced post-stroke infection but had no effect on mortality.⁷² Most of the included trials used broad-spectrum antibiotics, started within 24 h of stroke onset and continued for three to five days.^{73,74} While antibiotic prophylaxis prevented infections overall, there was no reduction in pneumonia. This was recently confirmed by two large randomized controlled trials. The Preventive Antibiotics in Stroke Study (PASS) randomized 2250 unselected patients with acute stroke patients to prophylactic ceftriaxone and reported an overall reduction in infections but no effect on pneumonia.⁷⁵ Similarly, the Stroke-Inf study, a cluster-randomized study including 1217 patients with acute ischemic stroke found no effect on pneumonia of prophylaxis based on co-amoxiclav and clarithromycin although urinary tract infection was reduced.⁷⁶ While antibiotic prophylaxis is clearly effective in the prevention of extra-pulmonary infections, there is now strong evidence

Table 2. Design considerations for future randomised controlled trials in the management of post-stroke dysphagia

Criteria	Approaches	Comments
<i>Subjects</i>		
Participants	Mixed or pure population of stroke	Focus on stroke
Timing after stroke	- Acute phase - Subacute phase - Chronic phase	Depends on study aim
Identification	- Dysphagia versus aspiration - Clinical bedside assessment, but many different tests and poor sensitivity and specificity - Instrumental procedures: VFS and FEES	- Screening versus diagnostic tests - Ideally, training needs should be minimal - Large trials will need to avoid instrumental tests
<i>Intervention</i>		
Active	- As already studied (Table 1) - Novel approach	
Comparator	- Placebo – against active drug - Sham – against active device⁹² - No comparator	Large trials may need a control group comprising only standard care
Background evidence	Based on systematic review(s), ideally using individual patient data	See Table 1
<i>Outcomes</i>		
Explanatory or mechanistic phase II trials	- Resolution of aspiration, e.g. using FEES or VFS - Resolution of clinical dysphagia - Chest infection or pneumonia	- FEES/VFS have limited availability - Measure at end of treatment or 1–2 weeks - Outcomes need to be assessed blinded to assigned intervention - A validated definition is needed for pneumonia - Pneumonia may be masked in stroke
Efficacy phase III trials	- Resolution of clinical dysphagia - Avoid chest infection, pneumonia - Avoid vomiting, aspiration - Enhance cough reflex - Avoid, or early removal, of PEG/RIG tube - Improve functional outcome, e.g. mRS⁹³ - Reduce case fatality	Measure at end of trial, e.g. day 90 Outcomes need to be assessed blinded to assigned intervention
Impact	- Health economics, based on: - EuroQoL-5D⁹⁴ - Cost of mRS outcomes - Reduce length of stay in hospital	
<i>Methodology</i>		
Design	- Parallel group (most trials), or factorial⁶¹ - Active + standard care vs Standard care - Active vs Standard care	Assess medical and therapist-delivered interventions in factorial design
Randomisation	- Simple - Stratified/minimised⁹⁵	Treatment must be assigned randomly to allow concealment of allocation
Sample size	10s of patients, single or few sites, for phase II 100–1000s of patients, 10–100s of sites, for phase III	What effect size is reasonable to expect?
Training	For clinical bedside assessments, VFS and FEES	

(continued)

Table 2. Continued

Criteria	Approaches	Comments
Funding	• Academic • Commercial • Mixed academic-commercial⁹²	• Placebo or sham-controlled studies are expensive

DSRS: Dysphagia severity rating scale; EQ-5D: Euro-Qol 5 dimensions (from which health utility status can be calculated); FEES: fiberoptic endoscopic evaluation of swallowing; mRS: modified Rankin Scale; PEG: Percutaneous Endoscopic Gastrostomy; RIG: Radiologically Inserted Gastrostomy; VFS: videofluoroscopy.

form trials using a range of different antibiotics that such prophylaxis does not prevent pneumonia.

Cough is a well-known side effect of angiotensin converting enzyme inhibitors (ACEIs) and could potentially reduce pneumonia. This has only been tested in patients with chronic stroke, and effects appeared to be more pronounced in Asian than Caucasians,⁷⁷ a population that are more sensitive to ACE-I induced cough. Cilostazol, an antiplatelet agent with vasodilator effects has also been shown to reduce pneumonia in the chronic phase of stroke; the mechanism for this is unknown, but might involve bradykinin and substance P, as for ACEIs.⁷⁸ Excessive tracheobronchial secretions (bronchorrhoea) have been described in posterior circulation strokes, and anticholinergic agents could reduce secretions and pneumonia in this group.⁷⁹

Pneumonia is an early complication of stroke, and usually associated with aspiration soon after the acute event.⁸⁰ The risk of aspiration declines within the first two weeks after stroke.¹⁶ Therefore, prevention should be started early and continue over the first two weeks, the period when patients are most at risk of aspiration and pneumonia. As there is no agreed definition of post-stroke pneumonia,²⁸ comparison of the effectiveness of interventions aimed at prevention of pneumonia is difficult. Future studies should use agreed definitions.²⁷

Oral care

Poor oral care and dental hygiene increase risk of pneumonia, cause discomfort, and reduce quality of life after stroke. There are guidelines for best practice.⁸¹ The majority of data, on which the recommendations are based, are from ventilated patients on intensive care units.^{82,83} Nursing home residents, people with dementia, or with learning difficulties are high-risk groups for poor mouth care. Poor dental hygiene is recognized as being associated with vascular disease and is more common in older people. It is likely that poor oral care is a cause for pneumonia in this group, particularly if there is also dysphagia and in individuals who are enterally fed (Beavan, Meagher & Robertson, unpublished).

Patients with neurodisability have difficulty undertaking their own oral and dental care due to physical, perceptual, and cognitive difficulties and therefore rely

on help. They may be reluctant to ask for help, as oral care is not seen as a priority.⁸⁴ Lack of help is associated with poor oral and dental care.

The best way to deliver oral care is uncertain and practice varies widely.⁸¹ Nurses worry about causing aspiration and therefore, although recommended, few use toothbrushes or toothpaste. Electric and suction toothbrushes are a potential option, but they are expensive and it is uncertain if they are of benefit after acute stroke.⁸⁵ The flora of the oral cavity is altered by the stroke itself,⁶⁹ by concurrent use of antibiotics, the development of candida infections, and by the build-up of oropharyngeal residues and dental plaque. The solutions used for oral care vary between units. The best agent to use in stroke patients is unclear but using some form of diluted chlorhexidine as part of an oral care regime, as in intensive care, may be beneficial.⁸² The effectiveness and risks of pineapple juice (which contains sugar), artificial saliva and glycerin sticks are unclear. Glycerin sticks are discouraged as they may dry the mouth. The production and consistency of saliva may change post stroke and drying of the oral cavity may be affected by poor oral closure and positioning.

Patient and carer perspectives

When admitted to hospital following an acute stroke, patients and their relatives are often unaware that stroke can cause swallowing problems. They are frequently surprised, and distressed, when a “*nil by mouth*” order is placed until the swallow has been checked although this practice is evidence-based and supported by stroke guidelines.⁸⁶ This surprise is perhaps understandable as dysphagia is not a symptom a lay person would associate with stroke and does not feature in the act FAST campaign, even though dribbling saliva is common.

A swallow screen should be performed as early as possible in the person’s assessment. If the swallow is considered unsafe, and the person is put “*nil by mouth*,” the patients’ and carers’ distress are frequently exacerbated. Further problems can ensue if no one who can do a more detailed assessment is available to say whether the patient must remain nil by mouth, or if they could manage a modified diet or fluids safely.

Table 3. Ongoing studies as identified by electronic searches of WHO International Clinical Trials Registry, ISRCTN and ClinicalTrials.com databases.

Study	Identifier	Patients	Control	Outcome	Design	Sites	Patients	Funder
<i>Dihuang Yinzi</i>								
Huang et al.	ChiCTR-TRC-14004235	PSD	Placebo	VFS	RCT	1	60	
<i>GTN</i>								
ENOS ¹⁰¹	ISRCTN99414122	Acute stroke	No GTN	mRS, feeding	Single-blind RCT	173	4011	MRC UK
RIGHT-2	ISRCTN26986053	Ultra-acute stroke	Sham	mRS, feeding	Single-blind RCT	30+	800	BHF UK
<i>Metoclopramide</i>								
PRECIOUS		Acute stroke	No met.	mRS	Single-blind RCT	100+	3800	EU H2020
MAPS-2		Acute stroke + PSD	Placebo	Mortality, mRS, pneumonia	2x2 double-blind RCT	40	1160	
<i>NMES</i>								
EMSS	ISRCTN80084036	PSD		MASA, FOIS, PAS, SWAL-QOL	RCT	1	30	Ampcare LLC UK
TENSDEG	NCT01971320	PSD		Dysphagia	Single-blind RCT	6	118	Urostim I
<i>PES</i>								
STEPS	ISRCTN25681641	PSD + VFS, PAS > 3	PES sham	VFS, PAS	Single-blind RCT	14	120	Phagenesis Ltd UK
MAPS	N/A	PSD	N/A	Dysphagia	Academic database	4	10+	Unfunded
PHADER	ISRCTN87110165	PSD	N/A	DSRS, FOIS, PAS	Phase IV registry		300	Phagenesis Ltd UK
PHADR-TRAC	ISRCTN18137204	PSD in ICU				7	72	Phagenesis Ltd UK
<i>TCDS</i>								
	ISRCTN97286108	PSD		Swallowing	Dose response	1	45	NIHR UK
<i>TMS</i>								
	ChiCTR-IPC-14005435	PSD		Motor evoked potential	RCT	1	20	NSF China
	NCT02090231	PSD	Sham	Aus TOMs	RCT	1	50	Magstim Rapid2

DSRS: Dysphagia severity rating scale; FOIS: functional oral intake scale; GTN: glyceryl trinitrate; ICU: intensive care unit; N/A: not applicable; NMES: neuromuscular electrical stimulation; PAS: pharyngeal aspiration score; PES: pharyngeal electrical stimulation; PSD: post-stroke dysphagia; TCDS: transcranial direct current stimulation; TMS: transcranial magnetic stimulation; VFS: videofluoroscopy.

Even a modified diet may cause further distress as it can be aspirated, causing coughing, or if the patient is unable to swallow it, collect in a cheek causing “pouching.”⁸⁷ Attention to oral care is particularly important in these patients for safety and because retained food debris can cause halitosis, causing further indignity and carer distress.

All staff working with stroke patients should have the knowledge and skills appropriate to their role in the pathway⁸⁸ including those for the detection and management of dysphagia and its complications. Inter-professional competences have been developed to inform the training and organization of teams in all aspects of dysphagia.⁸⁹ Implementation has the potential to reduce waiting times for swallowing assessments, improve patient’s safety at mealtimes, and optimizing dysphagia management, improving both patients and carers experience.

Training of carers in addition to training of staff is recommended because difficulties with swallowing may arise not only in hospital but also after discharge, and those in close contact with the patient have the unique opportunity to notice the signs: delayed cough after seemingly drinking competently. Patients are frequently distressed by the constant stream of saliva. Even if they are able to eat, patients may not eat in the presence of others because of failing to meeting other people’s expectations of well-mannered behavior. This not only affects the patient but also their carers and friends.⁹⁰ Swallowing problems may persist long-term, and low mood and clinical depression may result.⁹¹

Trial design considerations

The design and results of completed trials help when designing future studies. Key trial designs cover both generic and dysphagia-specific factors (Table 2). Trials must be designed to minimize the potential for bias and therefore use true randomization that conceals allocation from the investigator, and outcomes must be assessed blinded to treatment. Some potential treatments for dysphagia may allow a double-blind design by using matching placebo for drug therapy or sham intervention for device studies.⁹² Where possible, trials should allow masking of the treating healthcare professional as well as the patient. However, large trials may need to have no placebo or sham if they are to replicate real-world use of the intervention. Either way, trials involving acupuncture, physical stimulation, or behavioral therapies will need a treating speech and language therapist or other professional and therefore will inherently have to be open label, albeit with blinded outcome assessment.

Dysphagia-specific trial design considerations cover the type of intervention and outcomes. The primary

outcome will depend on whether the trial is assessing primarily mechanisms (phase II) or efficacy (phase III or IV). Mechanistic studies need to focus on tolerability of the intervention and whether prognostic measures of aspiration (with assessment using FEES or VFS⁹⁶) and dysphagia (using a clinical scale such as the DSRS⁶⁰) are reduced. In contrast, phase III trials will need to assess real-world outcomes that may be dysphagia-related (such as pneumonia or need for PEG feeding) or functional (such as the modified Rankin Scale). Once the primary outcome is decided, an optimal method of analysis should be used to minimize sample size for a given power (with power typically set at 0.90); efficient statistical analyses can reduce sample size in stroke trials by 20–30%.⁹⁷

One caveat when considering the choice of primary outcome and its analysis is that treatment effects may move in opposite directions. For example, the large FOOD-2 trial of timing of tube feeding post stroke observed a non-significant reduction in death and non-significant increase in poor functional outcome (modified Rankin Scale 4 or 5).⁹⁸ (A similar divergence was seen in the CLOTS-3 trial of intermittent pneumatic compression stockings with less death but more severe dependency.^{99,100}) The underlying issue is that effective treatment of stroke complications, such as dysphagia (or pulmonary embolism as in CLOTS-3), may reduce death but thereby create a surviving population of patients with severe stroke who have significant impairment and disability.

A number of trials or observational studies are ongoing, as summarised in Geeganage et al.⁶¹ and Table 3, the latter focusing on ongoing studies.

Summary

The optimal diagnosis and treatment of PSD remain unclear and reported trials do not define optimal management. Ongoing studies may identify new strategies although their number is few. Nevertheless, their results, whether positive, neutral or negative, will help identify strategies that need testing or rejecting; if any trial is positive then a further one will probably be needed to validate the findings.

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and to establish how this might underpin development of future studies. The present report summarizes discussions at the meeting and is co-authored by meeting participants. It covers key PSD aspects including epidemiology, mechanisms, complications, diagnosis, patient and carer perspectives, therapy and medical treatment. A second workshop focused on design issues and outlined a potential academic protocol for a future trial in PSD. The SRN support covered travel and organization costs. We thank the UK Stroke Research Network, through Mrs Lucie Robinson, for supporting the workshop, Mrs Lauren Dunn for helping to organize the meeting, and Mr Wim Clarke for administering finances. PMB is Stroke Association Professor of Stroke Medicine.

Authors' contributions

Each author individually wrote parts of the review. CR collated these and did initial editing with DC. PMB did final editing and submission.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: PMB organized the NIHR SRN workshop; is senior author of a Cochrane review on PSD (see literature^{62,63}); is Chief Investigator of the STEPS trial of PES (with funding by Phagenesis Ltd); has received honoraria and travel expenses from Phagenesis Ltd for his work on STEPS and PHADER; and coordinates the academic MAPS database of real-world use of PES. SH is inventor of PES, and owns stock in Phagenesis Ltd. PMB, CR, DLC, AW were Principal Investigators in the STEPS trial. PMB, CMcL have submitted clinical data to the MAPS database. PMB, SH, CMcL DS spoke at a Phagenesis Ltd-sponsored symposium and received travel expenses to attend. DLC has received travel expenses from Phagenesis Ltd.

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References

- Kumar S, Selim MH and Caplan LR. Medical complications after stroke. *Lancet Neurol* 2010; 9: 105–118.
- Smithard DG, O'Neill PA, Park C, et al. Complications and outcome after acute stroke Does dysphagia matter? *Stroke* 1996; 27: 1200–1204.
- Mann G, Hankey GJ and Cameron D. Swallowing disorders following acute stroke: prevalence and diagnostic accuracy. *Cerebrovasc Dis* 2000; 10: 380–386.
- Smithard D, Smeeton N and Wolfe C. Long-term outcome after stroke: does dysphagia matter? *Age Ageing* 2007; 36: 90–94.
- Wilson RD. Mortality and cost of pneumonia after stroke for different risk groups. *J Stroke Cerebrovasc Dis* 2012; 21: 61–67.
- Rofes L, Arreola V, Almirall J, et al. Diagnosis and management of oropharyngeal dysphagia and its nutritional and respiratory complications in the elderly. *Gastroenterol Res Pract* 2011; 2011: 13.
- Mackay J and Mensah G. *Atlas of heart disease and stroke*. Geneva, Switzerland: World Health Organization, 2004.
- Martino R, Foley N, Bhogal S, Diamant N, Speechley M and Teasell R. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. *Stroke* 2005; 36: 2756–2763.
- Leder S, Acton L, Lisitano H and Murray J. Fiberoptic endoscopic evaluation of swallowing (FEES) with and without blue-dyed food. *Dysphagia* 2005; 20: 157–162.
- Schmidt J, Holas M, Halvorson K and Reding M. Videofluoroscopic evidence of aspiration predicts pneumonia and death but not dehydration following stroke. *Dysphagia* 1994; 9: 7–11.
- Smithard D, O'Neill P, England R, et al. The natural history of dysphagia following a stroke. *Dysphagia* 1997; 12: 188–193.
- Ramsey D, Smithard D and Kalra L. Silent aspiration: what do we know? *Dysphagia* 2005; 20: 218–225.
- Falsetti P, Acciai C, Palilla R, et al. Oropharyngeal dysphagia after stroke: incidence, diagnosis, and clinical predictors in patients admitted to a neurorehabilitation unit. *Cerebrovasc Dis* 2009; 18: 329–335.
- Mann G, Hankey G and Cameron D. Swallowing function after stroke prognosis and prognostic factors at 6 months. *Stroke* 1999; 30: 744–748.
- Leder S, Cohn S and Moller B. Fiberoptic endoscopic documentation of the high incidence of aspiration following extubation in critically ill trauma patients. *Dysphagia* 1998; 13: 208–212.
- Kidd D, Lawson J, Nesbitt R and MacMahon J. The natural history and clinical consequences of aspiration in acute stroke. *Quarter J Med* 1995; 88: 409–413.
- Smith C, Logemann J, Colangelo L, Rademaker A and Pauloski B. Incidence and patient characteristics associated with silent aspiration in the acute care setting. *Dysphagia* 1999; 14: 1–7.
- Aviv J, Martin J, Sacco R, et al. Supraglottic and pharyngeal sensory abnormalities in stroke patients with dysphagia. *Ann Otol Rhinol Laryngol* 1996; 105: 92–97.
- Hamdy S, Aziz Q, Rothwell J, et al. The cortical topography of human swallowing musculature in health and disease. *Nat Med* 1996; 2: 1217–1224.
- Hamdy S and Aziz Q. Recovery of swallowing after dysphagic stroke relates to functional reorganization in the intact motor cortex. *Gastroenterology* 1998; 115: 1104–1112.
- Li S, Luo C, Yu B, et al. Functional magnetic resonance imaging study on dysphagia after unilateral hemispheric stroke: a preliminary study. *J Neurol Neurosurg Psychiatry* 2009; 80: 1320–1329.
- Teismann IK, Suntrup S, Warnecke T, et al. Cortical swallowing processing in early subacute stroke. *BMC Neurol* 2011; 11: 34.
- Barritt A and Smithard D. Role of cerebral cortex plasticity in the recovery of swallowing function following dysphagic stroke. *Dysphagia* 2009; 24: 83–90.
- Westendorp W, Nederkoorn P, Vermeij J, Dijkgraaf M and van de Beek D. Post-stroke infection: a systematic review and meta-analysis. *BMC Neurol* 2011; 11: 110.

25. Hoffmann S, Malzahn U, Harms H, et al. Development of a clinical score (A2DS2) to predict pneumonia in acute ischemic stroke. *Stroke* 2012; 43: 2617–2623.
26. Smith C and Tyrrell P. Current and emerging treatments for acute stroke: relationships with infection. *Infect Disord Drug Targets* 2010; 10: 112–121.
27. Smith C, Kishore A, Vail A, et al. Diagnosis of stroke-associated pneumonia: recommendations from the pneumonia in stroke consensus group. *Stroke* 2015; 46: 2335–2340.
28. Kishore A, Vail A, Chamorro A, et al. How is pneumonia diagnosed in clinical stroke research? A systematic review and meta-analysis. *Stroke* 2015; 46: 1202–1209.
29. Finlayson O, Kapral M, Hall R, Asllani E, Selchen D and Saposnik G. Risk factors, inpatient care, and outcomes of pneumonia after ischemic stroke. *Neurology* 2011; 77: 1338–1345.
30. Rohweder G, Ellekjaer H, Salvesen O, Naalsund E and Indredavik B. Functional outcome after common post-stroke complications occurring in the first 90 days. *Stroke* 2015; 46: 65–70.
31. Govan L, Langhorne P and Weir C. Does the prevention of complications explain the survival benefit of organized inpatient (stroke unit) care? Further analysis of a systematic review. *Stroke* 2007; 38: 2536–2540.
32. Tong X, Kuklina E, Gillespie C and George M. Medical complications among hospitalizations for ischemic stroke in the United States from 1998 to 2007. *Stroke* 2010; 41: 980–986.
33. Foley NC, Martin RE, Salter KL, et al. A review of the relationship between dysphagia and malnutrition following stroke. *J Rehabil Med* 2009; 41: 707–713.
34. McHorney C, Robbins J, Lomax K, et al. The SWAL-QOL and SWAL-CARE outcomes tool for oropharyngeal dysphagia in adults: III. Documentation of reliability and validity. *Dysphagia* 2002; 17: 97–114.
35. Perry L and Love C. Screening for dysphagia and aspiration in acute stroke: a systematic review. *Dysphagia* 2001; 16: 7–19.
36. Leder S, Sasaki C and Burrell M. Fiberoptic endoscopic evaluation of dysphagia to identify silent aspiration. *Dysphagia* 1998; 13: 19–21.
37. O'Neill P. Swallowing and prevention of complications. *Br Med Bull* 2000; 56: 457–465.
38. Daniels S, Anderson J and Willson P. Valid items for screening dysphagia risk in patients with stroke: a systematic review. *Stroke* 2012; 43: 829–897.
39. Martino R, Silver F, Teasell R, et al. The toronto bedside swallowing screening test (TOR-BSST): development and validation of a dysphagia screening tool for patients with stroke. *Stroke* 2009; 40: 555–561.
40. Trapl M, Enderle P, Nowotny M, et al. Dysphagia bedside screening for acute-stroke patients: the gugging swallowing screen. *Stroke* 2007; 38: 2948–2952.
41. DePippo K, Holas M and Reding M. Validation of the 3-oz water swallow test for aspiration following stroke. *Arch Neurol* 1992; 49: 1259–1261.
42. Nathadwarawala K, Nicklin J and Wiles C. A timed test of swallowing capacity for neurological patients. *J Neurol Neurosurg Psychiatry* 1992; 55: 822–825.
43. Gordon C, Hewer R and Wade D. Dysphagia in acute stroke. *Br Med J* 1987; 295: 411–414.
44. Crary M and Baron J. Endoscopic and fluoroscopic evaluations of swallowing: comparison of observed and inferred findings. *Dysphagia* 1997; 2: 108.
45. Langmore S, Schatz K and Olson N. Endoscopic and videofluoroscopic evaluations of swallowing and aspiration. *Ann Otol Rhinol Laryngol* 1991; 100: 678–681.
46. Colodny N. Effects of age, gender, disease, and multisystem involvement on oxygen saturation levels in dysphagic persons. *Dysphagia* 2001; 16: 48–57.
47. Perie S, Laccourreye L, Flahault A, Hazebrucq V, Chaussade S and St Guily JL. Role of videoendoscopy in assessment of pharyngeal function in oropharyngeal dysphagia: comparison with videofluoroscopy and manometry. *Laryngoscope* 1998; 108: 1712–1716.
48. Kelly A, Leslie P, Beale T, Payten C and Drinnan M. Fiberoptic endoscopic evaluation of swallowing and videofluoroscopy: does examination type influence perception of pharyngeal residue severity? *Clin Otolaryngol* 2006; 31: 425–432.
49. Rao N, Brady S, Chaudhuri G, Donzelli J and Wesling M. Gold-standard? Analysis of the videofluoroscopic and fiberoptic endoscopic swallow examinations. *J Appl Res Clin Experiment Therapeut* 2003; 3: 89–96.
50. Wu C, Hsiao T, Chen J, Chang Y and Lee S. Evaluation of swallowing safety with fiberoptic endoscope: comparison with videofluoroscopic technique. *Laryngoscope* 1997; 107: 396–401.
51. Lowery D. Assessment and measurement tools used in the evaluation of swallowing. *Curr Opin Otolaryngol Head Neck Surg* 2001; 9: 134–138.
52. Langmore S, Schatz K and Olsen N. Fiberoptic endoscopic examination of swallowing safety: a new procedure. *Dysphagia* 1988; 2: 216–219.
53. Langmore S. Laryngeal sensation: a touchy subject. *Dysphagia* 1998; 13: 93–94.
54. Bulow M, Olsson R and Ekberg O. Videomanometric analysis of supraglottic swallow, effortful swallow, and chin tuck in healthy volunteers. *Dysphagia* 1999; 14: 67–72.
55. Speyer R, Baijens L, Heijen M and Zwijnenberg I. Effects of therapy in oropharyngeal dysphagia by speech and language therapists: a systematic review. *Dysphagia* 2010; 25: 40–65.
56. Clave P, De Kraa M, Arreola V, Girvent M, Palomera E and Serra-Prat M. The effect of bolus viscosity on swallowing function in neurogenic dysphagia. *Aliment Pharm Therap* 2006; 24: 1385–1394.
57. Payne C, Methven L, Bell A and Fairfield C. Variability of starch based thickened fluids in the hospital setting. *J Text Stud* 2012; 43: 95–105.
58. Robbins J, Kays S, Gangon R, et al. The effects of lingual exercise in stroke patients with dysphagia. *Arch Phys Med Rehabil* 2007; 88: 150–158.
59. Carnaby-Mann G and Crary M. McNeill dysphagia therapy programme: a case-control study. *Arch Phys Med Rehabil* 2010; 91: 743–749.
60. Jayasekaran V, Singh S, Tyrrell P, et al. Adjunctive functional pharyngeal electrical stimulation reverses

- swallowing disability after brain lesions. *Gastroenterology* 2010; 138: 1737–1746.
61. Geeganage C, Beavan J, Ellender S and Bath PM. Interventions for dysphagia and nutritional support in acute and subacute stroke. *Cochrane Database Syst Rev* 2012; 10: CD000323.
 62. Bath PMW and Lee H. Cochrane systematic review of interventions for dysphagia in acute stroke. *Int J Stroke* 2014; 9: 22.
 63. Chamorro A, Urra X and Planas A. Infection after acute ischemic stroke: a manifestation of brain-induced immunodepression. *Stroke* 2007; 38: 1097–1103.
 64. Dines D, Baker W and Scantland W. Aspiration pneumonia – Mendelson's syndrome. *J Am Med Assoc* 1961; 176: 229–231.
 65. Hinchey J, Shepard T, Furie K, Smith D, Wang D and Tonn S. Formal dysphagia screening protocols prevent pneumonia. *Stroke* 2005; 36: 1972–1976.
 66. Titsworth W, Abram J, Fullerton A, et al. Prospective quality initiative to maximize dysphagia screening reduces hospital-acquired pneumonia prevalence in patients with stroke. *Stroke* 2013; 44: 3154–3160.
 67. Ingeman A, Anderson G, Hundborg H, Svendsen M and Johnsen S. Processes of care and medical complications in patients with stroke. *Stroke* 2011; 42: 167–172.
 68. Cuesy P, Sotomayor P and Pina J. Reduction in the incidence poststroke nosocomial pneumonia by using the 'turn-mob' programme. *J Stroke Cerebrovasc Dis* 2010; 19: 23–28.
 69. Gosney M, Martin M and Wright A. The role of selective decontamination of the digestive tract in acute stroke. *Age Ageing* 2006; 35: 42–47.
 70. Gomes G, Pisani J, Macedo E and Campos A. The nasogastric feeding tube as a risk factor for aspiration and aspiration pneumonia. *Curr Opin Clin Nutr Metabol Care* 2003; 6: 327–333.
 71. Warusevitane A, Karuntilake D, Lally F, Sim J and Roffe C. The safety and effect of metoclopramide to prevent pneumonia in stroke patients fed via nasogastric tubes (MAPS trial). *Stroke* 2015; 46: 454–460.
 72. Westendorp W, Vermeij J, Vermeij F, et al. Antibiotic therapy for preventing infections in patients with acute stroke. *Cochrane Database Syst Rev* 2012; 1: CD008530.
 73. Harms H, Prass K, Meisel C, et al. Preventive antibacterial therapy in acute ischemic stroke: a randomized controlled trial. *PLoS One* 2008; 3: e2158.
 74. Chamorro A, Horcajada J, Obach V, et al. The early systemic prophylaxis of infection after stroke study: a randomized clinical trial. *Stroke* 2005; 36: 1495–1500.
 75. Westendorp W, Vermeij J and Zock E. The Preventive Antibiotics in Stroke Study (PASS): a pragmatic randomised open-label masked endpoint clinical trial. *Lancet* 2015; 385: 1519–1526.
 76. Kalra L, Irshad S, Hodsoll J, et al. Prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF): a prospective, cluster-randomised, open-label, masked endpoint, controlled clinical trial. *Lancet* 2015; 386: 1835–1844.
 77. Liu C, Shau W, Wu C and Lai M. Angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers and pneumonia risk among stroke patients. *J Hypertension* 2012; 30: 2223–2229.
 78. Shinohara Y. Antiplatelet cilostazol is effective in the prevention of pneumonia in ischemic stroke patients in the chronic stage. *Cerebrovasc Dis* 2006; 22: 57–60.
 79. Sung C, Lee T and Chu N. Bronchorrhea following stroke. *Eur Neurol* 2012; 67: 57–62.
 80. Dziewas R, Ritter M, Schilling M, et al. Pneumonia in acute stroke patients fed by nasogastric tube. *J Neurol Neurosurg Psychiatry* 2004; 75: 852–856.
 81. Gerodontology BSo. *Guidelines for the oral healthcare of stroke survivors*. UK: British Society of Gerodontology, 2010.
 82. Shi Z, Xie H, Wang P, et al. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. *Cochrane Database Syst Rev* 2013; 8: CD008367.
 83. Brady M, Furlanetto D, Hunter R, Lewis S and Milne V. Staff-led interventions for improving oral hygiene in patients following stroke. *Cochrane Database Syst Rev* 2006; 4: CD003864.
 84. Yaacob M, Worthington H, Deacon S, et al. Powered versus manual toothbrushing for oral health. *Cochrane Database Syst Rev* 2014; 6: CD002281.
 85. Chalmers J, Spencer A, Wright F and Carter K. The oral health assessment tool – validity and reliability. *Aust Dent J* 2005; 50: 191–199.
 86. Intercollegiate Stroke Working Party. *National clinical guideline for stroke*, 4th ed. Great Britain: Author, 2012.
 87. Edmans J. *Occupational therapy and stroke*, 2nd ed. New Jersey, USA: Wiley-Blackwell, 2010.
 88. Watkins C, Jenkinson D, Scoular P, et al. Stroke specific education framework (SSEF). Journal [serial on the Internet]. Department of Health, 2009.
 89. Boaden E, Davies S, Storey L and Watkins C. *Inter professional dysphagia framework*. Preston: University of Central Lancashire, 2006.
 90. Jacobsson C, Axelsson K, Osterlind P and Norberg A. How people with stroke and healthy older people experience the eating process. *J Clin Nurs* 2000; 9: 255–264.
 91. Ekberg O, Hamdy S, Woisard V, Wuttge-Hannig A and Ortega P. Social and psychological burden of dysphagia: it's impact on diagnosis and treatment. *Dysphagia* 2002; 17: 139–146.
 92. Bath P, Brainin M, Brown C, et al. Testing devices for the prevention and treatment of stroke and its complications. *Int J Stroke* 2014; 9: 683–695.
 93. Lees KR, Bath PMW, Schellinger PD, et al. Contemporary outcome measures in acute stroke research: choice of primary outcome measure. *Stroke* 2012; 43: 1163–1170.
 94. Brooks R. EuroQol: the current state of play. *Health Policy* 1996; 37: 53–72.
 95. Weir CJ and Lees KR. Comparison of stratification and adaptive methods for treatment allocation in an acute stroke clinical trial. *Stat Med* 2003; 22: 705–726.
 96. Warnecke T, Ritter MA, Kroger B, et al. Fiberoptic endoscopic dysphagia severity scale predicts outcome after acute stroke. *Cerebrovasc Dis* 2009; 28: 283–289.

97. Bath PM, Lees KR, Schellinger PD, et al. Statistical analysis of the primary outcome in acute stroke trials. *Stroke* 2012; 43: 1171–1178.
98. The FOOD Trial Collaboration. Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial. *Lancet* 2005; 365: 764–772.
99. Dennis M, Sandercock P, Reid J, Graham C, Forbes J and Murray G. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. *Lancet* 2013; 382: 516–524.
100. Collaboration CT. Effect of intermittent pneumatic compression on disability, living circumstances, quality of life, and hospital costs after stroke: secondary analyses from CLOTS 3, a randomised trial. *Lancet Neurol* 2014; 13: 1186–1192.
101. Bath P, Woodhouse L, Scutt P, et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. *Lancet* 2014; 385: 617–628.