National Institute for Health and Care Excellence

FINAL

Stroke and transient ischaemic attack in over 16s: diagnosis and initial management

[G] Evidence review for head positioning

NICE Guideline NG128

Intervention evidence review

May 2019

FINAL

This evidence review was developed by the National Guideline Centre

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1 Head positioning

1.1 Review question: What is the optimal head positioning (sitting up or lying flat) after a stroke to improve outcomes?

1.2 Introduction

Head positioning following acute stroke may be a simple but important factor affecting eventual outcome after stroke. After an acute ischemic stroke, mechanisms controlling blood flow to the brain can be impaired, meaning that brain blood flow becomes directly dependent on the systemic blood pressure. In this situation a 'lying flat' position could help maintain blood flow to vulnerable 'at risk' brain regions through gravity and/or collateral supply. Conversely a lying flat position may increase the risk of post stroke complications such as aspiration pneumonia. The committee were aware of wide variations in clinical practice across stroke units in head positioning within the first few days of stroke with no national standard and limited evidence to guide practice.

This review has been prompted following the publication of an international randomised control trial.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People aged over 16 with acute stroke
Interventions	Lying flat (head elevation less than 30 degrees) within 24 hours or beyond 24 hours (time-points to be reported separately)
Comparisons	Sitting up (head elevated to at least 30 degrees) within 24 hours or beyond 24 hours (time-points to be reported separately) Usual care (no specific positioning regime)
Outcomes	Critical Modified Rankin scale (mRS) score 0-2 and ordinal shift at 7 days, 3 months and 1 year Barthel score if mRS not reported Mortality at 7 days, 3 months and 1 year Important Recurrent stroke 3 months Adverse events (pulmonary embolism [PE]/deep vein thrombosis [DVT]/pressure sores/pneumonia/falls) at 3 months Quality of life (both health- and social-related quality) at 3 months and 1 year Length of hospital stay Acute neurological deterioration (worsening of National Institutes of Health Stroke Scale [NIHSS])
Study design	Randomised controlled trials Systematic reviews and meta-analyses of the above

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[8] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy upto March 2018, and NICE's 2018 conflicts of interest policy from April 2018.

1.5 Clinical evidence

1.5.1 Included studies

Three studies were previously included in the original guideline for this topic area[31-33]. However, the 3 previously included studies did not match our revised protocol and so are not relevant to this review. One was a systematic review of 4 studies assessing the impact of body position on oxygen saturation, which does not match our outcomes. One was a cross-sectional study of the effect of nursing position on upper airway obstruction after stroke, which is an incorrect study design and outcome for the new protocol. The third did not match the new protocol intervention as it was about gait relearning through locomotor activities compared with traditional therapy.

We undertook a search of all years to address our revised review protocol.

Two studies reported in 6 papers were included in the review;[3, 5, 7, 18, 26, 29] these are summarised in Table 2 below and compare lying flat with sitting up within the first 24 hours. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

Both of the studies are PROBE design (prospective, randomized, open-label, controlled trial with blinded outcome evaluation). It is noted that although this is the highest quality of study design suitable for these trials, subjective outcomes (EQ-5D and modified Rankin Scale) have been downgraded due to no blinding of the interventions for the patient or care giver. Both of the trials are in people aged 18 and over, but this was considered similar enough to our protocol of 16 years and over not to warrant a downgrade in evidence.

It is noted that the HeadPoST trial was a cluster-randomised, crossover trial.[3, 5, 18] The clusters were different hospitals, which were randomised to implement either the lying flat or the sitting up position as the intital phase. At crossover all subsequent patients enrolled in a given hospital received the second randomised intervention and individual patients experienced nursing in just one of the randomised positions, depending on whether they were enrolled during the initial or crossover phase. Therefore, this is not a within-patient comparison and the effect of paired data should be minimal. The interperiod correlation was reported as 0.076, indicating the level of correlation of patients from different periods within the same cluster was high such that the baseline characteristics of paitents recruited during different periods at a single site were comparable. Regarding the extent to which two members of one cluster/hospital are more similar than two people from different clusters/hospital, the reported intracluster correlation coefficient was 0.083, which suggests that 2 patients within a study site had more similar characteristics than 2 pateints at different sites. This was taken into account in the analysis of the mRS and NIHSS ordinal shift scores and quality of life outcome which all used a hierarchical linear mixed model with adjustment for the design, including a fixed group effect, a fixed period effect, a random cluster effect, and an effect of the interaction between random cluster and period to calculate an adjusted odds ratio. This was not considered to constitue a meaningful risk of bias for the remaining outcomes where it was not possible to account for this intracluster correlation coefficient.

The HeadPoST pilot trial{Olavarria, 2017 #599} was cluster-randomised, with the clusters being months, not centers, which enabled teams to follow a monthly protocol. However, the intra-cluster correlation coefficient was not reported. This was considered to be a risk of bias because individuals within a cluster may tend to be more similar to each other than to members of other groups, therefore, comparing all the individuals in the intervention groups with all those in control groups may have spuriously overestimated the differences.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.5.2 Excluded studies

See the excluded studies list in appendix H.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Anderson 2017 [3, 5, 18] **HeadPoST trial**	**Lying-flat** (0°) as soon as possible after presentation, and for at least 24 hours versus **Sitting-up** with head elevated at least 30° immediately upon presentation to the ED, and for at least 24 hours.	N = 11,093 Clinical diagnosis of acute stroke (ischaemic [85%] or intracerebral haemorrhage [8.4%], but not subarachnoid haemorrhage; note that the remaining final diagnoses were conditions mimicking stroke and TIA) 114 centres across 9 countries Age ≥18 Mean age (SD) intervention = 67.8 (13.9) control = 68.1 (13.7) Median (IQR) NIHSS score: 4 (2-9); 4 (2-8) in the lying flat and sitting up groups, respectively	• mRS score at 7 days and 90 days • Mortality at 90 days • Recurrent stroke at 90 days • Pneumonia at 90 days • EQ-5D at 90 days • Length of hospital stay • Acute neurological deterioration (worsening of NIHSS) at 90 days	Median (IQR) time from stroke onset to intervention was **14 (5.0 - 35.0) hours** (7 hours from hospital admission) in both groups. Median (IQR) time spent **lying flat: 23.3 (20.0-24.0) hours** versus median (IQR) time spent **sitting up: 24.0 (23.0-24.0) hours** Cluster-randomised, crossover trial
Olavarria 2017 [7, 26, 29] **HeadPoST pilot**	**Lying flat** (0°) as soon as possible after the diagnosis of acute ischaemic stroke and after performing baseline TCD, and maintained for 24 hours. The side-lying position was recommended for prevention of aspiration (proportion positioned on their side not stated). From 24 to 48 h, patients may have their head raised slowly to a maximum of 15°.	N = 94 Acute ischaemic stroke confirmed by brain imaging 2 centres in Chile and 1 in Australia (very low recruitment in Australian centre) Age ≥18 Mean age (SD) intervention = 70 (14) control = 74 (14)	• mRS score at 90 days • Mortality at 90 days • Recurrent stroke at 90 days • Pneumonia at 7 days • Length of hospital stay • Acute neurological deterioration (worsening of NIHSS) at 90 days	Cluster-randomised trial Mean (SD) time from symptom onset to commencement of positioning **5.5 (3.3) hours** in lying flat group and **5.0 (2.8) hours** in sitting up group Median (IQR) time spent **lying flat: 45 (40-45) hours** versus

Study	Intervention and comparison	Population	Outcomes	Comments
	After 48 h, the patient may have their head elevated further to the standard 30° or more. **Sitting up** with head elevated to 30° or more as soon as possible after the diagnosis, and maintained this for at least 48 hours.	Median (IQR) NIHSS score: 6 (3-10); 7 (4-15) in the lying flat and sitting up groups, respectively		median (IQR) time spent **sitting up: 44 (40-44) hours**

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: sitting up versus lying flat in acute stroke

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sitting up	Risk difference with Lying flat (95% CI)
mRS ordinal shift - 7 days (OR >1 favours sitting up)	10972 (1 study)	⨁⨁⊖⊖ LOW1 due to risk of bias	OR 1.02 (0.93 to 1.12)		Unavailable2 See also Appendix I:
mRS ordinal shift - 90 days (OR >1 favours sitting up)	9748 (1 study)	⨁⨁⊖⊖ LOW1 due to risk of bias	OR 1.01 (0.92 to 1.11)		Unavailable2 See also Appendix I:
mRS ordinal shift - 90 days (OR >1 favours lying flat)	94 (1 study)	⨁⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	OR 1.38 (0.64 to 2.98)		Unavailable2 See also Appendix I:
mRS 0-2 - 7 days	9748 (1 study)	⨁⨁⊖⊖ LOW1 due to risk of bias	RR 0.96 (0.94 to 0.99)	716 per 1000	29 fewer per 1000 (from 7 fewer to 43 fewer)
mRS 0-2 - 90 days	9840 (2 studies)	⨁⊖⊖⊖ VERY LOW1,3,4	RR 1.07 (0.9 to	622 per 1000	44 more per 1000 (from 62 fewer to 162 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sitting up	Risk difference with Lying flat (95% CI)
		due to risk of bias, inconsistency, imprecision	1.26)		
Mortality at 90 days	10945 (2 studies)	⨁⨁⨁⨀ MODERATE1 due to risk of bias	RR 1 (0.87 to 1.14)	67 per 1000	0 fewer per 1000 (from 9 fewer to 9 more)
Recurrent stroke at 90 days	11185 (2 studies)	⨁⨁⨁⨀ MODERATE1 due to risk of bias	RR 1.05 (0.9 to 1.23)	55 per 1000	3 more per 1000 (from 6 fewer to 13 more)
Pneumonia at 7 days	91 (1 study)	⨁⨀⨀⨀ VERY LOW1,3 due to risk of bias, imprecision	OR 0.16 (0 to 8.32)	20 per 1000	17 fewer per 1000 (from 20 fewer to 125 more)
Pneumonia at 90 days	11093 (1 study)	⨁⨁⨀⨀ LOW1,3 due to risk of bias, imprecision	RR 0.91 (0.74 to 1.11)	34 per 1000	3 fewer per 1000 (from 9 fewer to 4 more)
EQ-5D VAS at 90 days (scale 0-100 for general health; high score is good outcome)	8830 (1 study)	⨁⨁⨀⨀ LOW1 due to risk of bias			The mean EQ-5D VAS at 90 days in the intervention groups was 1.3 higher (0.46 to 2.14 higher)
EQ-5D at 90 days – Mobility (summarized using counts and percentages and compared across treatments arms; OR>1 favours sitting up)	8943 (1 study)	⨁⨁⨀⨀ LOW1 due to risk of bias	OR 1 (0.9 to 1.11)		Unavailable2
EQ-5D at 90 days - Self-care (summarized using counts and percentages and compared across treatments arms; OR>1 favours sitting up)	8944 (1 study)	⨁⨁⨀⨀ LOW1 due to risk of bias	OR 0.97 (0.88 to 1.07)		Unavailable2

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sitting up	Risk difference with Lying flat (95% CI)
EQ-5D at 90 days - Usual activities (summarized using counts and percentages and compared across treatments arms; OR>1 favours sitting up)	8945 (1 study)	⨁⨁◯◯ LOW1 due to risk of bias	OR 0.93 (0.83 to 1.04)		Unavailable2
EQ-5D at 90 days - Pain/discomfort (summarized using counts and percentages and compared across treatments arms; OR>1 favours sitting up)	8930 (1 study)	⨁⨁◯◯ LOW1 due to risk of bias	OR 0.95 (0.84 to 1.07)		Unavailable2
EQ-5D at 90 days - Anxiety/depression (summarized using counts and percentages and compared across treatments arms; OR>1 favours sitting up)	8924 (1 study)	⨁⨁◯◯ LOW1 due to risk of bias	OR 1.02 (0.89 to 1.17)		Unavailable2
Length of hospital stay	94 (1 study)	⨁⨁◯◯ LOW1,3 due to risk of bias, imprecision			The mean length of hospital stay in the intervention groups was 4 days lower (9.99 lower to 1.99 higher)
NIHSS - ordinal shift at 7 days (OR >1 favours sitting up)	9840 (2 studies) 90 days	⨁⨁⨁◯ MODERATE1 due to risk of bias	OR 0.98 (0.9 to 1.07)	0 per 1000	Unavailable2

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Absolute risk difference could not be calculated as adjusted event rates to match the factors adjusted for in the OR calculation (including a fixed group effect, a fixed period effect, a random cluster effect, and an effect of the interaction between random cluster and period) were not reported and because the analysis compared shift across all categories of the mRS scale.
3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
4 Downgraded by 1 increment for heterogeneity that could not be explained by pre-defined subgroups.

Although no data were available to compare outcomes for our pre-specified strata of positioning within or beyond 24 hours, the HeadPoST trial did report a pre-specified subgroup analysis for ordinal shift data on mRS and NIHSS based on time to therapy. The subgroups were defined as <6 hours, 6-11 hours and 12 or more hours for the comparison of lying flat versus sitting up. The results are presented in Table 4.

Table 4: Clinical evidence summary: sitting up versus lying flat in acute stroke – subgroup analysis for time to therapy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sitting up	Risk difference with Lying flat (95% CI)
mRS ordinal shift 90 days - <6 hours (OR >1 favours sitting up)	9748 (1 study)	⨁⨁⊖⊖ LOW1 due to risk of bias	OR 1.03 (0.88 to 1.21)	Unavailable2	
mRS ordinal shift 90 days - 6-11 hours (OR >1 favours sitting up)	9748 (1 study)	⨁⨁⊖⊖ LOW1 due to risk of bias	OR 1 (0.84 to 1.19)	Unavailable2	
mRS ordinal shift 90 days - 12+ hours (OR >1 favours sitting up)	9748 (1 study)	⨁⨁⊖⊖ LOW1 due to risk of bias	OR 1 (0.89 to 1.12)	Unavailable2	
NIHSS ordinal shift 7 days - <6 hours (OR >1 favours sitting up)	9748 (1 study)	⨁⨁⊖⊖ LOW1 due to risk of bias	OR 0.98 (0.83 to 1.16)	Unavailable2	
NIHSS ordinal shift 7 days - 6-11 hours (OR >1 favours sitting up)	9748 (1 study)	⨁⊖⊖⊖ VERY LOW1,3 due to risk of bias, imprecision	OR 1.03 (0.85 to 1.25)	Unavailable2	
NIHSS ordinal shift 7 days - 12+ hours (OR >1 favours sitting up)	9748 (1 study)	⨁⨁⊖⊖ LOW1 due to risk of bias	OR 0.94 (0.83 to 1.06)	Unavailable2	

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Absolute risk difference could not be calculated as adjusted event rates to match the factors adjusted for in the OR calculation (including a fixed group effect, a fixed period effect, a random cluster effect, and an effect of the interaction between random cluster and period) were not reported, because the

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sitting up	Risk difference with Lying flat (95% CI)
analysis compared shift across all categories of the mRS scale and because the numbers of participants in each subgroup was not reported. 3 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs					

See appendix F for full GRADE tables.

Table 5: Data that could not be analysed

Study	Outcome	Results	Risk of bias
Anderson 2017 [3]	Median time to hospital discharge	Median (IQR): 9 (4-15) days in both groups	High

1.6 Economic evidence

1.6.1 Included studies

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix G.

1.7 Resource costs

The recommendations made by the committee based on this review (see section **Error! R eference source not found.**) are not expected to have a substantial impact on resources for the NHS in England.

1.8 Evidence statements

1.8.1 Clinical evidence statements

- The HeadPost pilot trial of 94 people showed a possible clinical benefit of lying flat compared with sitting up for ordinal shift in mRS at 90 days (Very Low quality). However, this was not replicated in the fully powered clinical trial in 11093 people where no clinically important difference was reported for this outcome.
- The HeadPost pilot trial of 94 people also showed a clinical benefit of sitting up for reduced length of hospital stay (Low quality), but this effect was not seen in the larger trial.
- No clinically important difference was seen for any of the other reported outcomes, including mortality at 90 days (2 studies; n=10945; Moderate quality), recurrent stroke (2 studies; n=11185; Moderate quality), pneumonia at 7 days (1 study; n=91; Very low quality) and 90 days (1 study; n=11093; Low quality), EQ-5D (1 study; n=8830; Low quality) and shift in NIHSS at 7 days (2 studies; n=9840; Moderate quality)
- Subgroup analysis for those positioned within 6 hours of onset also did not show any clinical difference for ordinal shift in mRS (1 study; n=9748; Very Low and Low quality).

1.8.2 Health economic evidence statements

- No relevant health economic evaluations were identified.

1.9 The committee's discussion of the evidence

1.9.1 Interpreting the evidence

1.9.1.1 The outcomes that matter most

The critical outcomes identified for this review were functional outcome (mRS or Barthel index) and mortality at 7 days, 3 months and 1 year. The committee considered both outcomes to be vital in decision making. Important outcomes included recurrent stroke, adverse events, length of hospital stay, acute neurological deterioration and quality of life.

1.9.1.2 The quality of the evidence

Two RCTs detailed in 6 papers were included in the review. The trials were both prospective randomised open blinded end-point (PROBE) trials. This meant that patient and care givers were not blinded to the intervention, but the outcome assessors were. Subjective outcomes (mRS and quality of life) were therefore downgraded for risk of bias. Additionally, the evidence was further downgraded for risk of attrition bias as a high proportion of eligible participants declined or were lost to follow-up. Some outcomes, including pneumonia, had very few events and therefore had estimates of effect with wide confidence intervals and were downgraded for imprecision.

Evidence ranged from very low to moderate quality, with the majority of the evidence rated as low quality.

1.9.1.3 Benefits and harms

The evidence from a small pilot trial showed a possible clinical benefit of lying flat for the outcomes of 'ordinal shift in mRS at 90 days' and 'NIHSS at 7 days', and showed a reduced length of hospital stay. However, the committee were not confident in the effect estimates owing to the imprecision of the results caused by the small sample size. Also, these findings were not replicated in the fully powered trial, which showed no clinical difference across all reported outcomes, including a subgroup analysis for those positioned within 6 hours of onset. In the overall analysis, no clinical difference was seen for mRS 0-2, mortality, recurrent stroke, pneumonia, EQ-5D and shift in NIHSS at 7 days. The committee discussed the finding for mRS 0-2 at 7 days and agreed that the small benefit in absolute risk difference favouring sitting up was not clinically meaningful owing to the low quality of the evidence.

Overall, there is evidence that in a population representing relatively mild stroke, positioned in a median time of 14 hours from stroke onset, there is no clinical difference on outcomes between lying flat and sitting up. Therefore, the committee agreed to provide guidance on what to consider when deciding how to position people after stroke. Patients should be assessed to establish their optimum position, which should be individually suited to each patient. The points to consider are in line with standard care, including taking account of individual requirements, as dictated by concomitant conditions and personal preferences. The committee agreed that factors such as comfort, medical condition, pressure care, pain, physical and cognitive abilities, orientation, alignment, postural control as well as the patient's compliance should all be considered when positioning patients with acute stroke. The committee noted that lying flat is often difficult and uncomfortable for patients, potentially adding to a sense of disorientation after stroke, but may be of benefit for some. The committee agreed that standard care for stroke patients would often be to adopt a semi-recumbent position initially before sitting up. Sitting up, with support if required, may be beneficial as it enables patients to interact with their surroundings and is a more natural posture for eating and drinking. A patient's tolerance to sitting up might need to be increased over time as part of their rehabilitation. Sitting up is often the precursor for more challenging functional activity such as mobilisation.

1.9.2 Cost effectiveness and resource use

No cost effectiveness evidence was identified for optimal head positioning following stroke. The committee thought that sitting up and lying flat are not likely to result in a difference in costs. The committee opted to recommend that people with stroke are assessed for their personal preferences with regards to head positioning. The committee noted that there would not be a significant resource impact associated with this recommendation as it is in line with current practice in most hospitals.

The committee noted that the indication in the low-quality, small pilot trial that lying flat after stroke was associated with a shorter length of stay in hospital than sitting up was not replicated in the much larger trial. The committee was therefore confident that their recommendation would not have a resource impact.

In conclusion, the committee chose to make a recommendation to position people with stroke following an assessment of their condition and preferences. This is not likely to result in a resource impact as it is in line with current practice.

1.9.3 Other factors the committee took into account

The committee discussed the limitations of the large trial regarding its generalisability as a large numbers of patients were excluded from enrolment due to physician discretion, in particular concerning their ability to tolerate the lying flat position. Also, the average stroke severity was lower and not representative of the range of stroke severities managed within UK stroke centres. In addition the proportion of people with large artery stroke was low. The corresponding author of the HeadPoST trial confirmed that there were more than 5000 participants in the trial within the moderate to severe (NIHSS 5-42) subgroup (*unpublished data, included with permission*) in which no clear difference was seen between lying flat and sitting up for the mRS outcomeat 90 days. There was therefore no evidence to provide a rationale for formulating a research recommendation as it is unlikely that findings would differ from those already published.

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Appendix A: Review protocols

Table 6: Review protocol: head positioning

Field	Content
Review question	What is the optimal head positioning (sitting up or lying flat) after a stroke to improve outcomes?
Type of review question	Intervention A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To examine the effects of head positioning on recovery.
Eligibility criteria – population / disease / condition / issue / domain	People aged over 16 with acute stroke
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Lying flat (head elevation less than 30 degrees) within 24 hours or beyond 24 hours (time-points to be reported separately)
Eligibility criteria – comparator(s) / control or reference (gold) standard	Sitting up (head elevated to at least 30 degrees) within 24 hours or beyond 24 hours (time-points to be reported separately) Usual care (no specific positioning regime)
Outcomes and prioritisation	<u>Critical</u> mRS score (or Barthel score if mRS not available) at 7 days, 90 days and 1 year Mortality at 7 days, 90 days and 1 year <u>Important</u> Recurrent stroke at 90 days Adverse events (PE/DVT/pressure sores/pneumonia/falls) at 90 days Quality of life (both health- and social-related quality) at 90 days and 1 year Length of stay Acute neurological deterioration (worsening of NIHSS) at 90 days and 1 year
Eligibility criteria – study design	Randomised controlled trials Systematic reviews and meta-analyses of the above
Other inclusion exclusion criteria	Inclusion Language: Restrict to English only Settings: Hospital/stroke units/pre-hospital
Proposed sensitivity / subgroup	<u>Subgroups to be assessed if heterogeneity is present:</u> Stroke severity (Mild/moderate or severe stroke according to NIHSS) Ischaemic/haemorrhagic stroke

analysis, or meta-regression	Thrombolysis with or without thrombectomy Dysphagia (yes or no)
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• EndNote will be used for reference management, sifting, citations and bibliographies. • EviBASE will be used for data extraction and quality assessment for clinical studies. • Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	Databases: Medline, Embase, Cochrane Library, Language: Restrict to English only Date restriction: no cut-off Key papers 1. Tyson SF, Nightingale P. The effects of position on oxygen saturation in acute stroke: a systematic review. Clinical Rehabilitation 2004;18(8):863–871. 2. Turkington PM, Bamford J, Wanklyn P et al. Prevalence and predictors of upper airway obstruction in the first 24 hours after acute stroke. Stroke 2002;33(8):2037–2042. 3. Anderson CS., et al. Cluster-Randomized, Crossover Trial of Head Positioning in Acute Stroke. N Engl J Med 2017; 376:2437-2447
Identify if an update	Yes Date cut off of 2007 in CG68 Question in CG68: Does placing patients with acute stroke in specific positions reduce mortality and morbidity? Recommendations from CG68 1.7.1.2 People with acute stroke should be helped to sit up as soon as possible (when their clinical condition permits).
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10071
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual

at outcome / study level	The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jason Kendall in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 7: Health economic review protocol

Review question	**All questions – health economic evidence**
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis).

	• Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B2 of reviews. For questions being updated, the search will be run from 2007, which was the cut-off date for the searches conducted for NICE guideline CG68. For the new review question on endovascular therapy, the search will be run from 2007 as studies published before 2007 are not likely to be relevant.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2002 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[22] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded health economic studies in appendix H. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland).

	• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	01 January 2007 – 26 March 2018	Exclusions
Embase (OVID)	01 January 2007 – 26 March 2018	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews 2007 to 2018, Issue 3 of 12 CENTRAL 2007 to 2018 Issue 2 of 12 DARE, and NHSEED 2007 to 2015 Issue 2 of 4 HTA to 2007 to 2016 Issue 2 of 4	None

Medline (Ovid) search terms

1.	exp Stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	exp Intracranial Hemorrhages/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	exp Brain infarction/
9.	exp "Intracranial Embolism and Thrombosis"/
10.	exp Carotid Artery Thrombosis/
11.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
12.	exp Brain Ischemia/

13.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
14.	Ischemic Attack, Transient/
15.	(isch?emi* adj2 attack*).ti,ab.
16.	TIA*.ti,ab.
17.	or/1-16
18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	limit 36 to English language
38.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
39.	37 not 38
40.	Patient Positioning/
41.	exp Posture/
42.	(mobilis* or mobiliz*).ti,ab.
43.	((head or patient or person or people or body or bodies) adj3 (supine or prone or position* or posture* or placing or place* or up*)).ti,ab.
44.	HeadPOST.ti,ab.
45.	or/40-44
46.	39 and 45

Embase (Ovid) search terms

1.	*cerebrovascular accident/ or cardioembolic stroke/ or exp experimental stroke/ or lacunar stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	*brain hemorrhage/ or *brain ventricle hemorrhage/ or *cerebellum hemorrhage/ or *subarachnoid hemorrhage/

6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	*brain infarction/ or *brain infarction size/ or *brain stem infarction/ or *cerebellum infarction/
9.	*brain embolism/
10.	*Carotid Artery Thrombosis/
11.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
12.	*brain ischemia/ or *hypoxic ischemic encephalopathy/
13.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
14.	*Transient ischemic attack/
15.	(isch?emi* adj2 attack*).ti,ab.
16.	TIA*.ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	case report/ or case study/
22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental Animal/
30.	animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	limit 34 to English language
36.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
37.	35 not 36
38.	*patient position support/ or *patient positioning/
39.	*body position/ or *prone position/ or *supine position/
40.	(mobilis* or mobiliz*).ti,ab.
41.	((head or patient or person or people or body or bodies) adj3 (supine or prone or position* or posture* or placing or up*)).ti,ab.
42.	HeadPOST.ti,ab.
43.	or/38-42
44.	37 and 43

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Stroke] explode all trees
#2.	(stroke or strokes):ti,ab
#3.	((cerebro* or cerebral*) near/2 (accident* or apoplexy)):ti,ab
#4.	(CVA or poststroke or poststrokes):ti,ab
#5.	MeSH descriptor: [Intracranial Hemorrhages] explode all trees
#6.	(brain near/2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)):ti,ab
#7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) near/3 (hemorrhag* or haemorrhag* or bleed*)):ti,ab
#8.	MeSH descriptor: [Brain Infarction] explode all trees
#9.	MeSH descriptor: [Intracranial Embolism and Thrombosis] explode all trees
#10.	MeSH descriptor: [Carotid Artery Thrombosis] explode all trees
#11.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) near/3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab
#12.	MeSH descriptor: [Brain Ischemia] explode all trees
#13.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) near/3 isch?emi*):ti,ab
#14.	MeSH descriptor: [Ischemic Attack, Transient] explode all trees
#15.	(isch?emi* near/2 attack*):ti,ab
#16.	TIA*:ti,ab
#17.	(or #1-#16)
#18.	MeSH descriptor: [Patient Positioning] explode all trees
#19.	MeSH descriptor: [Posture] explode all trees
#20.	(mobilis* or mobiliz*):ti,ab
#21.	((head or patient or person or people or body or bodies) near/3 (supine or prone or position* or posture* or placing or place* or up*)):ti,ab
#22.	HeadPOST:ti,ab
#23.	(or #18-#22)
#24.	#17 and #23

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the stroke population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 9: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2007 – 06 August 2018	Exclusions Health economics studies

Database	Dates searched	Search filter used
Embase	01 January 2007 – 06 August 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 01 January 2007 – 10 November 2017 NHSEED - 01 January 2007 – March 2015	None

Medline (Ovid) search terms

1.	exp Stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	exp Intracranial Hemorrhages/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	exp Brain infarction/
9.	exp Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	exp Brain Ischemia/
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	Ischemic Attack, Transient/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	or/1-15
17.	letter/
18.	editorial/
19.	news/
20.	exp historical article/
21.	Anecdotes as Topic/
22.	comment/
23.	case report/
24.	(letter or comment*).ti.
25.	or/17-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animals/ not humans/
29.	exp Animals, Laboratory/
30.	exp Animal Experimentation/
31.	exp Models, Animal/

32.	exp Rodentia/
33.	(rat or rats or mouse or mice).ti.
34.	or/27-33
35.	16 not 34
36.	limit 35 to English language
37.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
38.	36 not 37
39.	economics/
40.	value of life/
41.	exp "costs and cost analysis"/
42.	exp Economics, Hospital/
43.	exp Economics, medical/
44.	Economics, nursing/
45.	economics, pharmaceutical/
46.	exp "Fees and Charges"/
47.	exp budgets/
48.	budget*.ti,ab.
49.	cost*.ti.
50.	(economic* or pharmaco?economic*).ti.
51.	(price* or pricing*).ti,ab.
52.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
53.	(financ* or fee or fees).ti,ab.
54.	(value adj2 (money or monetary)).ti,ab.
55.	or/39-54
56.	38 and 55

Embase (Ovid) search terms

1.	*cerebrovascular accident/ or cardioembolic stroke/ or exp experimental stroke/ or lacunar stroke/
2.	(stroke or strokes).ti,ab.
3.	((cerebro* or cerebral*) adj2 (accident* or apoplexy)).ti,ab.
4.	(CVA or poststroke or poststrokes).ti,ab.
5.	*brain hemorrhage/ or *brain ventricle hemorrhage/ or *cerebellum hemorrhage/ or *subarachnoid hemorrhage/
6.	(brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)).ti,ab.
7.	((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)).ti,ab.
8.	*brain infarction/ or *brain infarction size/ or *brain stem infarction/ or *cerebellum infarction/
9.	*Carotid Artery Thrombosis/
10.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)).ti,ab.
11.	*brain ischemia/ or *hypoxic ischemic encephalopathy/

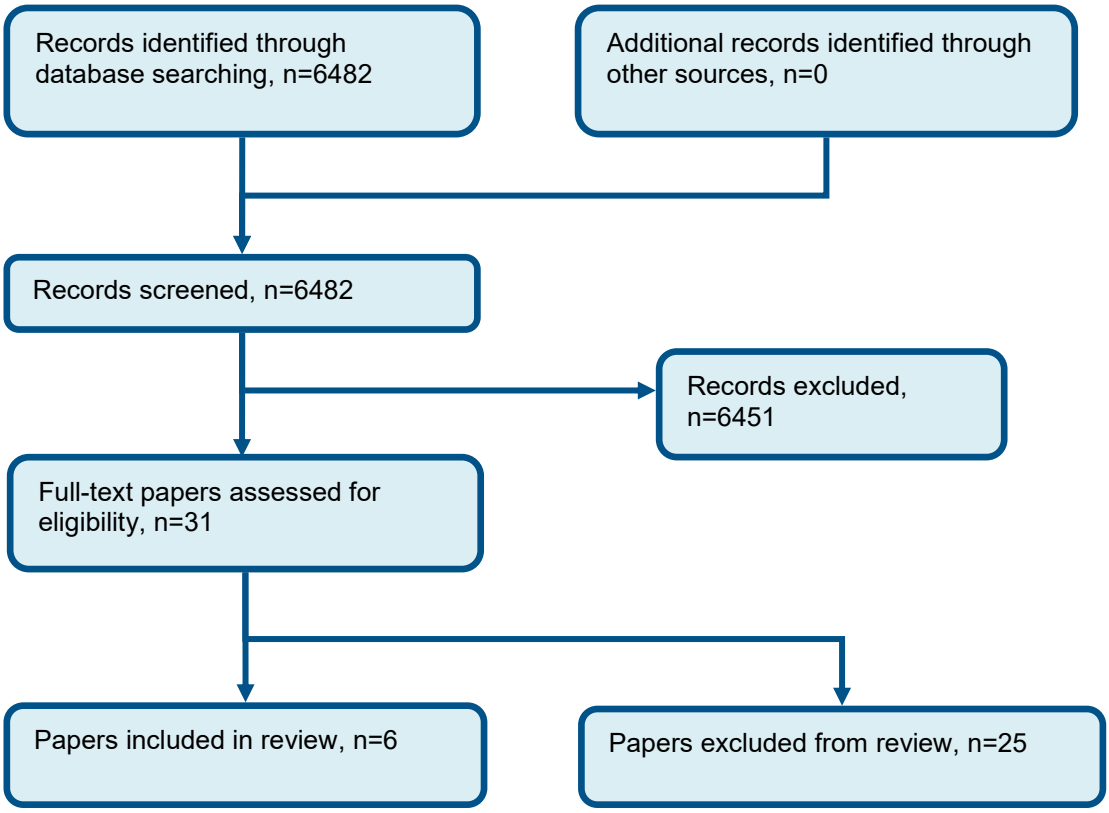
12.	((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*).ti,ab.
13.	*Transient ischemic attack/
14.	(isch?emi* adj2 attack*).ti,ab.
15.	TIA.ti,ab.
16.	or/1-15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	or/17-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice).ti.
32.	or/24-31
33.	16 not 32
34.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
35.	33 not 34
36.	health economics/
37.	exp economic evaluation/
38.	exp health care cost/
39.	exp fee/
40.	budget/
41.	funding/
42.	budget*.ti,ab.
43.	cost*.ti.
44.	(economic* or pharmaco?economic*).ti.
45.	(price* or pricing*).ti,ab.
46.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
47.	(finance* or fee or fees).ti,ab.
48.	(value adj2 (money or monetary)).ti,ab.
49.	or/36-48
50.	35 and 49

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Stroke EXPLODE 1 2
#2.	((stroke or strokes))
#3.	(((cerebro* or cerebral*) adj2 (accident* or apoplexy)))
#4.	((CVA or poststroke or poststrokes))
#5.	MeSH DESCRIPTOR Intracranial Hemorrhages EXPLODE ALL TREES
#6.	((brain adj2 (attack*1 or hemorrhag* or haemorrhag* or bleed* or infarct*)))
#7.	(((intracerebral or intracranial or cerebral* or cerebro* or cerebrum or cerebellum or subarachnoid* or choroidal or basal ganglia or subdural) adj3 (hemorrhag* or haemorrhag* or bleed*)))
#8.	MeSH DESCRIPTOR Brain Infarction EXPLODE ALL TREES
#9.	MeSH DESCRIPTOR Carotid Artery Thrombosis EXPLODE ALL TREES
#10.	(((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or transient or lacunar) adj3 (infarct* or thrombo* or emboli* or occlus* or hypoxi*)))
#11.	MeSH DESCRIPTOR Brain Ischemia EXPLODE ALL TREES
#12.	(((brain or brainstem or cerebr* or cerebell* or vertebrobasil* or verte brobasil* or hemisphere* or intracran* or intracerebral or infratentorial or supratentorial or mca*1 or anterior circulation or carotid or crescendo or transient or lacunar) adj3 isch?emi*))
#13.	MeSH DESCRIPTOR Ischemic Attack, Transient EXPLODE ALL TREES
#14.	((isch?emi* adj2 attack*))
#15.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of head positioning



Appendix D: Clinical evidence tables

Study (subsidiary papers)	Head PoST trial: Anderson 2017[3] (Billot 2017[5], Muñoz-venturelli 2015[18])
Study type	RCT (Cluster randomised; Crossover: Not applicable as the unit of randomisation was hospitals, so different patients were assigned to the interventions after cross-over)
Number of studies (number of participants)	1 (n=11093)
Countries and setting	Conducted in Australia, Brazil, Chile, China, Colombia, India, Sri Lanka, Taiwan, United Kingdom; Setting: 114 hospitals with an established acute stroke care program within a geographically defined area
Line of therapy	Not applicable
Duration of study	Intervention + follow up: Intervention for 24 hours and follow-up at 7 days (unless hospital discharge or death occurred first). 90-day assessment by telephone call to care-giver or patient.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis of acute stroke (ischaemic [85%] or intracerebral hemorrhage [8.4%], but not subarachnoid hemorrhage; note remaining final diagnoses were condition mimicking stroke and TIA)
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): Lying flat: 67.8 (13.9); sitting up: 68.1 (13.7) years. Gender (M:F): Define. Ethnicity: Not stated; but 43% from UK and Australia, 42% from China and Taiwan; 8% from South America; and 7% India and Sri Lanka.
Further population details	1. Dysphagia/no dysphagia: 2. Ischaemic/haemorrhagic stroke: Ischaemic stroke (Majority ischaemic stroke). 3. Stroke severity: Mild (Median NIHSS score : 4). 4. Thrombolysis/thrombolysis + thrombectomy: Not stated / Unclear (Most of the patients were enrolled after the time-window for thrombolytic treatment had passed).
Extra comments	Score of 0 on mRS before stroke: 60.8% in both groups Using aspirin/antiplatelets: 63% Median (IQR) NIHSS score: 4.0 (2.0-9.0) and 4.0 (2.0-8.0) in lying flat and sitting up groups respectively
Indirectness of population	No indirectness

Interventions	(n=5295) Intervention 1: Lying flat (head elevation less than 30 degrees) - Lying flat within 24 hours . Patients will be positioned lying-flat (0°) as soon as possible after presentation to the emergency department (ED) or other assessment area, unless there is a specific contraindication, and should remain in this position for at least 24 hours. Patients should have no more than three breaks of 30 minutes from a flat position in the first 24 hours, and breaks should not to be grouped together. All patients should be toileted in bed or in a commode near the bed, where possible. Gentle graded mobilisation with toilet privileges, and elevation of the head, can occur after the first 24 hours. The head may be raised gradually after 24 hours of lying-flat, if necessary. . Duration 24 hours. Concurrent medication/care: All patients with acute stroke should be managed by a dedicated team in an ASU (or high-dependency unit or intensive care unit) during the period of the intervention. Their management should be best practice standard of care according to regional guidelines, including use of a swallowing screen or swallowing assessment before any feeding is initiated. Patients are to be mobilised according to local stroke care guidelines.. Indirectness: No indirectness Comments: Median (IQR) time from stroke onset to intervention was 14 (5.0 - 35.0) hours (7 hours from hospital admission). Median (IQR) time spent lying flat 23.3 (20.0-24.0) hours; mean (SD) time 20.9 (5.2) hours (n=5799) Intervention 2: Sitting up (head elevated to at least 30 degrees) - Sitting up within 24 hours . Patients will be positioned sitting-up with head elevated at least 30° by raising the head of the bed or using extra pillows, whichever is more appropriate, immediately upon presentation to the ED, and they are to remain in this position for at least 24 hours. If a patient has to be nursed with the head lowered (e.g., to perform computed tomography), the same time-off restrictions are applied (i.e., no more than three breaks of 30 minutes in a lying-flat (0° or <30°) position in the first 24 hours and no break periods to be grouped together). . Duration 24 hours. Concurrent medication/care: All patients with acute stroke should be managed by a dedicated team in an ASU (or high-dependency unit or intensive care unit) during the period of the intervention. Their management should be best practice standard of care according to regional guidelines, including use of a swallowing screen or swallowing assessment before any feeding is initiated. Patients are to be mobilised according to local stroke care guidelines.. Indirectness: No indirectness Comments: Median (IQR) time from stroke onset to intervention was 14 (5.0 - 35.0) hours (7 hours from hospital admission). Median (IQR) time spent sitting up 24.0 (23.0-24.0) hours; mean (SD) time 22.5 (3.3) hours
Funding	Academic or government funding (National Health and Medical Research Council of Australia)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LYING FLAT WITHIN 24 HOURS versus SITTING UP WITHIN 24 HOURS

Protocol outcome 1: Degree of disability or dependence in daily activities (mRS or Barthel) at 7 days, 3 months and 1 year
- Actual outcome: mRS - ordinal shift (increase in odds of moving from a lower level of disability or stroke severity to a higher one in the lying flat group relative to the sitting up group) at 90 days: OR: Common odds ratio: 1.01 (0.92-1.10):

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 619, Reason: Declined to participate or lost to follow-up; Group 2 Number missing: 726, Reason: Declined to participate or lost to follow-up

- Actual outcome: mRS 0-2 at 90 days; Group 1: 2859/4676, Group 2: 3063/5072

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 619, Reason: Declined to participate or lost to follow-up; Group 2 Number missing: 726, Reason: Declined to participate or lost to follow-up

- Actual outcome: mRS 0-2 at 7 days; Group 1: 3228/5240, Group 2: 3631/5732

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 619, Reason: Declined to participate or lost to follow-up; Group 2 Number missing: 726, Reason: Declined to participate or lost to follow-up

- Actual outcome: mRS 3-6 at 90 days; OR; 0.94 (0.85-1.05), Comments: Hierarchical mixed logistic regression model (unclear if adjusted for cluster and period effects);

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 619, Reason: Declined to participate or lost to follow-up; Group 2 Number missing: 726, Reason: Declined to participate or lost to follow-up

- Actual outcome: mRS - ordinal shift (increase in odds of moving from a lower level of disability or stroke severity to a higher one in the lying flat group relative to the sitting up group) at 7 days; OR; Common odds ratio: 1.02 (0.93-1.12);

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 619, Reason: Declined to participate or lost to follow-up; Group 2 Number missing: 726, Reason: Declined to participate or lost to follow-up

Protocol outcome 2: Mortality at 7 days, 3 months and 1 year

- Actual outcome: Mortality at 90 days; Group 1: 379/5185, Group 2: 417/5669; Comments: OR: 0.98 (0.85-1.14)

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 619, Reason: Declined to participate or lost to follow-up; Group 2 Number missing: 726, Reason: Declined to participate or lost to follow-up

Protocol outcome 3: Recurrent stroke at 3 months

- Actual outcome: Acute stroke at 90 days; Group 1: 284/5295, Group 2: 295/5799; Comments: This is number of people with recurrent stroke. Number of events was 299 and 304. P-value from cluster-period level analysis using linear regression = 0.44

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 619, Reason: Declined to participate or lost to follow-up; Group 2 Number missing: 726, Reason: Declined to participate or lost to follow-up

Protocol outcome 4: Adverse events (PE, DVT, pressure sores, pneumonia, falls) at 3 months

- Actual outcome: Pneumonia at 90 days; Group 1: 164/5295, Group 2: 198/5798; Comments: OR: 0.86 (0.68-1.08)

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 619, Reason: Declined to participate or lost to follow-up; Group 2 Number missing: 726, Reason: Declined to participate or lost to follow-up Protocol outcome 5: Quality of life at 3 months and 1 year - Actual outcome: EQ-5D at 90 days; Group 1: mean 72.9 (SD 19.8); n=4246, Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 619, Reason: Declined to participate or lost to follow-up; Group 2 Number missing: 726, Reason: Declined to participate or lost to follow-up - Actual outcome: EQ-5D at 90 days; ORs for each domain, Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 619, Reason: Declined to participate or lost to follow-up; Group 2 Number missing: 726, Reason: Declined to participate or lost to follow-up Protocol outcome 6: Length of stay - Actual outcome: Time to hospital discharge at 90 days; Group 1: n=5360 ; Group 2: n=5734; HR 0.99; Lower CI 0.94 to Upper CI 1.04; Log rank variance: p-value 0.70; Comments: 9 (4-15) days in both groups Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 619, Reason: Declined to participate or lost to follow-up; Group 2 Number missing: 726, Reason: Declined to participate or lost to follow-up Protocol outcome 7: Acute neurological deterioration (worsening of NIHSS) at 7 days and 3 months - Actual outcome: NIHSS - ordinal shift (OR <1 favours lying flat) at 7 days; OR; Common odds ratio: 0.98 (0.90-1.07); Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 619, Reason: Declined to participate or lost to follow-up; Group 2 Number missing: 726, Reason: Declined to participate or lost to follow-up	
Protocol outcomes not reported by the study	

Study (subsidiary papers)	HeadPoST pilot trial: Olavarria 2017[29] (Brunser 2016[7], Olavarría 2017[26])
Study type	RCT (Cluster randomised; Parallel)
Number of studies (number of participants)	1 (n=94)
Countries and setting	Conducted in Australia, Chile; Setting: Presenting to emergency department
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 48 hours intervention; 7- and 90-day follow-up (90 day follow-up conducted by trained staff
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Acute ischaemic stroke confirmed by brain imaging
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Consecutive - clusters are months
Age, gender and ethnicity	Age - Mean (SD): Lying flat: 70(14); upright: 74(14) years. Gender (M:F): Define. Ethnicity: Not stated: 96% from Chile; 4% Australia
Further population details	1. Dysphagia/no dysphagia: Not dysphagic (11% had dysphagia). 2. Ischaemic/haemorrhagic stroke: Ischaemic stroke 3. Stroke severity: Mild (Median (IQR) NIHSS 6(3-10) and 7 (4-15) in lying flat and sitting up groups respectively). 4. Thrombolysis/thrombolysis + thrombectomy: Thrombolysis (Majority had thrombolysis (63% and 53% lying flat and sitting up groups respectively); minority had thrombectomy (7% and 14% lying flat and sitting up groups respectively).).
Extra comments	. No patients were recruited to the sitting up group in the Australian centre
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Lying flat (head elevation less than 30 degrees) - Lying flat within 24 hours . Patients are positioned to 0° as soon as possible after the diagnosis of AIS is made and after performing baseline TCD (most often in the emergency department), and this position is maintained for the next 24 h. The side-lying position is recommended for prevention of aspiration. From 24 to 48 h, patients may have their head raised slowly to a maximum of 15_ to ensure no alteration in neurological condition (i.e. avoidance of a decline in Glasgow coma scale (GCS) scores of >1 point or an increase in NIHSS score of >4 points). After 48 h, the patient may have their head elevated further to the standard 30° or more.

	. Duration 48 hours. Concurrent medication/care: In all patients, checks of their position are made hourly during 48h after commencement of the positioning intervention. 5% required enteral feeding, 95% used antiplatelets, 100% statins 25% anti-hypertensives and 0% intubation/ventilation. . Indirectness: No indirectness Comments: Mean 5.5 (3.3) h from symptom onset to commencement of positioning and median (IQR) duration 45 (40-45) hours (n=51) Intervention 2: Sitting up (head elevated to at least 30 degrees) - Sitting up within 24 hours . Patients are positioned with their head up to 30_ or more as soon as possible after the diagnosis of AIS, and maintain this for at least the next 48 h. If there is clear neurological deterioration, defined by a decline in GCS scores of 1 point or an increase in NIHSS of >4 points, the patient's position can be changed.. Duration 48 hours. Concurrent medication/care: In all patients, checks of their position are made hourly during 48h after commencement of the positioning intervention. 10% required enteral feeding, 84% used antiplatelets, 92% statins 54% anti-hypertensives and 4% intubation/ventilation.. Indirectness: No indirectness Comments: Mean 5.0 (2.8) h from symptom onset to commencement of positioning and median (IQR) duration 44 (40-44) hours
Funding	Academic or government funding (Clinica Alemana de Santiago and the George Institute for Global Health Australia)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LYING FLAT WITHIN 24 HOURS versus SITTING UP WITHIN 24 HOURS

Protocol outcome 1: Degree of disability or dependence in daily activities (mRS or Barthel) at 7 days, 3 months and 1 year
- Actual outcome: mRS - ordinal shift (odds of a decrease in score of 1; OR >1 favours lying flat) at 90 days; OR; Common odds ratio: 1.38 (0.64-3.00);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Differences in proportion with congestive heart failure and atrial fibrillation; more in the sitting up group;
Group 1 Number missing: 2, Reason: Did not tolerate the head position; Group 2 Number missing: 1, Reason: Transfer to another hospital
- Actual outcome: mRS 0-2 at 90 days; Group 1: 33/42, Group 2: 32/50
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Differences in proportion with congestive heart failure and atrial fibrillation; more in the sitting up group;
Group 1 Number missing: 2, Reason: Did not tolerate the head position; Group 2 Number missing: 1, Reason: Transfer to another hospital

Protocol outcome 2: Mortality at 7 days, 3 months and 1 year
- Actual outcome: Mortality at 90 days; Group 1: 4/41, Group 2: 3/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Differences in proportion with congestive heart failure and atrial fibrillation; more in the sitting up group;

Group 1 Number missing: 2, Reason: Did not tolerate the head position; Group 2 Number missing: 1, Reason: Transfer to another hospital Protocol outcome 3: Recurrent stroke at 3 months - Actual outcome: Recurrent stroke infarction at 90 days; Group 1: 2/41, Group 2: 3/50 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in proportion with congestive heart failure and atrial fibrillation; more in the sitting up group; Group 1 Number missing: 2, Reason: Did not tolerate the head position; Group 2 Number missing: 1, Reason: Transfer to another hospital Protocol outcome 4: Adverse events (PE, DVT, pressure sores, pneumonia, falls) at 3 months - Actual outcome: Pneumonia: lung infiltrates on chest x-ray plus 3 or more of fever >38C, rales or crackles on chest auscultation, sputum with large quantities of leukocytes, or sputum cultures showing a respiratory pathogen. at 7 days; Group 1: 0/41, Group 2: 1/50 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in proportion with congestive heart failure and atrial fibrillation; more in the sitting up group; Group 1 Number missing: 2, Reason: Did not tolerate the head position; Group 2 Number missing: 1, Reason: Transfer to another hospital Protocol outcome 5: Length of stay - Actual outcome: Mean length of hospital stay at 90 days; Group 1: mean 9 (SD 8); n=43, Group 2: mean 13 (SD 20); n=51 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in proportion with congestive heart failure and atrial fibrillation; more in the sitting up group; Group 1 Number missing: 2, Reason: Did not tolerate the head position; Group 2 Number missing: 1, Reason: Transfer to another hospital Protocol outcome 6: Acute neurological deterioration (worsening of NIHSS) at 7 days and 3 months - Actual outcome: NIHSS - ordinal shift (odds of an increase in category of NIHSS in score of 1; OR <1 favours lying flat) at 7 days; OR; Common odds ratio: 0.87 (0.38-1.98); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in proportion with congestive heart failure and atrial fibrillation; more in the sitting up group; Group 1 Number missing: 2, Reason: Did not tolerate the head position; Group 2 Number missing: 1, Reason: Transfer to another hospital	
Protocol outcomes not reported by the study	Quality of life at 3 months and 1 year

Appendix E: Forest plots

E.1 Lying flat versus sitting up

Figure 2: mRS ordinal shift at 7 or 90 days

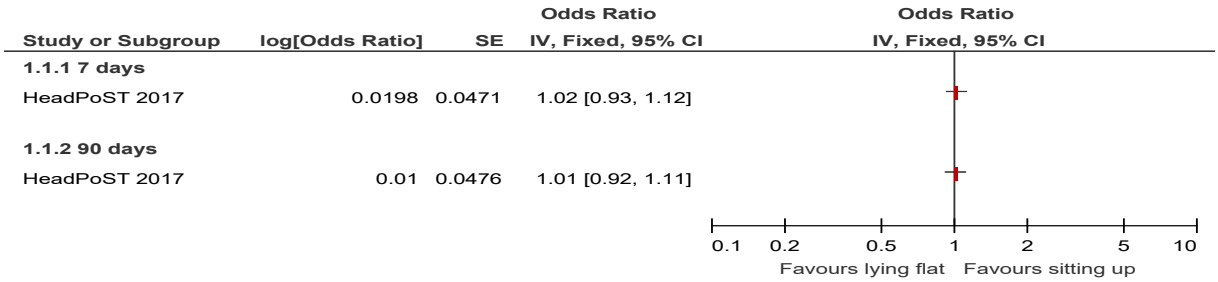


Figure 3: mRS ordinal shift at 90 days

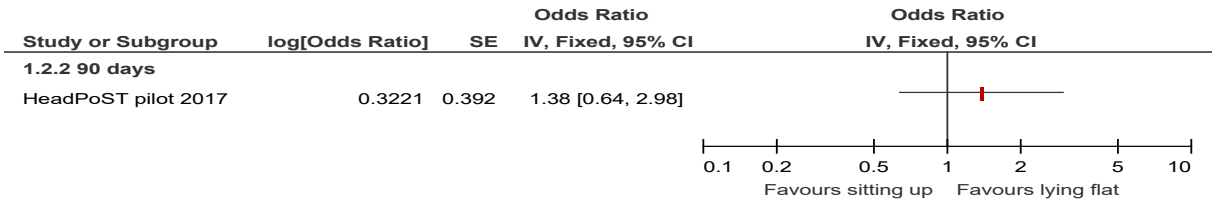


Figure 4: mRS 0-2 at 7 days

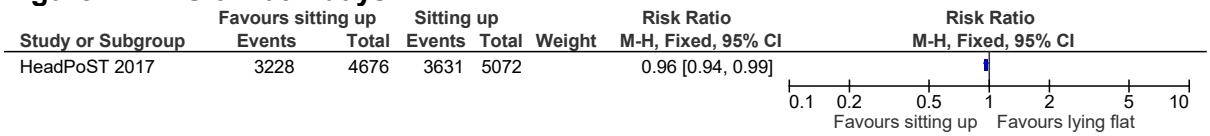


Figure 5: mRS 0-2 at 90 days

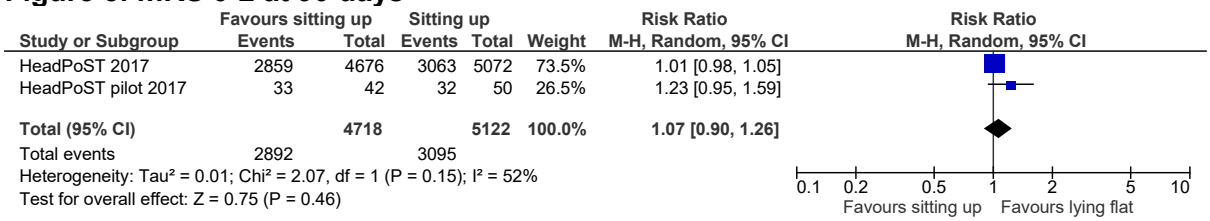


Figure 6: Mortality at 90 days

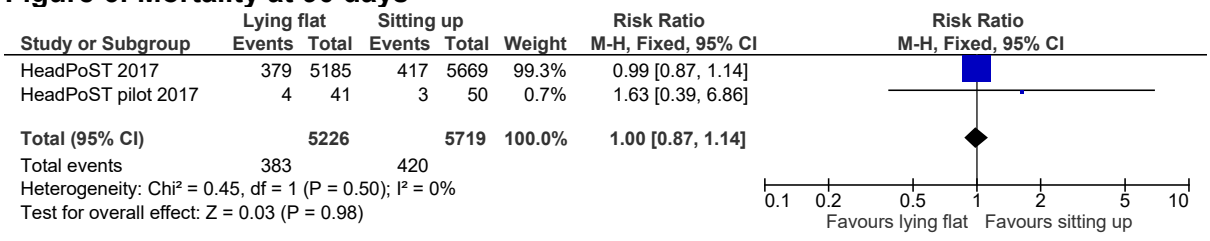


Figure 7: Recurrent stroke at 90 days

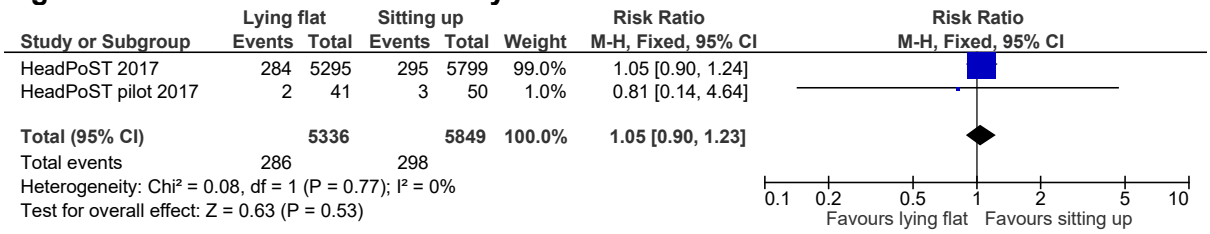


Figure 8: Pneumonia at 7 days

Figure 9: Pneumonia at 90 days

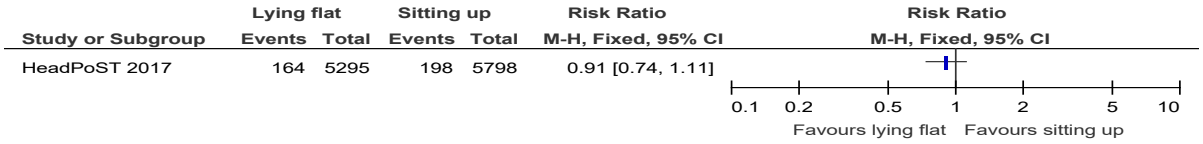


Figure 10: EQ-5D VAS (scale 0-100 for general health; high score is good outcome) at 90 days

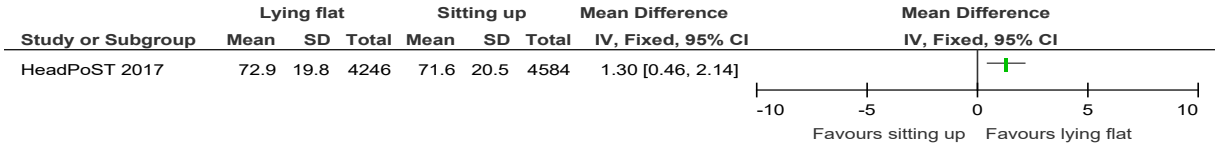


Figure 11: EQ-5D domains at 90 days; odds of poor outcome (summarised using counts and percentages and compared across treatments arms)

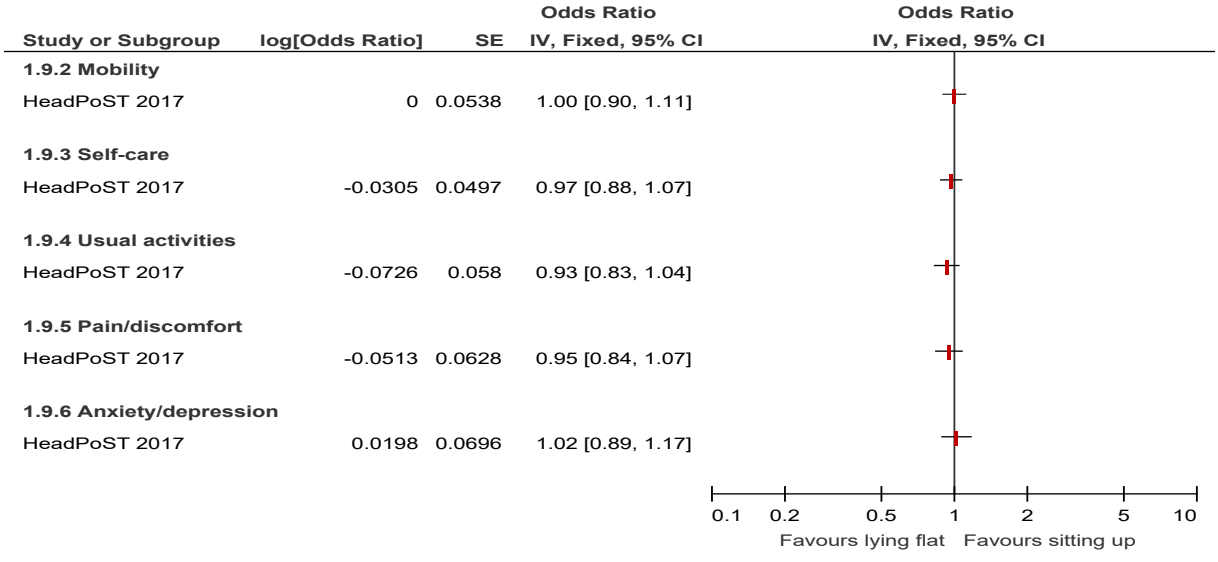


Figure 12: Length of hospital stay

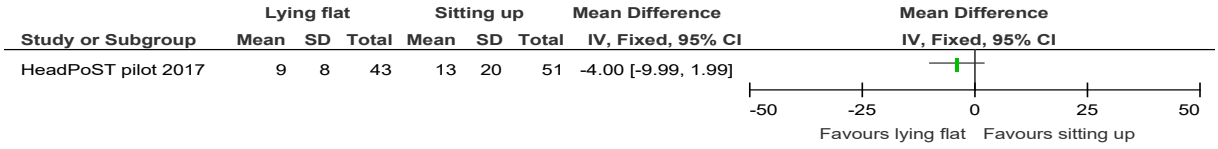
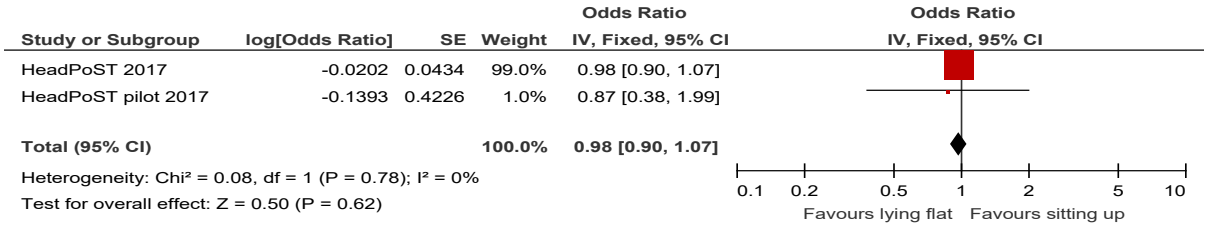


Figure 13: Neurological deterioration (shift in NIHSS) at 7 days



E.2 Lying flat versus sitting up (subgroup analysis for time to therapy)

Figure 14: mRS ordinal shift at 90 days

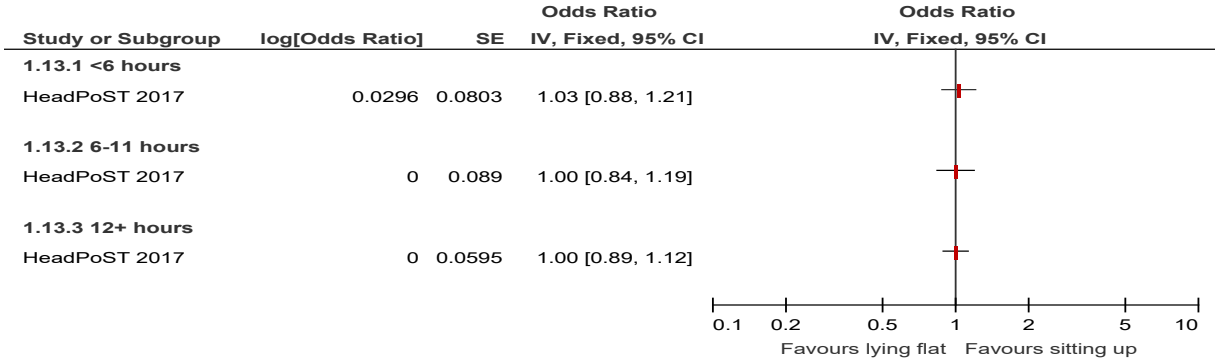
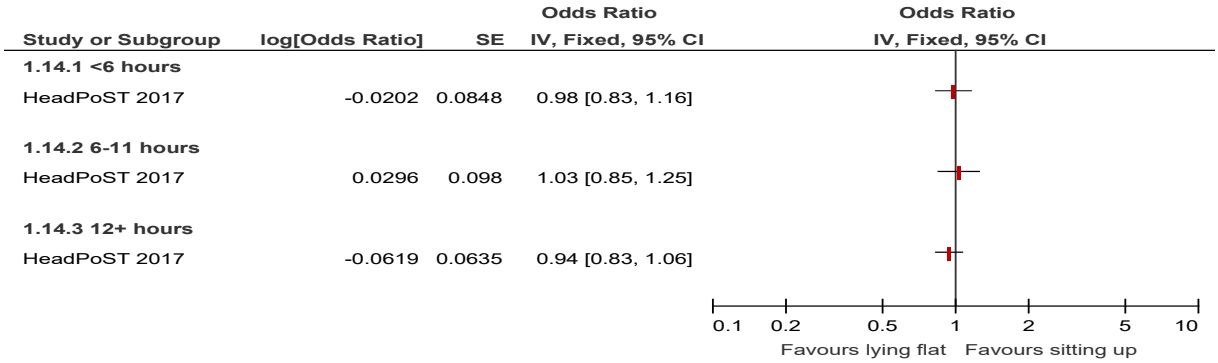


Figure 15: NIHSS or death ordinal shift at 7 days



Appendix F: GRADE tables

Table 10: Clinical evidence profile: lying flat versus sitting up

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lying flat	Sitting up	Relative (95% CI)	Absolute		
mRS ordinal shift - 7 days												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5240	5732	OR 1.02 (0.93 to 1.12)	Not available[2]-	⊕⊕OO LOW	CRITICAL
mRS ordinal shift (reported as negative outcome in the study) - 90 days												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4676	5072	OR 1.01 (0.92 to 1.11)	Not available[2]-	⊕⊕OO LOW	CRITICAL
mRS ordinal shift (reported as positive outcome in the study) - 90 days												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	43	51	OR 1.38 (0.64 to 2.98)	Not available[2]-	⊕OOO VERY LOW	CRITICAL
mRS 0-2 - 7 days												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3228/4676 (69%)	71.6%	RR 0.96 (0.94 to 0.99)	29 fewer per 1000 (from 7 fewer to 43 fewer)	⊕⊕OO LOW	CRITICAL

mRS 0-2 - 90 days												
2	randomised trials	very serious[1]	serious[4]	no serious indirectness	serious[3]	none	2892/4718 (61.3%)	62.2%	RR 1.07 (0.9 to 1.26)	44 more per 1000 (from 62 fewer to 162 more)	⊕OOO VERY LOW	CRITICAL
Mortality at 90 days												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	383/5226 (7.3%)	6.7%	RR 1 (0.87 to 1.14)	0 fewer per 1000 (from 9 fewer to 9 more)	⊕⊕⊕O MODERATE	CRITICAL
Recurrent stroke at 90 days												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	286/5336 (5.4%)	5.5%	RR 1.05 (0.9 to 1.23)	3 more per 1000 (from 6 fewer to 13 more)	⊕⊕⊕O MODERATE	IMPORTANT
Pneumonia at 7 days												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/41 (0%)	2%	OR 0.16 (0 to 8.32)	17 fewer per 1000 (from 20 fewer to 125 more)	⊕OOO VERY LOW	IMPORTANT
Pneumonia at 90 days												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	164/5295 (3.1%)	3.4%	RR 0.91 (0.74 to 1.11)	3 fewer per 1000 (from 9 fewer to 4 more)	⊕⊕OO LOW	IMPORTANT
EQ-5D VAS at 90 days (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4246	4584	-	MD 1.3 higher (0.46 to 2.14 higher)	⊕⊕OO LOW	IMPORTANT
EQ-5D at 90 days - Mobility												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4289	4654	OR 1 (0.9 to 1.11)	Not available[2]-	⊕⊕OO LOW	IMPORTANT
EQ-5D at 90 days - Self-care												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4291	4653	OR 0.97 (0.88 to 1.07)	Not available[2]-	⊕⊕OO LOW	IMPORTANT
EQ-5D at 90 days - Usual activities												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4292	4653	OR 0.93 (0.83 to 1.04)	Not available[2]-	⊕⊕OO LOW	IMPORTANT
EQ-5D at 90 days - Pain/discomfort												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4286	4644	OR 0.95 (0.84 to 1.07)	Not available[2]-	⊕⊕OO LOW	IMPORTANT
EQ-5D at 90 days - Anxiety/depression												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4281	4643	OR 1.02 (0.89 to 1.17)	Not available[2]-	⊕⊕OO LOW	IMPORTANT
Length of hospital stay (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	43	51	-	MD 4 lower (9.99 lower to 1.99 higher)	⊕⊕OO LOW	IMPORTANT
NIHSS - ordinal shift (follow-up 7 days)												

2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4719	5123	OR 0.98 (0.9 to 1.07)	Not available[2]-	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Absolute risk difference could not be calculated as adjusted event rates to match the factors adjusted for in the OR calculation (including a fixed group effect, a fixed period effect, a random cluster effect, and an effect of the interaction between random cluster and period) were not reported and because multiple categories were comparedthe analysis compared shift across all categories of the mRS scale.
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[4] Downgraded by 1 increment for heterogeneity that could not be explained by pre-defined subgroups

Table 11: Clinical evidence profile: lying flat versus sitting up (subgroup analysis for time to therapy)

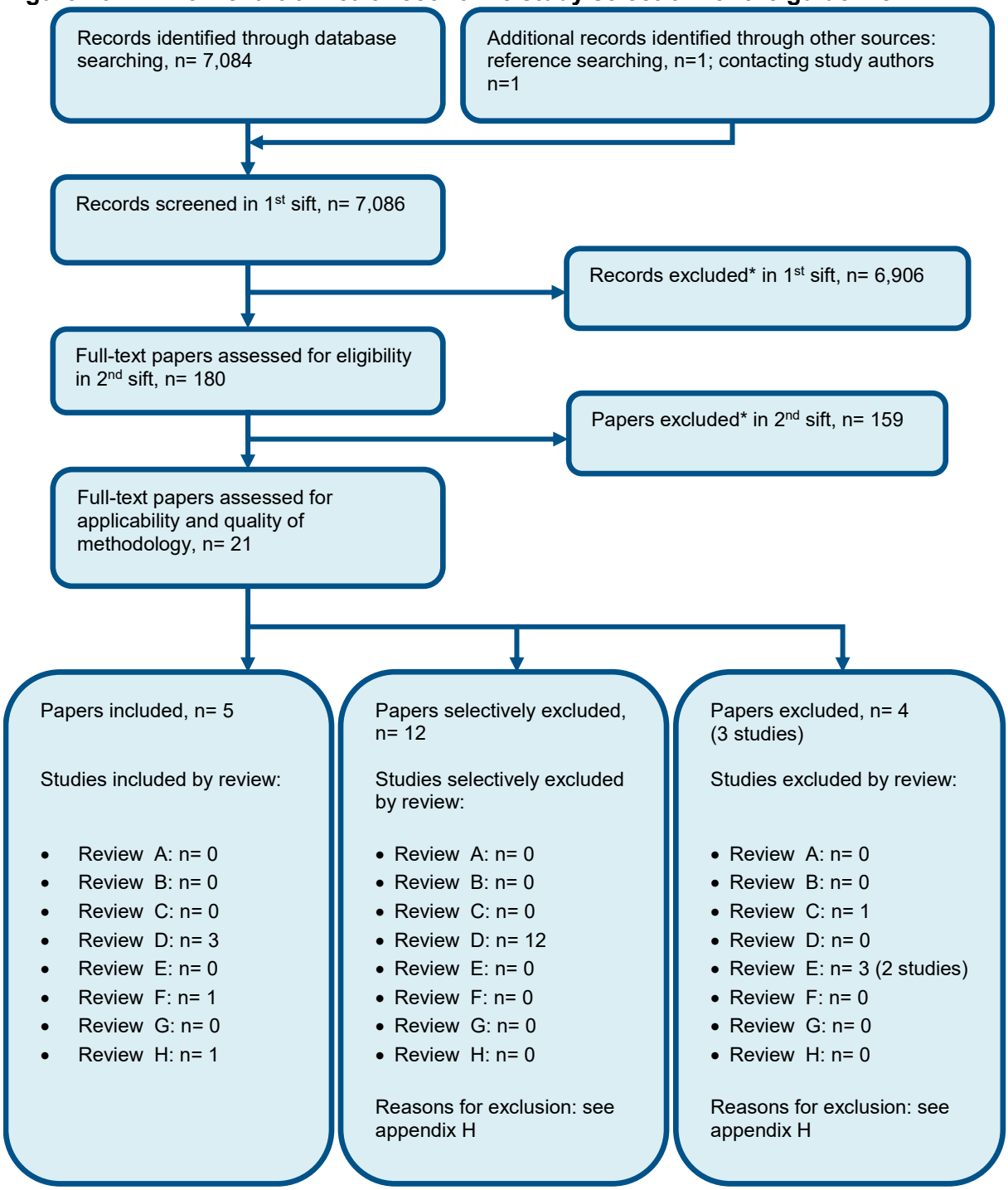
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lying flat**	**Sitting up**	**Relative (95% CI)**	**Absolute**		
mRS ordinal shift 90 days - <6 hours												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	OR 1.03 (0.88 to 1.21)	Not available[2]	⊕⊕OO LOW	CRITICAL
mRS ordinal shift 90 days - 6-11 hours												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	OR 1 (0.84 to 1.19)	Not available[2]	⊕⊕OO LOW	CRITICAL
mRS ordinal shift 90 days - 12+ hours												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	OR 1 (0.89 to 1.12)	Not available[2]	⊕⊕OO LOW	CRITICAL
NIHSS ordinal shift 7 days - <6 hours												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	OR 0.98 (0.83 to 1.16)	Not available[2]	⊕⊕OO LOW	IMPORTANT

NIHSS ordinal shift 7 days - 6-11 hours												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	Not reported	Not reported	OR 1.03 (0.85 to 1.25)	Not available[2]	⊕OOO VERY LOW	IMPORTANT
NIHSS ordinal shift 7 days - 12+ hours												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Not reported	Not reported	OR 0.94 (0.83 to 1.06)	Not available[2]	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Absolute risk difference could not be calculated as adjusted event rates were not reported, multiple categories were compared and the numbers of participants in each subgroup was not reportedto match the factors adjusted for in the OR calculation (including a fixed group effect, a fixed period effect, a random cluster effect, and an effect of the interaction between random cluster and period) were not reported, because the analysis compared shift across all categories of the mRS scale and because the numbers of participants in each subgroup was not reported.
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G: Health economic evidence selection

Figure 16: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 12: Studies excluded from the clinical review

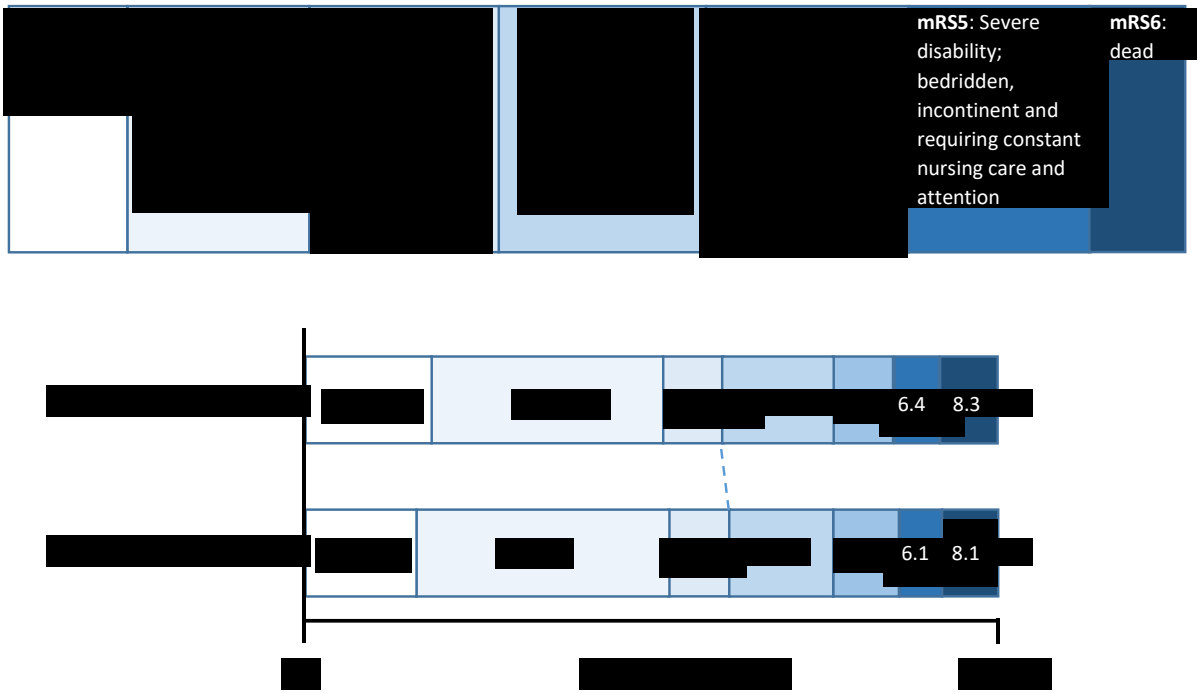
Study	Exclusion reason
Abouzari 2007[1]	Not acute stroke
Anderson 2015[2]	Conference abstract: not available
Arima 2013[4]	Conference abstract: no additional data to main reports
Boaden 2017[6]	Inappropriate comparison. Conference abstract
Forshaw 2017[9]	Conference abstract. Inappropriate comparison
Ishfaq 2009[10]	Not guideline condition
Karic 2015[11]	Inappropriate comparison
Kung 2013[12]	Incorrect study design
Lavados 2014[13]	Conference abstract
Lightbody 2017[14]	Inappropriate comparison. Conference abstract
Lim 2015[17]	Conference abstract
Lim 2016[16]	Conference abstract
Lim 2016[15]	Conference abstract
Munoz venturelli 2014[19]	Conference abstract
Munoz venturelli 2016[20]	Conference abstract. Incorrect interventions
Nakajima 2002[21]	Not Acute stroke
Neuvians 2018[23]	Not available
Olavarria 2012[24]	Conference abstract: not available
Olavarria 2013[25]	Conference abstract: not available
Olavarria 2014[27]	Systematic review: study designs inappropriate. Systematic review is not relevant to review question or unclear PICO
Olavarria 2015[30]	Conference abstract
Olavarria 2016[28]	Conference abstract
Watkins 2015[34]	Conference abstract
Wojner 2003[35]	Conference abstract. Incorrect interventions
Zhang 2011[36]	Non-randomised study with unadjusted data and incorrect outcomes

Appendix I: Additional details

Figure 17: Distribution in shift across categories of mRS at 90 days

Source: Data taken from Olavarria et al 2017 [29] and Anderson et al 2017[3].

Figure 18: Distribution in shift across categories of mRS at 7 days



Source: Data taken from Anderson et al 2017[3].