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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 institutionalisation due in part to aspiration, pneumonia and malnutrition. Although most patients recover swallowing spontaneously, a significant minority still have dysphagia at 6 months. Although multiple advances have been made in the hyper acute 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.

Background

Stroke is recognised 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 6 months.(2, 3) Persistent dysphagia independently predicts poor outcome and institutionalisation.(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.

Epidemiology of PSD

Globally, fifteen million people suffer a stroke annually *Atlas [7] and up to 65% have swallowing problems of whom half will be symptomatic.(7) Some early studies included people with diagnosed dysphagia who were referred for further assessment and this increased artificially the rate of aspiration.(8, 9) The true prevalence of dysphagia can only be established by studying an unselected stroke population (3, 10) and there have been no such recent studies.

In acute stroke the prevalence of dysphagia has been reported as between 28 and 65%,(3, 10-12) 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, 7) 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, 10) In general, if the swallow does not show any signs of recovery in the first ten days after stroke, the return of a safe swallow may take up two or three months to show signs of recovery.(13)

In hyperacute stroke studies, swallowing has been assessed using a water swallow test, a screening test rather than full assessment.(14) Many subsequent swallow screens have been based on this with or without a scoring mechanism.(15-18) Some tests require specialist training or are copyrighted (e.g. TOR-BSST).(15) Assessment later after the stroke is more comprehensive but will detect fewer cases as swallowing improves recovers.(10, 19) It is difficult to estimate how many patients simply have difficulty swallowing and how many are also aspirating as few studies have performed routine videofluoroscopy (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 fibreoptic endoscopic evaluation of swallowing (FEES) is relevant or whether a minor tongue movement abnormality on clinical examination is important if it does not cause symptoms.

Mechanisms of post-stroke dysphagia

PSD is thought to be due to damage to the cortex and subcortical structures. Cortical re-organisation 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.(20) A stroke lesion affecting the 'dominant swallowing hemisphere' may therefore be responsible for dysphagia following unilateral hemispheric stroke.

TMS studies in patients with hemispheric strokes showed that patients with dysphagia have smaller pharyngeal responses from the unaffected hemisphere as compared to non-dysphagic patients. This suggests that in dysphagic patients the non-dominant unaffected hemisphere may not be able to maintain swallowing.(21) In an attempt to understand the mechanism for recovery of swallowing after stroke, swallowing was studied by VFS and TMS in 28 hemispheric stroke patients at baseline (71% dysphagic), at 1 month (46% dysphagic) and at 3 months (41% dysphagic) to

examine pharyngeal cortical representation at each time point. Subjects who were non-dysphagic at baseline 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 when dysphagic. These findings suggest that re-organisation in the contralesional hemisphere is key in swallowing recovery.(22) This is illustrated in Figure 1: the subject had a left hemispheric stroke and the shaded areas correspond to the cortical areas representing the pharyngeal muscles with TMS; the subject recovered swallowing function at one month in parallel with expansion of pharyngeal cortical representation in the unaffected right hemisphere.

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 in the unaffected hemisphere are crucial in swallowing recovery.(23) Similarly, a magnetoencephalography (MEG) study imaged swallowing activations in subacute stroke patients with and without dysphagia and compared findings with healthy controls.(24) Increased pharyngeal motor representation in the contralesional hemisphere in hemispheric stroke patients without dysphagia was reported, consistent with findings by others. By contrast, in the dysphagic stroke patients there was almost absent cortical activation in the unaffected hemisphere during swallowing.

Neuroplasticity could play a significant role in the recovery of swallowing function. Neuroplasticity is an experience-driven process, which leads to long-term morphological or functional changes in the central nervous system and can result in behavioural changes.(25) Environmental changes, conditioning stimuli and brain lesions can evoke such plastic changes. Brain injury, such as hemispheric stroke affecting the pharyngeal motor cortex, is an example of this with plastic changes in the unaffected hemisphere occurring during recovery of swallowing function.(26) Traditionally, it has been believed that plastic changes occur at a synaptic level, when neurons fire together with co-existing activation of pre- and post- synaptic membranes leading to strengthening of the synapse.

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 hospitalised patients.(27) In those at greatest risk because of advanced age, severe stroke and PSD, the incidence of pneumonia may be as high as 40%.(28) Confirmed aspiration is strongly associated with pneumonia (relative risk 11.56; 95% CI 3.36 to 39.77).(7) Current thinking recognises the potential interplay between poor oral health, aspiration and immune suppression in determining susceptibility to pneumonia.(29) 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.(30) 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.(31)

Patients developing pneumonia are more likely to die or survive dependent on others,(27, 32, 33) 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).(34) 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.(35) 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.(36) 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 available (37) 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 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.(38) CBA predicts pharyngeal dysphagia poorly and has been criticised for its inaccuracy in identifying aspiration,(39, 40) missing up to 40% of people who aspirate.(39)

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 trans-nasally to the hypo-pharynx to view the larynx and pharynx. Food and drinks are dyed to aid visualisation 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 hypo pharynx and detect aspiration.(41, 42) 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 spoonful's of contrast given during VFS. However, FEES is not routinely available in many hospitals worldwide which, like VFS, limits the number of centres 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,(42-47) and they are the only two assessments

that can diagnose aspiration reliably.(48) 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.(48) Validation of FEES against VFS showed high sensitivity and specificity.(42, 49, 50) In one study FEES was shown to detect aspiration more reliably than VFS.(47) 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 individualised.

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.(51, 52)

Thickening liquids slows the bolus and increases bolus cohesion leading to a reduction in penetration and aspiration.(53) The quality and extent of modification of food and fluids is 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.(54)

Rehabilitation techniques such as oral and lingual exercises tend to focus on strength and endurance.(55) They result in an increase in isometric pressure, but are aimed at specific parts of the swallow so it is not clear how they generalise 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 programme.(56) More recently neuro-stimulation 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.(57) Recent reviews of dysphagia management report limited consistency of evidence for interventions, but with some evidence of effectiveness for behavioural interventions and PES on aspects of swallow and functional outcomes.(52, 58)

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 randomisation. Issues around subjectivity of fluid modification can be addressed by using pre-thickened bolus which has been shown to be more consistent.(55)

Medical treatment of dysphagia

There is no established medical treatment for PSD, although multiple studies have investigated a variety of interventions, including therapist-delivered, behavioural, acupuncture, electrical or magnetic stimulation, and drugs. Completed randomised controlled trials are summarised in a Cochrane Collaboration review (58) that is currently being updated.(59) Table 1 summarises 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-centre, 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,(7) and stroke-induced immunosuppression.(60) 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.(34) 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(61, 62) and early mobilisation.(63, 64) Pharmacologic approaches could further decrease the risk of pneumonia. Selective oral decontamination lowers oropharyngeal colonisation with pathogenic Gram negative bacteria, and was associated with a significant reduction in pneumonia in a study of 203 patients with acute stroke.(65) Prevention of vomiting and regurgitation is another promising approach, as stroke does not only cause dysphagia, but is also associated with lower oesophageal sphincter dysfunction, gastro-paresis, increased gastric residual volume and gastro-oesophageal reflux.(66) 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.(67)

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.(68) Most of the included trials used broad-spectrum antibiotics, started within 24 hours of stroke onset and continued for 3-5 days.(69, 70) While antibiotic prophylaxis prevented infections overall, there was no reduction in pneumonia. A recently published large randomised trial of prophylactic ceftriaxone in 2250 unselected patients with acute stroke confirmed these findings with an overall reduction in infections, but no effect on pneumonia.(71) The results of a further large study of antibiotic prophylaxis (Stroke-Inf) are likely to be available by the end of 2015 (http://www.isrctn.com/ISRCTN37118456).

Cough is a well- known side effect of angiotensin converting enzyme inhibitors (ACEIs) and could potentially reduce pneumonia, but this has only been tested in

patients with chronic stroke.(72) 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.(73) Excessive tracheobronchial sections (bronchorrhoea) have been described in posterior circulation strokes, and anticholinergic agents could reduce secretions and pneumonia in this group.(74)

Pneumonia is an early complication of stroke, and usually associated with aspiration soon after the acute event.(75) The risk of aspiration declines within the first two weeks after stroke.(76) 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,(31) comparison of the effectiveness of interventions aimed at prevention of pneumonia is difficult. Future studies should use agreed definitions.(30)

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.(77) The majority of data, on which the recommendations are based, are from ventilated patients on intensive care units.(78, 79) Nursing home residents, people with dementia or with learning difficulties are high risk groups for poor mouth care. Poor dental hygiene is recognised 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.(80) Lack of help is associated with poor oral and dental care.

The best way to deliver oral care is uncertain and practice varies widely.*[87] 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.(81) The flora of the oral cavity is altered by the stroke itself,(65) 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.(78) The effectiveness and risks of pineapple juice (which contains sugar), artificial saliva and glycerine sticks are unclear. Glycerine 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.(82) 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. 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".(83) 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 pathway *[91] including those for the detection and management of dysphagia and its complications. Inter-professional competences have been developed to inform the training and organisation of teams in all aspects of dysphagia.(84) Implementation has the potential to reduce waiting times for swallowing assessments,

improve patient's safety at mealtimes, and optimising 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 bat 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 behaviour. This not only affects the patient but also their carers and friends.(85) Swallowing problems may persist long-term, and low mood and clinical depression may result.(86)

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 minimise the potential for bias and therefore use true randomisation 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.(87) 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 behavioural 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 VFS (88)) and dysphagia (using a clinical scale such as the DSRS (57)) 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 Score). Once the primary outcome is decided, an optimal method of analysis should be used to

minimise 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%.(89)

A number of trials or observational studies are ongoing, as summarised in (90) and table 3, the latter focussing on ongoing studies.

Summary

The optimal diagnosis and treatment of PSD remains 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.

Acknowledgements

The UK NIHR Clinical Research Network, Stroke (formally Stroke Research Network, SRN) supports portfolio development workshops that bring together clinicians and researchers from multiple disciplines with the aim to develop high quality clinical trials. The first of a two part SRN funded workshop on PSD was held on 20th June 2014 in Nottingham UK. The meeting was attended by doctors, nurses, speech & language therapists (SLTs), clinical researchers and statisticians. The meeting aimed to summarise current knowledge on PSD and to establish how this might underpin development of future studies. The present report summarises 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 focussed on design issues and outlined a potential academic protocol for a future trial in PSD. The SRN support covered travel and organisation costs.

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Declarations of interest

PMB organised the NIHR SRN workshop; is senior author of a Cochrane review on PSD (see (59, 90)); 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.

Table 1. Potential treatments for post stroke dysphagia and their effects on important outcomes. Results from Cochrane Collaboration review,(90) currently being updated.(59) Data are odds ratio (95% confidence intervals); odds ratio less than 1.00 are compatible with benefit - significant results highlighted in bold.

Outcome	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)	-

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

Criteria	Approaches	Comments
Subjects		
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
Intervention		
Active	• As already studied (table 1) • Novel approach	
Comparator	• Placebo - against active drug • Sham - against active device (87) • No comparator	• Large trials may need a control group comprising only standard care
Background evidence	• Based on systematic review(s), ideally using individual patent data	• See Table 1
Outcomes		
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	• Measure at end of trial, e.g. day 90 • Outcomes need to be assessed blinded to assigned intervention

	• Avoid, or early removal, of PEG/RIG tube • Improve functional outcome, e.g. mRS (91) • Reduce case fatality	
Impact	Health economics, based on: • EuroQoL-5D (92) • Cost of mRS outcomes • Reduce length of stay in hospital	
Methodology		
Design	• Parallel group (most trials), or factorial (90) • Active + standard care vs Standard care • Active vs Standard care	• Assess medical and therapist-delivered interventions in factorial design
Randomisation	• Simple • Stratified/minimised (93)	• 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	
Funding	• Academic • Commercial • Mixed academic-commercial (87)	• 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: fibreoptic endoscopic evaluation of swallowing; mRS: modified Rankin Scale; PEG: Percutaneous Endoscopic Gastrostomy; RIG: Radiologically Inserted Gastrostomy; VFS: videofluoroscopy.

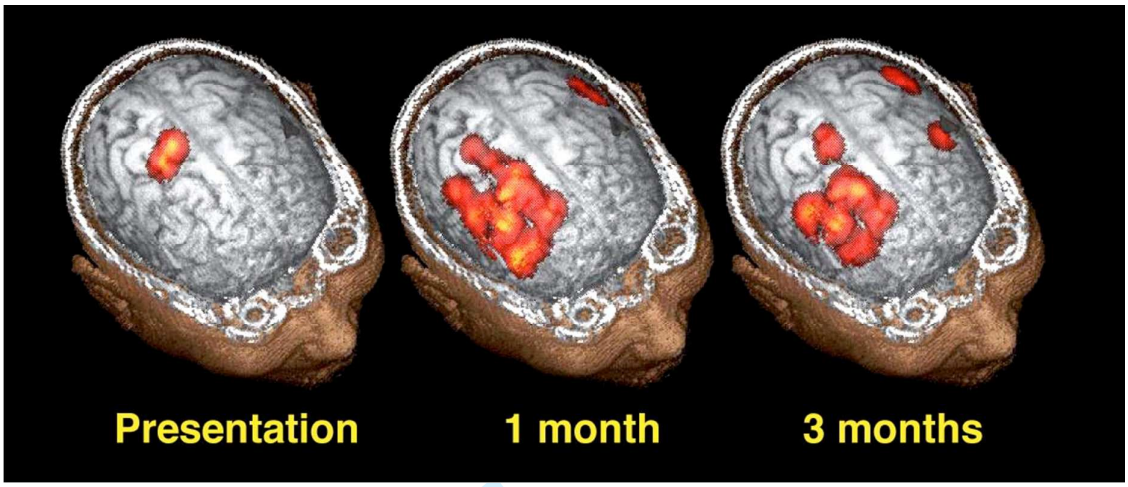
Table 3. Ongoing studies as identified by electronic searches of WHO International Clinical Trials Registry, ISRCTN and Clinicaltrials.com databases.

Study	Identifier	Patients	Control	Outcome	Design	Sites	Patients	Funder
Dihuang Yinzi								
Huang et al	ChiCTR-TRC-14004235	PSD	Placebo	VFS	RCT	1	60	
GTN								
ENOS (94)	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
Metoclopramide								
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	?
NMES								
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
PES								
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
Prophylactic								

antibiotics Stroke-Inf	ISRCTN37118456	Acute stroke +PSD	No PA	Pneumonia mRS	Cluster RCT	30+	1200	NIHR RfPB UK
TCDS	ISRCTN97286108	PSD	?	Swallowing	Dose response	1	45	NIHR UK
TMS	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

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.(22)



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References

1. Kumar S, Selim MH, Caplan LR. Medical complications after stroke. Lancet Neurol 2010;9(1):105-18.
2. Smithard DG, O'Neill PA, Park C, et al. Complications and outcome after acute stroke. Does dysphagia matter? Stroke 1996;27:1200-4.
3. Mann G, Hankey GJ, Cameron D. Swallowing disorders following acute stroke: prevalence and diagnostic accuracy. Cerebrovascular Diseases 2000;10:380-6.
4. Smithard D, Smeeton N, Wolfe C. Long-term outcome after stroke: does dysphagia matter? Age and Ageing 2007;36(1):90-4.
5. RD. W. Mortality and Cost of Pneumonia After Stroke for Different Risk Groups Journal of Stroke and Cerebrovascular Diseases 2012;21(1).
6. Rofes L, Arreola V, Almirall J, et al. Diagnosis andManagement of Oropharyngeal Dysphagia and
Its Nutritional and Respiratory Complications in the Elderly. Gastroenterology Research and Practice 2011;2011(818979):13.
7. Martino R, Foley N, Bhogal S, Diamant N, Speechley M, Teasell R. Dysphagia After Stroke: Incidence, Diagnosis, and Pulmonary Complications. Stroke 2005;36(12):2756-63.
8. Leder S, Acton L, Lisitano H, Murray J. Fiberoptic Endoscopic Evaluation of Swallowing (FEES) with and without Blue-Dyed Food. Dysphagia 2005;20(2):157-62.
9. Schmidt J, Holas M, Halvorson K, Redingm M. Videofluoroscopic evidence of aspiration predicts pneumonia and death but not dehydration following stroke. Dysphagia 1994;9(1):7-11.
10. Smithard D, O'Neill P, England R, et al. The natural history of dysphagia following a stroke. Dysphagia 1997;12:188-93.
11. Ramsey D, Smithard D, Kalra L. Silent aspiration: what do we know? Dysphagia 2005;20(3):218-25.
12. Falsetti P, Acciai C, Palilla R, et al. Oropharyngeal Dysphagia after Stroke: Incidence, Diagnosis, and Clinical Predictors in Patients Admitted to a Neurorehabilitation Unit. Cerebrovascular Disease 2009;18(5):329-35.
13. Mann G, Hankey G, Cameron D. Swallowing Function After Stroke Prognosis and Prognostic Factors at 6 Months. Stroke 1999;30:744-8.
14. Daniels S, Anderson J, Willson P. Valid Items for Screening Dysphagia Risk in Patients With Stroke
A Systematic Review. Stroke 2012;43:829-97.
15. 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;40:555-61.
16. Trapl M, Enderle P, Nowotny M, et al. Dysphagia Bedside Screening for Acute-Stroke Patients The Gugging Swallowing Screen. Stroke 2007;38(11):2948-52.
17. DePippo K, Holas M, Reding M. Validation of the 3-oz water swallow test for aspiration following stroke Archives of Neurology 1992;49(12):1259-61.
18. Nathadwarawala K, Nicklin J, Wiles C. A timed test of swallowing capacity for neurological patients. Journal of Neurology Neurosurgery and Psychiatry 1992;55(9):822-5.
19. Gordon C, Hewer R, Wade D. Dysphagia in acute stroke. British Medical Journal 1987;295(6595):411-4.
20. Hamdy S, Aziz Q, Rothwell J, et al. The cortical topography of human swallowing musculature in health and disease. NatureMedicine 1996;2(11):1217-24.
21. Hamdy S, Aziz Q, Rothwell J, et al. Explaining oropharyngeal dysphagia after unilateral hemispheric stroke. The Lancet 1997;350(9097):686-92.

22. Hamdy S, Aziz Q. Recovery of Swallowing After Dysphagic Stroke Relates to Functional Reorganization in the Intact Moror Cortex. Gastroenterology 1998;115(5):1104-12.
23. Li S, Luo C, Yu B, et al. Functional magnetic resonance imaging study on dysphagia after unilateral hemispheric stroke: a preliminary study. Journal of Neurology Neurosurgery and Psychiatry 2009;80(12):1320-9.
24. Teismann IK, Suntrup S, Warnecke T, et al. Cortical swallowing processing in early subacute stroke. Bmc Neurology 2011;11.
25. Martin R. Neuroplasticity and Swallowing. Dysphagia 2009;24:218-29.
26. Barritt A, Smithard D. Role of cerebral cortex plasticity in the recovery of swallowing function following dysphagic stroke. Dysphagia 2009;24(1):83-90.
27. Westendorp W, Nederkoorn P, Vermeij J, Dijkgraaf M, van de Beek D. Post-stroke infection: A systematic review and meta-analysis. BMC Neurology 2011;11:110.
28. Hoffmann S, Malzahn U, Harms H, et al. Development of a clinical score (A2DS2) to predict pneumonia in acute ischemic stroke. Stroke 2012;43(10):2617-23.
29. Smith C, Tyrrell P. Current and emerging treatments for acute stroke: relationships with infection. Infectious Disorders - Drug Targets 2010;10(2):112-21.
30. Smith C, Kishore A, Vail A, et al. Diagnosis of Stroke-Associated Pneumonia: Recommendations From the Pneumonia in Stroke Consensus Group. Stroke 2015;46(8):2335-40.
31. 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(5):1202-9.
32. Finlayson O, Kapral M, Hall R, Asllani E, Selchen D, Saposnik G. Risk factors, inpatient care, and outcomes of pneumonia after ischemic stroke. Neurology 2011;77(14):1338-45.
33. Rohweder G, Ellekjaer H, Salvesen O, Naalsund E, Indredavik B. Functional outcome after common poststroke complications occurring in the first 90 days. Stroke 2015;46(1):65-70.
34. Govan L, Langhorne P, 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(9):2536-40.
35. Tong X, Kuklina E, Gillespie C, George M. Medical complications among hospitalizations for ischemic stroke in the United States from 1998 to 2007. Stroke 2010;41(5):986-6.
36. Foley NC, Martin RE, Salter KL, Teasell RW. A review of the relationship between dysphagia and malnutrition following stroke. J Rehabil Med 2009;41(9):707-13.
37. 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(2):97-114.
38. Perry L, Love C. Screening for dysphagia and aspiration in acute stroke: a systematic review. Dysphagia 2001;16(1):7-19.
39. Leder S, Sasaki C, Burrell M. Fiberoptic endoscopic evaluation of dysphagia to identify silent aspiration. Dysphagia 1998;13(1):19-21.
40. O'Neill P. Swallowing and prevention of complications. British Medical Bulletin 2000;56(2):457-65.
41. Crary M, Baron J. Endoscopic and Fluroscopic Evaluations of Swallowing: Comparison Of Observed and Inferred Findings. Dysphagia 1997;2:108.
42. Langmore S, Schatz K, Olson N. Endoscopic and videofluoroscopic evaluations of swallowing and aspiration. Annals of Otology, Rhinology and Laryngology 1991;100(8):678-81.

43. Colodny N. Effects of age, gender, disease, and multisystem involvement on oxygen saturation levels in dysphagic persons. Dysphagia 2001;16(1):48-57.
44. Perie S, Laccourreye L, Flahault A, Hazebroucq V, S. C, St Guily J. Role of videoendoscopy in assessment of pharyngeal function in oropharyngeal dysphagia: comparison with videofluoroscopy and manometry. Laryngoscope 1998;108(11):1712-6.
45. Kelly A, Leslie P, Beale T, Payten C, Drinnan M. Fibreoptic endoscopic evaluation of swallowin g andvideofluoroscopy: does examination type influenceperception of pharyngeal residue severity? Clinical Otolaryngology 2006;31(5):425-32.
46. Rao N, Brady S, Chaudhuri G, Donzelli J, Wesling M. Gold-Standard? Analysis of the Videofluoroscopic and Fiberoptic Endoscopic
Swallow Examinations. The Journal of Applied Research In Clinical and Experimental Therapeutics 2003;3(1):89-96.
47. Wu C, Hsiao T, Chen J, Chang Y, Lee S. Evaluation of swallowing safety with fiberoptic endoscope: comparison with videofluoroscopic technique. Laryngoscope 1997;107(3):396-401.
48. Lowery D. Assessment and measurement tools used in the evaluation of swallowing. Current Opinion in Otolaryngology & Head and Neck Surgery 2001;9(3):134-8.
49. Langmore S, Schatz K, Olsen N. Fiberoptic endoscopic examination of swallowing safety: a new procedure. Dysphagia 1988;2(4):216-9.
50. Langmore S. Laryngeal Sensation: A Touchy Subject. Dysphagia 1998;13:93-4.
51. Bulow M, Olsson R, Ekberg O. Videomanometric analysis of supraglottic swallow, effortful swallow, and chin tuck in healthy volunteers. Dysphagia 1999;14:67-72.
52. Speyer R, Baijens L, Heijen M, Zwijnenberg I. Effects of Therapy in Oropharyngeal Dysphagia by Speech and Language Therapists: A Systematic Review. Dysphagia 2010;25(1):40-65.
53. Clave P, De Kraa M, Arreola V, Girvent M, Palomera E, Serra-Prat M. The effect of bolus viscosity on swallowing function in neurogenic dysphagia. Alimentary Pharmacology and Therapeutics 2006;24:1385-94.
54. Payne C, Methven L, Bell A, Fairfield C. Variability of Starch based thickened fluids in the hospital setting. Journal of Texture Studies 2012;43:95-105.
55. Robbins J, Kays S, Gangon R, et al. The effects of lingual exercise in stroke patients with dysphagia. Archives of Physical Medicine and Rehabilitation 2007;88(2):150-8.
56. Carnaby-Mann G, Crary M. McNeill dysphagia therapy programme: a case-control study. Archives of Physical Medicine and Rehabilitation 2010;91(5):743-9.
57. Jayasekeran V, Singh S, Tyrrell P, et al. Adjunctive functional pharyngeal electrical stimulation reverses swallowing disability after brain lesions. Gastroenterology 2010;138(5):1737-46.
58. Geeganage C, Beavan J, Ellender S, Bath P. Interventions for dysphagia and nutritional support in acute and subacute stroke. The Cochrane Collection John Wiley and Sons ltd 2012:1-97.
59. Bath PMW, Lee H. Cochrane systematic review of interventions for dysphagia in acute stroke. International Journal of Stroke 2014;9(4):22.
60. Chamorro A, Urra X, Planas A. Infection after acute ischemic stroke: a manifestation of brain-induces immunodepression. Stroke 2007;38:1097-103.
61. Hinchey J, Shepard T, Furie K, Smith D, Wang D, Tonn S. Formal dysphagia screening protocols prevent pneumonia. Stroke 2005;36:1972--.
62. Titsworth W, Abram J, Fullerton A, et al. Prospective quality initiative to maximize dysphagia screening reduces hospital-aquired pneumonia prevalence in patients with stroke. Stroke 2013;44:3154-60.

63. Ingeman A, Anderson G, Hundborg H, Svendsen M, Johnsen S. Processes of care and medical complications in patients with stroke Stroke 2011;42:167-72.
64. Cuesy P, Sotomayor P, Pina J. Reduction in the incidence poststroke nosocomial pneumonia by using the 'turn-mob' programme. Journal of Stroke and Cerebrovascular Diseases 2010;19:23-8.
65. Gosney M, Martin M, Wright A. The role of selective decontamination of the digestive tract in acute stroke. Age and Ageing 2006;35:42-7.
66. Gomes G, Pisani J, Macedo E, Campos A. The nasogastric feeding tube as a risk factor for aspiration and aspiration pneumonia. Current Opinion in Clinical Nutrition and Metabolic Care 2003;6:327-33.
67. Warusevitane A, Karuntilake D, Lally F, Sim J, Roffe C. The safety and effect of metoclopramide to prevent pneumonia in stroke patients fed via nastrogastric tubes (MAPS trial). Stroke 2015;46:454-60.
68. Westendorp W, Vermeij J, Vermeij F, et al. Antibiotic therapy for preventing infections in patients with acute stroke. Cochrane Database of Systematic Reviews 2012;1(CD008530).
69. Harms H, Prass K, Meisel C, et al. Preventive antibacterial therapy in acute ischemic stroke: a randomized controlled trial PLOS One 2008;3:e2158.
70. Chamorro A, Horcajada J, Obach V, et al. The early systemic prophylaxis of infection after stroke study: a randomized clinical trial. Stroke 2005;36:1495-500.
71. Westendorp W, Vermeij J, Zock E. The Preventiative Antibiotics in Stroke Study (PASS): a pragmatic randomised open-label masked endpoint clinical trial. The Lancet 2015;385:1519-26.
72. Liu C, Shau W, Wu C, Lai M. Angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers and pneumonia risk among stroke patients. Journal of Hypertension 2012;30:2223-9.
73. Shinohara Y. Antiplatelet Cilostazol Is Effective in the Prevention of Pneumonia in Ischemic Stroke Patients in the Chronic Stage. Cerebrovascular Disease 2006;22:57-60.
74. Sung C, Lee T, Chu N. Bronchorrhea following stroke. European Neurology 2012;67:57-62.
75. Dziewas R, Ritter M, Schilling M, et al. Pneumonia in acute stroke patients fed by nasogastric tube. Journal of Neurology Neurosurgery and Psychiatry 2004;75(6):852-6.
76. Kidd D, Lawson J, Nesbitt R, MacMahon J. The natural history and clinical consequences of aspiration in acute stroke. Quarterly Journal of Medicine 1995;88:409-13.
77. Gerodontology BSo. Guidelines for the Oral Healthcare of Stroke Survivors. 2010 [cited.
78. Shi Z, Xie H, Wang P, et al. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. Cochrane Database System Review 2013;8(CD008367).
79. Brady M, Furlanetto D, Hunter R, Lewis S, Milne V. Staff-led interventions for improving oral hygiene in patients following stroke. Cochrane Database System Review 2006;4(CD003864).
80. Yaacob M, Worthington H, Deacon S, et al. Powered versus manual toothbrushing for oral health. Cochrane Collaboration 2014;Online(CD002281).
81. Chalmers J, Spencer A, Wright F, Carter K. The oral health assessment tool - validity and reliability. Australian Dental Journal 2005;50(3):191-9.
82. Intercollegiate Stroke Working Party. National Clinical Guideline for Stroke. 4th edition ed. Great Britain; 2012.
83. Edmans J. Occupational Therapy and Stroke. 2nd Edition ed: Wiley-Blackwell; 2010.

84. Boaden E, Davies S, Storey L. Inter Professional Dysphagia Framework; 2006 Contract No.: Document Number|.
85. Jacobsson C, Axelsson K, Osterlind P, Norberg A. How people with stroke and healthy older people experience the eating process. Journal of Clinical Nursing 2000;9(2):255-64.
86. Ekberg O, Hamdy S, Woisard V, Wuttge-Hannig A, Ortega P. Social and psychological burden of dysphagia: it's impact on diagnosis and treatment. Dysphagia 2002;17(2):139-46.
87. Bath P, Brainin M, Brown C, et al. Testing devices for the prevention and treatment of stroke and its complications. International Journal of Stroke 2014;9(6):683-95.
88. Warnecke T, Ritter MA, Kroger B, et al. Fiberoptic Endoscopic Dysphagia Severity Scale Predicts Outcome after Acute Stroke. Cerebrovascular Diseases 2009;28(3):283-9.
89. Bath PM, Lees KR, Schellinger PD, et al. Statistical analysis of the primary outcome in acute stroke trials Stroke 2012;43(4):1171-8.
90. Geeganage C BJ, Ellender S, Bath PMW. Interventions for dysphagia and nutritional support in acute and subacute stroke. The Cochrane Collection John Wiley and Sons ltd 2012:1-97.
91. Lees KR, Bath PMW, Schellinger PD, et al. Contemporary outcome measures in acute stroke research: choice of primary outcome measure Stroke 2012;43(4):1163-70.
92. Brooks R, with the EuroQol Group. EuroQol: the current state of play. Health Policy 1996;37:53-72.
93. Weir CJ, Lees KR. Comparison of stratification and adaptive methods for treatment allocation in an acute stroke clinical trial. StatMed 2003;22:705-26.
94. 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. The Lancet 2014;385(9968):617-28.