National Institute for Health and Care Excellence

FINAL

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

[F] Evidence review for very early mobilisation

NICE Guideline NG128

Intervention evidence review

May 2019

FINAL

This evidence review was developed by the National Guideline Centre

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1.1 Review question: Does early mobilisation versus treatment as usual reduce mortality and morbidity in people with acute stroke?

1.2 Introduction

In recent years patients with acute stroke have been assessed and mobilised earlier as part of their rehabilitation programme. In practice, mobilisation refers to 'out of bed' activity such as sitting out of bed, standing and walking. Mobilisation is aimed at reducing the complications associated with immobility and promoting functional recovery. Previous NICE Guidance on stroke (CG68) suggests that people with acute stroke should be mobilised as soon as possible as part of an active management programme on a specialist stroke unit and that they should be helped to sit up as soon as possible. However, the impact of early mobilisation on mortality and morbidity is unclear. There has been limited evidence available to guide when and how early after stroke mobilisation should take place. In addition, the optimum frequency and duration of mobilisation is unknown. As a result clinical practice is variable and further guidance is required.

A large international randomised controlled trial was published since the previous version of this guideline was released. This trial tested a protocol of very early mobilisation, carried out more frequently and for longer than usual care. This has prompted a further review of the evidence in order to establish if early mobilisation versus usual care reduces mortality and morbidly in people with stroke.

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	Early mobilisation (within 72 hours) Very early mobilisation (within 24 hours) Mobilisation is defined as out of bed activity
Comparisons	Usual care (as defined by the studies, for example assessment within 24 hours and mobilisation as appropriate) Late mobilisation (first mobilisation after 72 hours) Different intensities of mobilisation (grouped as <3, 3 or >3 sessions per day) Interventions compared with each other
Outcomes	Critical Modified Rankin scale (mRS) score at 7 days, 90 days and 1 year Barthel score if Modified Rankin Scale not reported Mortality at 7 days, 90 days and 1 year

	Important Recurrent stroke at 90 days Adverse events (pulmonary embolism [PE]/deep vein thrombosis [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 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.[31] 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 up to March 2018, and NICE's 2018 conflicts of interest policy from April 2018.

1.5 Clinical evidence

1.5.1 Included studies

Eight studies reported in 18 papers were included in the review. [83, 84, 15, 17, 18, 23-25, 30, 36, 37, 42, 47, 57, 58, 72, 79, 86] These are summarised in Table 2 below; 6 used very early mobilisation and 2 used early mobilisation as the intervention. Two papers were Cochrane reports[24, 25] and they reported on one study that is included in the review.[36, 37, 79, 86] Evidence from all the studies is summarised in the clinical evidence summary below (Table 3).The intensity and timing of mobilisation varied across the studies for both the interventions and comparisons. Analyses according to stroke severity based on the NIHSS (mild, moderate and severe stroke) were not possible because the included studies did not stratify the results according to stroke severity.

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 H.

1.5.2 Excluded studies

See the excluded studies list in appendix I.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention	Comparison	Population	Outcomes	Comments
Very early mobilisation					
AKEMIS 2012[83, 84] Norway	Very early mobilisation First mobilisation within 24 hours of admission Out-of-bed activity performed by physiotherapists, nursing staff and occupational therapists until discharge, no strict protocol for the amount or type of exercise and patients' needs and abilities were considered, all were mobilised out of bed several times a day	First mobilisation between 24 and 48 hours after admission. Out-of-bed activity performed by physiotherapists, nursing staff and occupational therapists until discharge, no strict protocol for the amount or type of exercise and patients' needs and abilities were considered, all were mobilised out of bed several times a day	Acute stroke (ischaemic and haemorrhagic) n=65	90 day: Mortality Modified Rankin Scale 0 to 2	Intervention: Median (IQR) time from stroke onset to first mobilisation was 13.1 (8.5-25.6) hours (5 patients were not mobilised within 24 hours; 3 within 48 hours and 2 within 72 hours). Comparison Median (IQR) time from stroke onset to first mobilisation was 33.3 (26.0-39.0) hours (1 patient was mobilised only 85 hours after admission).
AVERT II 2009[24, 25, 36, 37, 79, 86] Australia	Very early mobilisation First mobilisation within 24 hours of admission Upright and out of bed (sitting, standing or walking), at least twice/day, 6 days per week Mobilisation continued for 14 days	Conventional stroke care only which included a mobilisation component	Acute stroke (ischaemic and haemorrhagic) n=71	7 day: Mortality 90 day: Mortality Modified Rankin Scale 0 to 2 Recurrent stroke Adverse events (pressure sores, pneumonia, deep vein thrombosis,	Intervention: First mobilisation at a median (IQR): 18.1 (12.8 to 21.5) hours Comparison: First mobilisation at a median (IQR): 30.8 (23.0 to 39.9) hours Total amount per person (mins), median (IQR) Intervention: 167 (63 to 305) Comparison: 69 (31 to 115)

Study	Intervention	Comparison	Population	Outcomes	Comments
				pulmonary embolism, falls) 12 month: Mortality Modified Rankin Scale Assessment of Quality of Life (AQoL) scale	
AVERT III 2015[15, 17, 18, 23, 58] 56 hospitals in five countries: UK (England, Scotland, Northern Ireland and Wales), Australia, New Zealand, Singapore and Malaysia	Very early mobilisation First mobilisation within 24 hours of admission Frequent out-of-bed activity (mobilisation), task specific out-of-bed activity, targeting recovery of active sitting, standing, and walking activity, only resting in bed for long periods if medically unstable, intensity and titration according to the patient's level of functional ability Mobilisation was delivered in at least 3 out of bed sessions Sitting for more than 50 mins at one time was discouraged Target was 5 hours less than usual care for first mobilisation	Usual post-stroke care, the number and type of mobilisations were not prescribed	Acute stroke (ischaemic and haemorrhagic) n=2104	90 day: Mortality Modified Rankin Scale 0 to 2 Length of hospital stay 12 month: Mortality AQoL scale	Intervention: First mobilisation at a median (IQR): 18.5 (12.8 to 22.3) hours Comparison: First mobilisation at a median (IQR): 22.4 (16.5 to 29.3) hours Note median is within 24 hours Total amount per person (mins), median (IQR) Intervention: 201 (108 to 340) Comparison: 70 (32-130)
Chippala 2016[30]	Very early mobilisation First mobilisation within 24 hours of symptom onset	Routine stroke care including passive and, if possible, active	Acute stroke (ischaemic and haemorrhagic)	Discharge: Length of hospital stay	Intervention: First mobilisation at a median (IQR): 18 (16.6-19.8) hours

Study	Intervention	Comparison	Population	Outcomes	Comments
India	Mobilisation (upright and out of bed activities) duration of mobilisation was determined by patient tolerance (5-30 minutes) and frequency was at least twice a day, activities included sitting supported in bed, sitting unsupported out of bed, transfer along with assistance, roll and sit up, sitting without support, transfer feet to the floor, standing activities, walk-early gait and advanced gait activities	mobilisation, correct positioning in bed, mobilisation in bed, sitting balance activities, facilitation of limb and trunk control activities, education of patient and caregiver	n=86	Barthel index 90 day: Mortality Barthel index	Comparison: First mobilisation at a median (IQR): 30.5 (29-35) hours
SEVEL 2012[47] France	Very early mobilisation First mobilisation within 24 hours of symptom onset Seated out of bed as soon as possible, minimum duration of first sitting was 15 minutes, with duration determined by patient fatigue and tolerance (return to bed for any of the following: neurological worsening, vagal reaction >40 mmHg increase in blood pressure exceeding 180/100 mmHg, or symptomatic decrease in blood pressure)	Day 0: the patient would be positioned in bed at 30°; day 1: 45°; day 2: 60°; day 3: sitting out of bed, minimum duration 15 minutes	Ischaemic stroke n=167	7 day Modified Rankin Scale 0 to 2 90 day: Mortality Modified Rankin Scale 0 to 2 Neurological deterioration Adverse events (pneumonia, deep vein thrombosis, falls, pressure sores)	Length of fist sitting (mins), mean (SD) Intervention 56.6 (41.7) Comparison 83.7 (94.7)
VERITAS 2010[57] Australia UK	Very early mobilisation First mobilisation within 24 hours of symptom onset Standard care plus early mobilisation based on AVERT trial	Standard care: immediate transfer to a multidisciplinary stroke unit where the aim was to get patients to sit, stand and walk from the day of admission	Acute stroke (ischaemic and haemorrhagic) n=32	90 day: Mortality Modified Rankin Scale 0 to 2 Length of hospital stay	Intervention: First mobilisation at a median (IQR): 27.3 (26.0 to 29.0) hours Note longer than protocol aim Comparison:

Study	Intervention	Comparison	Population	Outcomes	Comments
	aim to get patients to sit stand and walk within 24 hours of stroke and continue this at least 4 times a day				First mobilisation at a median (IQR): 32.0 (22.5 to 47.3) hours
Early mobilisation					
Diserens 2012[42] Switzerland	Early mobilisation Head laid flat for the first 24 hours, then raised to 45 for 24 hours and mobilisation out of bed to a sitting or standing position started at 52 hours by physiotherapist	Head of bed progressively elevated over 6 days, and mobilised out of bed on day 7	Ischaemic stroke (NIHSS score >6) n=50	90 day: Mortality Modified Rankin Scale 0 to 2 Worsening of NIHSS by >4 points Adverse events (pneumonia) Length of hospital stay	
Poletto 2015[72] Brazil	Early mobilisation First mobilisation within 48 hours of symptom onset Trained physical therapists focused on sitting out of bed in a chair or standing (whenever and as soon as possible) and conducting functional training and motor relearning (in line with the Bobath concept), exercises performed bilaterally with at least 5 repetitions for each joint and each exercise and emphasis on deficits in the impaired side	Conventional physical therapy performed when requested by the staff according to the patients' needs and availability of physical therapists, included global motor exercises and respiratory therapy (ordinarily in bed), duration of standard-care therapy sessions was approximately 15 min and most did not leave their beds	Ischaemic stroke n=39	90 day: Mortality Modified Rankin Scale 0 to 2 Neurological deterioration Adverse events (pneumonia, deep vein thrombosis, falls, pressure sores) Length of hospital stay	Intervention: First mobilisation at a median (IQR): 43 (28 to 48) hours Comparison: First mobilisation at a median (IQR): 72 (61 to 108) hours Total amount per person (mins), median (IQR) Intervention: 135 (85 to 313) Comparison: 0 (0 to 50)

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: very early mobilisation versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard care - subgroups	Risk difference with Very early mobilisation (95% CI)
Mortality at 7 days	71 (1 study)	⨁⨁◯◯ LOW[a] due to imprecision	RR 3.47 (0.41 to 29.56)	30 per 1000	74 more per 1000 (from 18 fewer to 857 more)
Mortality at 90 days	2475 (6 studies)	⨁⨁⨁◯ MODERATE[a] due to imprecision	RD 0.01 (-0.03 to 0.05)	69 per 1000	11 more per 1000 (from 30 fewer to 51 more)[b]
Mortality at 12 months	2149 (2 studies)	⨁⨁⨁◯ MODERATE[a] due to imprecision	RR 1.21 (0.97 to 1.51)	148 per 1000	31 more per 1000 (from 4 fewer to 75 more)
mRS 0 to 2 at 7 days	191 (2 studies)	⨁⨁◯◯ LOW[a,c] due to risk of bias, imprecision	RR 0.82 (0.66 to 1.03)	657 per 1000	118 fewer per 1000 (from 223 fewer to 20 more)
mRS 0 to 2 at 90 days	2377 (5 studies)	⨁⨁⨁⨁ HIGH	RR 0.94 (0.86 to 1.01)	438 per 1000	26 fewer per 1000 (from 61 fewer to 4 more)
mRS 0 to 2 at 12 months	2152 (2 studies)	⨁⨁⨁◯ MODERATE[d] due to inconsistency	RR 0.93 (0.85 to 1.02)	372 per 1000	26 fewer per 1000 (from 56 fewer to 7 more)
Recurrent stroke at 90 days	71 (1 study)	⨁⨁◯◯ LOW[a] due to imprecision	OR 6.48 (0.13 to 329.67)	0 per 1000	30 more per 1000 (from 50 fewer to 100 more)[b]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard care - subgroups	Risk difference with Very early mobilisation (95% CI)
Neurological deterioration (worsening NIHSS >4 points) at 90 days	138 (1 study)	⊕⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	OR 8.94 (0.17 to 457.29)	0 per 1000	20 more per 1000 (from 30 fewer to 60 more) [b]
Adverse events at 90 days	209 (2 studies)	⊕⊕⊕⊖ MODERATE[a] due to imprecision	RR 0.88 (0.72 to 1.08)	476 per 1000	57 fewer per 1000 (from 133 fewer to 38 more)
Barthel index at discharge Scale: 0-100 (high is good outcome)	90 (1 study)	⊕⊕⊕⊖ MODERATE[c] due to risk of bias		The mean Barthel index at discharge in the control group was 68.25	The mean Barthel index at discharge in the intervention group was 8 higher (1.61 to 14.39 higher)
Barthel index at 90 days Scale: 0-100 (high is good outcome)	80 (1 study)	⊕⊕⊕⊖ MODERATE[c] due to risk of bias		The mean Barthel index at discharge in the control group was 75.25	The mean Barthel index at 90 days in the intervention group was 13.12 higher (8.37 to 17.87 higher)
Length of hospital stay	124 (1 study)	⊕⊕⊖⊖ LOW [a,c] due to risk of bias, imprecision		The mean length of hospital stay in the control groups was 10.53 days	The mean length of hospital stay in the intervention groups was 0.75 days lower (2.68 lower to 1.18 higher)

[a] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[b] Calculated from risk difference
[c] 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
[d] Heterogeneity, I^2=55%, unexplained by subgroup analysis

Table 4: Clinical evidence summary: early mobilisation versus usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard care	Risk difference with Early mobilisation (95% CI)
Mortality at 90 days	75 (2 studies)	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 0.67 (0.15 to 2.98)	88 per 1000	29 fewer per 1000 (from 75 fewer to 174 more)
mRS 0 to 2 at 90 days	75 (2 studies)	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 1.03 (0.61 to 1.72)	441 per 1000	13 more per 1000 (from 172 fewer to 318 more)
Neurological deterioration (worsening NIHSS >4 points) at 90 days	75 (2 studies)	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RD 0 (-0.14 to 0.09)	59 per 1000	21 fewer per 1000 (from 140 fewer to 90 more)[c]
Adverse events at 90 days	75 (2 studies)	⨁⊖⊖⊖ VERY LOW[a,b,d] due to risk of bias, `inconsistency, imprecision	RR 0.58 (0.09 to 3.92)	235 per 1000	99 fewer per 1000 (from 214 fewer to 686 more)
Length of hospital stay	42 (1 study)	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision		The mean length of hospital stay in the control groups was11.7 days	The mean length of hospital stay in the intervention groups was 2 days higher (1.47 lower to 5.47 higher)

[a] 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
[b] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[c] Calculated from risk difference
[d] Heterogeneity, I^2=66%, unexplained by subgroup analysis

See appendix F for full GRADE tables.

Table 5: Data not suitable for meta-analysis

Study	Scale	Early mobilisation	n	Usual care	n	Risk of bias
AVERT III 2015[15, 17, 18, 23, 58]	Quality of life: Assessment of Quality of Life instrument at 12 months Median (IQR) Scale (-0.04-1.00) High is good outcome	0.47 (0.07 to 0.81)	1048	0.49 (0.08 to 0.81))	1050	Low
AVERT II 2009[24, 25, 36, 37, 79, 86]		0.32	38	0.24	33	Low
AVERT III[15, 17, 18, 23, 58]	Length of hospital stay (days), median (IQR)	16 (5 to 44)	1048	18 (6 to 43)	1050	Low
Chippala 2016[30]		8 (7 to 9)	40	10 (8 to 12.75)	40	High
Poletto 2015[72]		8 (5 to 14)	16	10 (4 to 25)	17	High
VERITAS 2010[57]		10 (5 to 14)	16	12 (6 to 16)	16	High

1.6 Economic evidence

1.6.1 Included studies

One health economic study was identified with the relevant comparison and has been included in this review. [85] This is summarised in the health economic evidence profile below (Table 6) and the health economic evidence table in appendix H.

1.6.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

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

1.6.3 Summary of studies included in the economic evidence review

Table 6: Health economic evidence profile: Very early mobilisation and standard care versus standard care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Tay-Teo 2008 [85] (Australia)	Partially applicable (a)	Potentially serious limitations (b)	Within-trial analysis of AVERT phase II RCT. Resource items for hospital perspective: Time cost for implementing very early mobilisation, acute-phase hospitalisation, interim care arrangement, emergency attendance, rehospitalisation, inpatient rehabilitation, and outpatient rehabilitation. Resource use data determined from medical records and patient/next-of-kin interviews. Unit costs applied to resource items.	Saves £2,659(c) (hospital perspective)	Adjusted OR (mRS 0-2 at 90 days): 4.10 (95% CI: 0.99-16.88; p=0.051)	Dominant(d) (da) (hospital perspective)	Probability very early mobilisation dominant (hospital perspective): NR

Abbreviations: da: deterministic analysis; ICER: incremental cost-effectiveness ratio; NR: not reported; OR: odds ratio; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Australian societal perspective, recalculated as hospital perspective

(b) High recruitment of moderate to severe strokes to AVERT II could limit generalisability. Health outcomes and resource use are based on the AVERT phase II trial only. Health effects not expressed as QALYs, diverging from NICE reference case. mRS score is dichotomised; ordinal shift not used. Medications and diagnostic investigations not included in resource use. Aspects of resource use obtained through patient/next-of-kin interviews could be subject to recall bias. Potential conflicts of interest are not reported

(c) Converted using 2004 purchasing power parities[71]

(d) A dominant treatment option is one that is both less costly and results in better health outcomes than the comparator treatment

1.6.4 Unit costs

Table 7: UK costs of very early mobilisation

Currency Description	Unit Cost	Source
REHABL2 Specialist rehabilitation services level 2 (rehabilitation for stroke, admitted patient care)	£422	NHS Reference Costs 2016-2017
Hospital-based nurse, cost per working hour (band 2-3)	£22 - £25	PSSRU 2017
Hospital-based scientific and professional staff, cost per working hour, band 5 – band 7(physiotherapist - physiotherapist advanced/specialist))	£34 - £55	PSSRU 2017
Hospital-based scientific and professional staff, cost per working hour, band 2- band 3 (clinical support worker - clinical support worker (higher level))	£24 - £27	PSSRU 2016

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

1.8.1.1 Very early mobilisation versus usual care

- Evidence from 6 studies in 2475 people suggested that very early mobilisation may be associated with a clinical harm in terms of increased mortality at 7 days, 90 days and 12 months (Low and Moderate quality).
- There was also a suggestion of clinical harm from reduced numbers of people achieving mRS of 0-2 at 7 days with very early mobilisation compared to usual care in 2 studies with 191 participants (Low quality). However, no clinical difference in the numbers achieving mRS 0-2 was seen at 90 days (5 studies; n=2377; High quality) or 12 months (2 studies; n=2152; Moderate quality).
- No clinical difference was seen between very early mobilisation and usual care for recurrent stroke (1 study; n=71; Low quality), neurological deterioration (1 study; n=138; Very Low quality) or adverse events (2 studies; n=209; Moderate quality) or length of hospital stay (1 study; n=124; Low quality).
- Evidence from 1 study showed a clinical benefit of very early mobilisation for the Barthel index measured at discharge and at 90 days (1 study; n=90; Moderate quality).

1.8.1.2 Early mobilisation versus usual care

- Evidence from 2 studies in 75 people found clinical benefit of early mobilisation compared to usual care in terms of reduced mortality and fewer adverse events at 90 days (Very Low quality).
- No clinical difference was seen for the numbers achieving an mRS of 0-2 or experiencing neurological deterioration at 90 days (2 studies; n=75; Very Low quality).

- One study suggested that length of stay was longer in the early mobilisation group (n=42; Very Low quality).

1.8.2 Health economic evidence statements

One health economic analysis based on the AVERT II trial found that very early mobilisation with standard care was dominant (more effective and less costly) compared with standard care alone. The study was assessed as partially applicable with potentially serious limitations.

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 the mRS at 7 days, 90 days and 1 year, and mortality at 7 days, 90 days and 1 year. The committee considered both outcomes to be vital in decision making. Important outcomes included recurrent stroke, neurological deterioration, quality of life, length of hospital stay and adverse events (pulmonary embolism, deep vein thrombosis, pressure sores, pneumonia, and falls).

1.9.1.2 The quality of the evidence

Eight studies were included in the review. Six studies compared very early (within 24 hours) mobilisation versus usual care and two compared early (within 48 hours) mobilisation versus usual care. Six studies were 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 in these six trials (mRS and quality of life) were therefore downgraded for risk of bias. Two studies ensured that the patients and care givers were blinded to the intervention, and one of these studies provided the majority of the body of evidence. Heterogeneity was found for the outcomes of mortality at 90 days and mRS at both 6 and 12 months for very early intervention versus usual care. One study dominated the evidence for these outcomes. It had the most intense mobilisation treatment and also had a control arm mobilising patients earlier than the intervention arm in other studies. Exclusion of this study did not explain the heterogeneity. It is possible that heterogeneity was a result of the varying types of mobilisation strategies used across the studies. Heterogeneity was also found for adverse events in early mobilisation versus usual care and this could not be explained by subgroup analysis. Outcomes such as renal failure, neurological deterioration and adverse events were rare, resulting in estimates of effect with wide confidence intervals, and therefore were downgraded for imprecision.

Evidence ranged from very low to high quality. For the very early mobilisation comparison the majority was moderate quality, while for the early mobilisation comparison the majority of the evidence was very low quality.

1.9.1.3 Benefits and harms

The committee noted that the evidence was difficult to interpret due to the differences in intensity, timing and type of mobilisation used in the trials, as well as the unclear reporting of how mobilisation was defined in some cases.

Very early mobilisation (within 24 hours)

There were 6 studies of very early (within 24 hours) mobilisation.

There was a suggestion of harm from very early mobilisation in terms of increased mortality and worse functional outcome on mRS. However, it was not possible to delineate the relationship between intensity of mobilisation and the timing of mobilisation. This is because the majority of the evidence was from the AVERT III 2016 trial in which the median time to first mobilisation was within 24 hours for both the intervention and comparison groups, but the intervention group received much more frequent mobilisation sessions and had a greater overall duration of mobilisation. Therefore, although the intervention group were mobilised a median of 3.9 hours earlier, they also received a greater intensity of mobilisation (frequency, duration of daily activity or total activity) and any combination of these factors could have influenced the outcome.

In the AVERT Trial the intention was to offer at least three additional out of bed sessions compared to usual care, with mobilisation to begin within the first 24 hours of stroke onset and to focus on sitting, standing and walking (i.e. out of bed) activity. The intervention summary for the trial shows that usual care consisted of a median of 3 (IQR: 2 - 4.5) mobilisation sessions per day compared with a median of 6.5 (IQR: 4.0 - 9.5) in the very early mobilisation group. Therefore, a median of 3.5 additional sessions were offered in the very early mobilisation group. This was based on both nursing and therapist data.

In the usual care group, the median time to first mobilisation (TTFM) was 22.4 (IQR: 16.5 - 29.3) hours of stroke onset compared with 18.5 hours (IQR: 12.8 - 22.3) in the very early mobilisation group. This this was only 3.9 hours earlier.

In the usual care group, the median daily amount of out of bed activity was 10 minutes (IQR 0 - 18) compared with 31 (IQR: 16.5 and 50.5) minutes in the very early mobilisation group. The median total amount of out of bed activity over the length of stay or until 14 days after stroke was 70 (IQR: 32 – 130) minutes in the usual care group compared with 201.5 (IQR: 108 – 340) minutes in the very early mobilisation group. It is important to note that the amount of minutes is derived only from physiotherapist data and does not include nursing time.

The committee discussed a published regression analysis of the results which suggested that increased frequency of mobilisation was associated with a good functional outcome and reduced odds of death, while increased total duration of mobilisation reduced the odds of a good outcome. However, this analysis was not robust enough to inform a recommendation.

The results for the outcome of Barthel Index showed some benefit of very early mobilisation but the committee did not consider this to be clinically meaningful. The committee noted that there was no clinical difference of very early intervention for the outcomes of recurrent stroke, neurological deterioration, adverse events and length of hospital stay.

The committee made a recommendation advising not to start intense mobilisation (more frequent mobilisations of a longer duration than ‘usual care’) within the first 24 hours of stroke onset because of the findings of the AVERT III 2016 study, which gave a signal for harm. This harm could be explained by the potential to reduce cerebral perfusion when mobilising very early at high intensity.

However, based on their clinical experience they discussed that this harm was most relevant to those who need help to sit out of bed, stand or walk, and so the recommendation is limited to this group. The committee acknowledged that approximately 40% of the AVERT trial participants were able to mobilise independently but that the results were not stratified according to this. Nevertheless, they did not want to prevent appropriate early mobilisation in people who are independently mobile after having a stroke. Where clinically appropriate people who are able to participate in out of bed activity with minimal or no assistance and have been mildly affected by their stroke, should not be discouraged from doing so within the first 24 hours. This was a consensus agreement.

Early mobilisation (within 48 hours)

The committee noted that in two studies examining early (within 48 hours) mobilisation there was no clinically important difference for the outcomes of mortality, mRS, recurrent stroke, adverse events and length of hospital stay.

Early mobilisation may be appropriate in some cases where patients require minimal assistance to mobilise such as in those who have suffered a mild stroke, are experiencing language and/or upper limb dysfunction alone. These patients often require little or no assistance to mobilise. The committee therefore considered that people should be mobilised after having a stroke when their clinical condition permits and a consensus recommendation was made. This was an amendment of the 2008 recommendation: People with acute stroke should be mobilised as soon as possible (when their clinical condition permits) as part of an active management programme in a specialist stroke unit.

1.9.2 Cost effectiveness and resource use

The results of a published within-trial cost effectiveness analysis of the AVERT phase II trial from the Australian hospital perspective estimated that very early mobilisation is dominant compared with standard care. However, the committee noted that the treatment effect for the health outcome mRS score 0-2 used in the economic analysis differs from the treatment effect calculated in the clinical review. The clinical review, incorporating the larger AVERT phase III trial, found no clear evidence for benefit or harm for this outcome. The committee thought that this difference in treatment effect would be likely to change the conclusions about cost effectiveness of very early and intense mobilisation. The committee therefore could not be confident in this economic evidence.

The committee therefore considered the clinical evidence. Notably, there was potential for clinical harm associated with very early and intense mobilisation for the outcome of mortality and no difference for other outcomes. The committee therefore chose to recommend that very early and intense mobilisation is not routinely offered.

The committee was confident that making this recommendation would not have a resource impact, as there was no indication that mobilising later leads to a longer length of stay. The committee noted that people will still be assessed and mobilised and there are not likely to be differences in staff costs. In current practice, mobilisation strategies differ according to stroke severity and the condition of the person with stroke. The strategy may also be impacted by the availability of different types of seating. The recommendation may change current practice in some patients and may mean ‘out of bed’ activities don’t commence until after 24 hours. This may lead to more need for in bed positioning, turning and pressure area care within this first 24 hour period.

In conclusion, the committee thought the cost effectiveness evidence was incongruous with the results of the clinical review which included a considerably larger phase III study. The committee therefore chose to make a recommendation in relation to very early and high intensity mobilisation based on the clinical evidence for mortality which was suggestive of clinical harm. This recommendation is not likely to have a resource impact.

1.9.3 Other factors the committee took into account

The committee emphasised that although mobilisation may not be started very early after stroke, patient assessment should still be undertaken as soon as possible and a plan for mobilisation made.

Limitations of the AVERT study were discussed, including not measuring the duration of nursing input as part of the duration of mobilisation, but only basing this on physiotherapist time; the possible confounding effect from those who have had a more severe stroke receiving less frequent mobilisation per the trial protocol; and the complexity of the

intervention protocol making it difficult to identify what caused the harm in the very early mobilisation group.

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Appendices

Appendix A: Review protocols

Table 8: Review protocol: Very early and early mobilisation

Field	Content
Review question	Does early mobilisation versus treatment as usual reduce mortality and morbidity in people with acute stroke?
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 early mobilisation 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)	Early mobilisation (within 72 hours) Very early mobilisation (within 24 hours) Mobilisation is defined as out of bed activity
Eligibility criteria – comparator(s) / control or reference (gold) standard	Usual care (as defined by the studies, for example assessment within 24 hours and mobilisation as appropriate) Late mobilisation (first mobilisation after 72 hours) Different intensities of mobilisation (grouped as <3, 3 or >3 sessions per day) Interventions compared with each other
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
Proposed sensitivity / subgroup analysis, or meta-regression	<u>Strata</u> Stroke severity (Mild/moderate or severe stroke according to NIHSS; or all severities if not reported separately) Rationale: Severity of stroke is highly likely to interact with the

	physiological tolerability and safety of early mobilisation Subgroups to be assessed if heterogeneity is present: Intensity (< 3, 3 or >3 sessions a day) Ischaemic/haemorrhagic stroke Thrombolysis/no thrombolysis Usual care definition (first mobilisation unclear or at mean of <24 hours, <72 hours, or >72 hours)
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: 2007 Key papers 1. Bernhardt J, Thuy MN, Collier JM et al. (2009) Very early versus delayed mobilisation after stroke. [Review] [56 refs]. Cochrane Database of Systematic Reviews CD006187. 2. Bernhardt J, Dewey H, Thrift A et al. (2008) A very early rehabilitation trial for stroke (AVERT): phase II safety and feasibility. Stroke 39:390-396. 3. Cumming TB, Thrift AG, Collier JM et al. (2011) Very early mobilization after stroke fast-tracks return to walking: further results from the phase II AVERT randomized controlled trial. Stroke 42:153-158. 4. Sorbello D, Dewey HM, Churilov L et al. (2009) Very early mobilisation and complications in the first 3 months after stroke: further results from phase II of A Very Early Rehabilitation Trial (AVERT). Cerebrovascular Diseases 28:378-383. 5. Tay-Teo K, Moodie M, Bernhardt J et al. (2008) Economic evaluation alongside a phase II, multi-centre, randomised controlled trial of very early rehabilitation after stroke (AVERT). Cerebrovascular Diseases 26:475-481. 6. AVERT Trial Collaboration group, Bernhardt J, Langhorne P et al. (4-7-2015) Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. Lancet 386:46-55. 7. Bernhardt J, Churilov L, Ellery F et al. (7-6-2016) Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT). Neurology 86:2138-2145.
Identify if an update	Yes. Cut off date 2007 in CG68 Question in CG68: Does early mobilisation versus treatment as usual reduce mortality and morbidity in patients with acute stroke? Recommendations from CG68 2007 1.7.1.1 People with acute stroke should be mobilised as soon as possible (when their clinical condition permits) as part of an active management programme in a specialist stroke unit.

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 at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual 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 9: Health economic review protocol

Review question	**All questions – health economic evidence**
Objective	To identify health economic studies relevant to any of the review questions.

s	
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).[68] **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 10: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	01 January 2007 – 26 March 2018	Exclusions

Database	Dates searched	Search filter used
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 11: Database date parameters and filters used

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

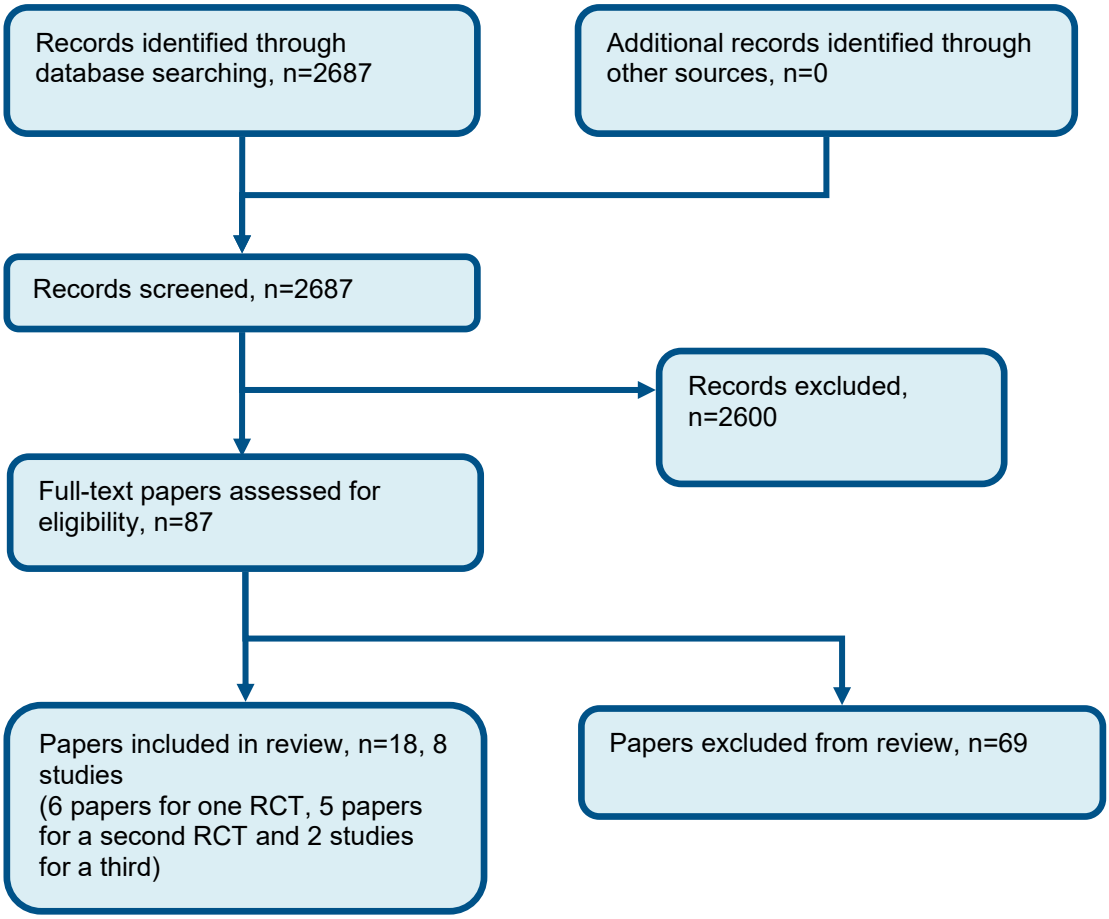
NHS EED and HTA (CRD) search terms

#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 early mobilisation



Appendix D: Clinical evidence tables

Study (subsidiary papers)	AKEMIS: Akersaus Early Mobilisation in Stroke Study trial: Sundseth 2012[83] (Sundseth 2014[84])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=65)
Countries and setting	Conducted in Norway; Setting: Stroke unit
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical assessment by a senior neurologist
Stratum	Overall: Mean NIHSS score: 9.2 (6.5) vs 7.5 (4.2); all severities included, but the majority (66%) were mild (NIHSS <8)
Subgroup analysis within study	Not applicable
Inclusion criteria	18 years or over admitted to the stroke until within 24 hours of stroke onset with cerebral infarction, first or recurrent stroke.
Exclusion criteria	mRS ≤1 on admission; a secondary intracerebral haemorrhage or acute coronary disease; underwent intravenous/intra-arterial thrombolysis or endovascular intervention; pregnancy; requiring palliative care.
Recruitment/selection of patients	Consecutive during week days
Age, gender and ethnicity	Age - Mean (SD): Early: 76.5 (9.7); control: 77.3 (9.3). Gender (M:F): 45/55%. Ethnicity: Not stated
Further population details	1. Ischaemic/haemorrhagic stroke: Ischaemic stroke 2. Thrombolysis/no thrombolysis: No thrombolysis

Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Very early mobilisation (within 24 hours) - Very early mobilisation (medium intensity: 3 sessions per day). Mobilised out of bed as soon as possible after allocation, at least within 24 hours of admission. Median (IQR) time from stroke onset to first mobilisation was 13.1 (8.5-25.6) hours (5 patients were not mobilised within 24 hours; 3 within 48 hours and 2 within 72 hours). Mobilisation was out-of-bed activity and was performed by physiotherapists, nursing staff and occupational therapists until discharge. There was no strict protocol for the amount or type of exercise and patients needs and abilities were considered. All were mobilised out of bed several times a day. Duration Unclear. Concurrent medication/care: Standard stroke unit care. Indirectness: No indirectness (n=33) Intervention 2: Early mobilisation (within 72 hours) - Early mobilisation (medium intensity: 3 sessions per day). Mobilised out of bed between 24 and 48 hours after admission. Median (IQR) time from stroke onset to first mobilisation was 33.3 (26.0-39.0) hours (1 patient was mobilised only 85 hours after admission). Mobilisation was out-of-bed activity and was performed by physiotherapists, nursing staff and occupational therapists until discharge. There was no strict protocol for the amount or type of exercise and patients needs and abilities were considered. All were mobilised out of bed several times a day. Duration Unclear. Concurrent medication/care: Standard stroke unit care. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VERY EARLY MOBILISATION (MEDIUM INTENSITY: 3 SESSIONS PER DAY) versus EARLY MOBILISATION (MEDIUM INTENSITY: 3 SESSIONS PER DAY)

Protocol outcome 1: Mortality at 7 days, 90 days and 1 year
- Actual outcome: Mortality at 90 days; Group 1: 7/27, Group 2: 2/29
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7, Reason: Misdiagnosis; recruited >24 hours after onset; missed follow-up; Group 2 Number missing: 5, Reason: Misdiagnosis; recruited >24 hours after onset; missed follow-up

Protocol outcome 2: Degree of disability or dependence in daily activities (mRS or Barthel) at 7 days, 90 days and 1 year
- Actual outcome: mRS 0-2 at 90 days; Group 1: 10/25, Group 2: 17/28
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No

indirectness ; Group 1 Number missing: 7, Reason: Misdiagnosis; recruited >24 hours after onset; missed follow-up; Group 2 Number missing: 5, Reason: Misdiagnosis; recruited >24 hours after onset; missed follow-up	
Protocol outcomes not reported by the study	Recurrent stroke at 90 days; Adverse events (PE, DVT, pressure sores, pneumonia, falls) at 90 days; Length of stay at Hospitalisation; Quality of life at 90 days and 1 year; Acute neurological deterioration (worsening of NIHSS) at 7 days and 90 days

Study (subsidiary papers)	AVERT III trial: Langhorne 2017[58] (Bernhardt 2015[15], Bernhardt 2015[17], Bernhardt 2016[18], Bernhardt 2015[23])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	3 (n=2104)
Countries and setting	Conducted in Multiple countries; Setting: Acute stroke unit
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 14 days + 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: NIHSS score
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged ≥ 18 years with a clinical diagnosis of first or recurrent stroke, infarct or haemorrhage, admitted to hospital within 24 hours of the onset of stroke and in an acute stroke unit, consciousness (at a minimum, the patient must at least be able to react to verbal commands). Patients could participate in AVERT if they were already recruited to non-intervention trials (e.g. imaging) if dual recruitment was permitted by the ethics committee. Patients who receive thrombolysis could be recruited if the attending physician permits and if mobilisation within 24 hours of stroke was permitted. Informed consent obtained from the patient or a responsible third party.
Exclusion criteria	Too disabled before stroke [prestroke modified Rankin scale (mRS)] score of 3, 4 or 5], TIA diagnosis, deterioration in patient's condition in the first hour of admission resulting in direct admission to intensive care unit, a documented clinical decision for palliative treatment (e.g. those with devastating stroke) or immediate surgery, concurrent diagnosis of rapidly deteriorating disease (e.g. terminal cancer), suspected or confirmed lower limb fracture at the time of stroke preventing the implementation of the mobilisation protocol, not be concurrently recruited to drug or other intervention trials, unstable coronary or other medical condition that were judged by the investigator to impose a hazard to the patient by involvement in the trial, unstable physiological variables (systolic blood pressure of <110 mmHg or >220 mmHg, oxygen saturation of <92% with supplementation, resting heart

	rate of <40 or >110 beats per minute, temperature of > 38.5°C.
Age, gender and ethnicity	Age - Median (IQR): 72.5 (62.9-80.3). Gender (M:F): 60/40%. Ethnicity: Not stated
Further population details	1. Ischaemic/haemorrhagic stroke: Not applicable (Mixed ischaemic and haemorrhagic stroke). 2. Thrombolysis/no thrombolysis: Not applicable (Mixed thrombolysis/no thrombolysis).
Indirectness of population	No indirectness
Interventions	(n=1054) Intervention 1: Very early mobilisation (within 24 hours) - Very early mobilisation (high intensity: >3 sessions per day). Frequent out-of-bed activity (mobilisation), task specific out-of-bed activity, targeting recovery of active sitting, standing, and walking activity, only resting in bed for long periods if medically unstable, intensity and titration according to the patient's level of functional ability, target was 5 hours less than usual care for first mobilisation Duration 14 days or discharge if earlier. Concurrent medication/care: Standard care. Indirectness: No indirectness (n=1050) Intervention 2: Usual Care. Usual care. Duration 14 days or discharge if earlier. Concurrent medication/care: Standard care. Indirectness: No indirectness
Funding	Academic or government funding (National Institute for Health Research (NIHR) Health Technology, National Health and Medical Research Council Australia, Singapore Health, Chest Heart and Stroke Scotland, Northern Ireland Chest Heart and Stroke, Stroke Association

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VERY EARLY MOBILISATION (HIGH INTENSITY: >3 SESSIONS PER DAY) versus USUAL CARE

Protocol outcome 1: Mortality at 7 days, 90 days and 1 year
- Actual outcome: Mortality at 90 days; Group 1: 88/1048, Group 2: 72/1050
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 56% vs 55%, moderate (8-16) 30% vs 31%, severe 14% vs 14%, premorbid mRS score, intervention vs control, mRS 0 76% vs 75%, mRS 14 vs 15%, mRS 2 10% vs 10%; Group 1 Number missing: 6, Reason: Unknown; Group 2 Number

missing: 0, Reason: No missing data - Actual outcome: Mortality at 12 months; Group 1: 139/1038, Group 2: 118/1042 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 56% vs 55%, moderate (8-16) 3o% vs 31%, severe 14% vs 14%, premorbid mRS score, intervention vs control, mRS 0 76% vs 75%, mRS 14 vs 15%, mRS 2 10% vs 10%; Group 1 Number missing: 16, Reason: Unknown; Group 2 Number missing: 8, Reason: Unknown Protocol outcome 2: Length of stay at Hospitalisation - Actual outcome: Length of hospital stay at 90 days; Intervention: median 16 days (interquartile range 5-44 days). Usual care: median 18 days (interquartile range 6-43 days). ; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 56% vs 55%, moderate (8-16) 3o% vs 31%, severe 14% vs 14%, premorbid mRS score, intervention vs control, mRS 0 76% vs 75%, mRS 14 vs 15%, mRS 2 10% vs 10%; Group 1 Number missing: 6, Reason: Unknown; Group 2 Number missing: 0, Reason: No missing data Protocol outcome 3: Degree of disability or dependence in daily activities (mRS or Barthel) at 7 days, 90 days and 1 year - Actual outcome: mRS 0 to 2 at 12 months; Group 1: 480/1038, Group 2: 525/1045 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 56% vs 55%, moderate (8-16) 3o% vs 31%, severe 14% vs 14%, premorbid mRS score, intervention vs control, mRS 0 76% vs 75%, mRS 14 vs 15%, mRS 2 10% vs 10%; Group 1 Number missing: 16, Reason: Declined follow-up or could not be found; Group 2 Number missing: 5, Reason: Declined follow-up or could not be found Protocol outcome 4: Quality of life at 90 days and 1 year - Actual outcome: AQol at 12 months; Mean; -0.04 to 1 Top=High is good outcome, Comments: Intervention median (interquartile range) 0.47 (0.07 to 0.81). Usual care median (interquartile range) 0.49 (0.08 to 0.81); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 56% vs 55%, moderate (8-16) 3o% vs 31%, severe 14% vs 14%, premorbid mRS score, intervention vs control, mRS 0 76% vs 75%, mRS 14 vs 15%, mRS 2 10% vs 10%; Group 1 Number missing: 191, Reason: 139 had died, 36 could not be completed (refused, incomplete, not collected by assessor) and 16 could not be contacted ; Group 2 Number missing: 153, Reason: 118 had died, 27 could not be completed and eight could not be contacted	
Protocol outcomes not reported by the study	Recurrent stroke at 90 days; Adverse events (PE, DVT, pressure sores, pneumonia, falls) at 90 days; Acute neurological deterioration (worsening of NIHSS) at 7 days and 90 days

Study (subsidiary papers)	**AVERT phase II trial: Bernhardt 2008[22] (Bernhardt 2009[24], Bernhardt 2009[25], Cumming 2008[36], Sorbello 2009[79], Tyedin 2010[86])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	6 (n=71)
Countries and setting	Conducted in Australia; Setting: Acute stroke unit
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 14 days, 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: WHO criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients >18 years with a first or recurrent stroke, as defined by the World Health Organization, admitted within 24 hours of symptom onset, stroke patients were required to react to verbal commands (but did not need to be fully alert) and to have a systolic blood pressure between 120 and 220 mm Hg, an oxygen saturation of >92% (with or without supplementation), a heart rate between 40 and 100 beats per minute, and a temperature <38.5°C.
Exclusion criteria	Patients with a premorbid (retrospective) modified Rankin Scale (mRS) score >3, deterioration within the first hour of admission to the stroke unit or direct admission to intensive care, a concurrent progressive neurologic disorder, acute coronary syndrome, severe heart failure, confirmed or suspected lower-limb fracture preventing mobilization, and those requiring palliative care.
Age, gender and ethnicity	Age - Mean (SD): 74.7 (12.5). Gender (M:F): 38/33. Ethnicity: Not stated
Further population details	1. Ischaemic/haemorrhagic stroke: Not stated / Unclear 2. Thrombolysis/no thrombolysis: Not stated / Unclear
Indirectness of population	No indirectness

Interventions	(n=38) Intervention 1: Very early mobilisation (within 24 hours) - Very early mobilisation (low intensity: <3 sessions per day). Upright and out of bed at least twice/day, 6 days per week. Duration 14 days or hospital discharge whichever earlier. Concurrent medication/care: Standard care. Indirectness: No indirectness (n=33) Intervention 2: Usual Care. Usual care. Duration 7 days or hospital discharge whichever earlier. Concurrent medication/care: Standard care. Indirectness: No indirectness
Funding	Academic or government funding (National Heart Foundation Australia, Affinity Health, and an equipment grant from the Austin Health Medical Research Fund. Dr Bernhardt was supported by a National Health and Medical Research Council (Australia) fellowship)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VERY EARLY MOBILISATION (LOW INTENSITY: <3 SESSIONS PER DAY) versus USUAL CARE

Protocol outcome 1: Recurrent stroke at 90 days
- Actual outcome: Recurrent stroke at 90 days; Group 1: 1/38, Group 2: 0/33
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 39% vs 46%, moderate (8-16) 34% vs 33%, severe 26% vs 21%, premorbid mRS score, intervention vs control, mRS 0 18% vs 20%, mRS 1 6% vs 8%, mRS 2 21% vs 6%, mRS 3 16% vs 9%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Mortality at 7 days, 90 days and 1 year
- Actual outcome: Mortality at 90 days; Group 1: 8/38, Group 2: 3/33
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 39% vs 46%, moderate (8-16) 34% vs 33%, severe 26% vs 21%, premorbid mRS score, intervention vs control, mRS 0 18% vs 20%, mRS 1 6% vs 8%, mRS 2 21% vs 6%, mRS 3 16% vs 9%; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Mortality at 7 days; Group 1: 4/38, Group 2: 1/33
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 39% vs 46%, moderate (8-16) 34% vs 33%, severe 26% vs 21%, premorbid mRS score, intervention vs control, mRS 0 18% vs 20%, mRS 1 6% vs 8%, mRS 2 21% vs 6%, mRS 3 16% vs 9%; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Mortality at 12 months; Group 1: 11/36, Group 2: 6/33
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 39% vs 46%, moderate (8-16) 34% vs 33%, severe 26% vs 21%, premorbid mRS score, intervention vs control, mRS 0 18% vs 20%, mRS 1 6% vs 8%, mRS 2 21% vs 6%, mRS 3 16% vs 9%; Group 1 Number missing: 2, Reason: Not stated; Group 2 Number missing: 0, Reason: No missing data

Protocol outcome 3: Adverse events (PE, DVT, pressure sores, pneumonia, falls) at 90 days
- Actual outcome: Pressure sores at 90 days; Group 1: 2/38, Group 2: 1/33
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 39% vs 46%, moderate (8-16) 34% vs 33%, severe 26% vs 21%, premorbid mRS score, intervention vs control, mRS 0 18% vs 20%, mRS 1 6% vs 8%, mRS 2 21% vs 6%, mRS 3 16% vs 9%; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Deep vein thrombosis at 90 days; Group 1: 0/38, Group 2: 0/33
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 39% vs 46%, moderate (8-16) 34% vs 33%, severe 26% vs 21%, premorbid mRS score, intervention vs control, mRS 0 18% vs 20%, mRS 1 6% vs 8%, mRS 2 21% vs 6%, mRS 3 16% vs 9%; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Pulmonary embolism at 90 days; Group 1: 0/38, Group 2: 0/33
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 39% vs 46%, moderate (8-16) 34% vs 33%, severe 26% vs 21%, premorbid mRS score, intervention vs control, mRS 0 18% vs 20%, mRS 1 6% vs 8%, mRS 2 21% vs 6%, mRS 3 16% vs 9%; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Falls at 90 days; Group 1: 27/38, Group 2: 28/33
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 39% vs 46%, moderate (8-16) 34% vs 33%, severe 26% vs 21%, premorbid mRS score, intervention vs control, mRS 0 18% vs 20%, mRS 1 6% vs 8%, mRS 2 21% vs 6%, mRS 3 16% vs 9%; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Pressure sores at 90 days; Group 1: 2/38, Group 2: 1/33
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 39% vs 46%, moderate (8-16) 34% vs 33%, severe 26% vs 21%, premorbid mRS score, intervention vs control, mRS 0 18% vs 20%, mRS 1 6% vs 8%, mRS 2 21% vs 6%, mRS 3 16% vs 9%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Degree of disability or dependence in daily activities (mRS or Barthel) at 7 days, 90 days and 1 year
- Actual outcome: mRS 0-2 vs 3 to 6 at 12 months; Group 1: 14/36, Group 2: 8/33
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 39% vs 46%, moderate (8-16) 34% vs 33%, severe 26% vs 21%, premorbid mRS score, intervention vs control, mRS 0 18% vs 20%, mRS 1 6% vs 8%, mRS 2 21% vs 6%, mRS 3 16% vs 9%; Group 1 Number missing: 2, Reason: States

withdrawal; Group 2 Number missing: - Actual outcome: mRS 0-2 vs 3 to 6 at 90 days; Group 1: 15/38, Group 2: 10/33 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: NIHSS score, intervention vs control: mild (1-7) 39% vs 46%, moderate (8-16) 34% vs 33%, severe 26% vs 21%, premorbid mRS score, intervention vs control, mRS 0 18% vs 20%, mRS 1 6% vs 8%, mRS 2 21% vs 6%, mRS 3 16% vs 9%; Group 1 Number missing: 2, Reason: States withdrawal; Group 2 Number missing: Protocol outcome 5: Quality of life at 90 days and 1 year - Actual outcome: Assessment of Quality of Life (AQoL) at 12 months; Median overall AQoL score was higher in the intervention group compared with control: 0.32 vs 0.24; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: NIHSS score, intervention vs control: mild (1-7) 39% vs 46%, moderate (8-16) 34% vs 33%, severe 26% vs 21%, premorbid mRS score, intervention vs control, mRS 0 18% vs 20%, mRS 1 6% vs 8%, mRS 2 21% vs 6%, mRS 3 16% vs 9%; Group 1 Number missing: 2, Reason: Refusal to participate or attend meeting; Group 2 Number missing: 1, Reason: Refusal to participate or attend meeting	
Protocol outcomes not reported by the study	Length of stay at Hospitalisation; Acute neurological deterioration (worsening of NIHSS) at 7 days and 90 days

Study	Chippala 2016[30]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=86)
Countries and setting	Conducted in India; Setting: Stroke unit
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 90 days
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall: All severities included (34% mild [NIHSS 0-7]; 52% moderate [NIHSS 8-16]; 14% severe [NIHSS >16])
Subgroup analysis within study	Not applicable
Inclusion criteria	18 years or older with acute stroke admitted to stroke unit within 24 hours of symptom onset; able to react to verbal commands; systolic blood pressure 120-180 mmHg; oxygen saturation >92%, heart rate 40-100 beats per minute, temperature <38.5C.
Exclusion criteria	Deterioration within first hour of admission (according to NIHSS); premorbid mRS >3; TIA; concurrent progressive neurological disorder; unstable coronary condition or other medical condition that would pose a hazard to the patient; physiological variables outside safety limits, severe heart failure, lower limb fracture preventing mobilisation; terminal cancer.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Early: 59.3 (9.8); usual care: 60.6 (11.3) years. Gender (M:F): 53/47%. Ethnicity: Not stated
Further population details	1. Ischaemic/haemorrhagic stroke: Ischaemic stroke (Mixed; 20% haemorrhagic). 2. Thrombolysis/no thrombolysis: Not stated / Unclear

Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Very early mobilisation (within 24 hours) - Very early mobilisation (low intensity: <3 sessions per day). Mobilisation (upright and out of bed activities) was started as soon as possible after recruitment and within 24 hours form symptom onset. Duration of mobilisation was determined by patient tolerance (5-30 minutes) and frequency was at least twice a day. The activities included sitting supported in bed, sitting unsupported out of bed, transfer along with assistance, roll and sit up, sitting without support, transfer feet to the floor, standing activities, walk-early gait and advanced gait activities. Median (IQR) time from symptom onset to first mobilisation 18 (16.6-19.8) hours. Duration 7 days or until discharge if sooner. Concurrent medication/care: Standard care for 45 minutes a day (see control group intervention). Indirectness: No indirectness (n=43) Intervention 2: Usual Care. Routine stroke care including passive and, if possible, active mobilisation, correct positioning in bed, mobilisation in bed, sitting balance activities, facilitation of limb and trunk control activities, education of patient and caregiver. Median (IQR) time from symptom onset to first mobilisation 30.5 (29-35) hours. Duration 7 days or until discharge if sooner. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VERY EARLY MOBILISATION (LOW INTENSITY: <3 SESSIONS PER DAY) versus USUAL CARE

Protocol outcome 1: Mortality at 7 days, 90 days and 1 year
- Actual outcome: Mortality at 90 days; Group 1: 0/40, Group 2: 0/40
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Family reasons; Group 2 Number missing: 3, Reason: Family reasons

Protocol outcome 2: Length of stay at Hospitalisation
- Actual outcome: Length of stay at 90 days; median (IQR): group 1: 8 (7-9); Group 2: 10 (8-12.75) days
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Family reasons; Group 2 Number missing: 3, Reason: Family reasons

Protocol outcome 3: Degree of disability or dependence in daily activities (mRS or Barthel) at 7 days, 90 days and 1 year
- Actual outcome: Barthel Index score change from baseline to 90 days; Group 1: mean 45.25 (SD 13.77); n=40, Group 2: mean 28.25 (SD 12.38); n=40; Comments: Final scores: 88.37 (10.08) vs 75.50 (11.53)

Baseline score: 43.12 (17.34) vs 47.25 (14.76) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Family reasons; Group 2 Number missing: 3, Reason: Family reasons - Actual outcome: Barthel Index score at Discharge; Group 1: mean 33.12 (SD 7.73); n=40, Group 2: mean 21 (SD 12.15); n=40; Comments: Final scores: 76.25 (16.16) vs 68.25 (14.34) Baseline score: 43.12 (17.34) vs 47.25 (14.76) Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Family reasons; Group 2 Number missing: 3, Reason: Family reasons	
Protocol outcomes not reported by the study	Recurrent stroke at 90 days; Adverse events (PE, DVT, pressure sores, pneumonia, falls) at 90 days; Quality of life at 90 days and 1 year; Acute neurological deterioration (worsening of NIHSS) at 7 days and 90 days

Study	Diserens 2012[42]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Switzerland; Setting: Hospital stroke unit
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CT- or MRI-confirmed stroke
Stratum	Moderate/severe stroke: NIHSS >6
Subgroup analysis within study	Not applicable
Inclusion criteria	Age >18 years; moderate-to-severe stroke (NIHSS score >6); ischaemic stroke confirmed by CT or MRI; inclusion within 12 hours of admission to the stroke unit; patient/family consent.
Exclusion criteria	TIA, intracerebral or subarachnoid haemorrhage.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Early: 72 (17); delayed: 71(14). Gender (M:F): 54/45%. Ethnicity: Not stated
Further population details	1. Ischaemic/haemorrhagic stroke: Ischaemic stroke 2. Thrombolysis/no thrombolysis: Not stated / Unclear
Extra comments	NIHSS at baseline: early: 14.4 (7.4); delayed: 17.1 (4.9)
Indirectness of population	No indirectness

Interventions	(n=25) Intervention 1: Early mobilisation (within 72 hours) - Early mobilisation (intensity unclear). Head laid flat for the first 24 hours, then raised to 45 for 24 hours and mobilisation out of bed to a sitting or standing position started at 52 hours by physiotherapists Duration Unclear. Concurrent medication/care: Both groups received the same interdisciplinary neurorehabilitation programme (twice a day for 30 minutes) beginning during bed rest by physical therapy (e.g., passive or active exercises, sensorimotor stimulation or hemi-neglect therapy, according to Bobath). In the case of a 2-point worsening of NIHSS the head position was lowered to 0• for 24 hours and the protocol restarted. If no further worsening after 48 hours the head position was raised to 90• for 4 hours before being moved out of bed Indirectness: No indirectness Comments: Median day first out of bed: day 6 (n=25) Intervention 2: Late mobilisation (after 72 hours) - Late mobilisation (intensity unclear). Head of bed progressively elevated over 6 days, and mobilised out of bed on day 7. Duration Unclear. Concurrent medication/care: Both groups received the same interdisciplinary neurorehabilitation programme (twice a day for 30 minutes) beginning during bed rest by physical therapy (e.g., passive or active exercises, sensorimotor stimulation or hemi-neglect therapy, according to Bobath). In the case of a 2-point worsening of NIHSS the head position was lowered to 0• for 24 hours and If no further worsening after 48 hours the head position was raised to 90• for 4 hours before being moved out of bed. Indirectness: No indirectness Comments: Median day first out of bed: day 2 (inconsistent with 52 hours?)
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EARLY MOBILISATION (INTENSITY UNCLEAR) versus LATE MOBILISATION (INTENSITY UNCLEAR) Protocol outcome 1: Mortality at 7 days, 90 days and 1 year - Actual outcome for Moderate/severe stroke: Mortality at 90 days; Group 1: 0/25, Group 2: 1/17; Comments: Caused by pulmonary embolism 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 ; Group 1 Number missing: 0; Group 2 Number missing: 8, Reason: Had to be transferred to local hospitals once specialist stroke unit treatment not required (only occurred in delayed group because length of stay had been increased according to the study protocol)	

Protocol outcome 2: Adverse events (PE, DVT, pressure sores, pneumonia, falls) at 90 days - Actual outcome for Moderate/severe stroke: Pneumonia at 90 days; Group 1: 2/25, Group 2: 5/17 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 ; Group 1 Number missing: 0; Group 2 Number missing: 8, Reason: Had to be transferred to local hospitals once specialist stroke unit treatment not required (only occurred in delayed group because length of stay had been increased according to the study protocol) Protocol outcome 3: Length of stay at Hospitalisation - Actual outcome for Moderate/severe stroke: Length of hospital stay at 90 days; Group 1: mean 13.7 days (SD 6.82); n=25, Group 2: mean 11.7 days (SD 4.66); n=17 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 ; Group 1 Number missing: 0; Group 2 Number missing: 8, Reason: Had to be transferred to local hospitals once specialist stroke unit treatment not required (only occurred in delayed group because length of stay had been increased according to the study protocol) Protocol outcome 4: Degree of disability or dependence in daily activities (mRS or Barthel) at 7 days, 90 days and 1 year - Actual outcome for Moderate/severe stroke: mRS 0-2 at 90 days; Group 1: 10/25, Group 2: 6/17 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 8, Reason: Had to be transferred to local hospitals once specialist stroke unit treatment not required (only occurred in delayed group because length of stay had been increased according to the study protocol) Protocol outcome 5: Acute neurological deterioration (worsening of NIHSS) at 7 days and 90 days - Actual outcome for Moderate/severe stroke: Worsening of NIHSS by >4 points at 90 days; Group 1: 2/25, Group 2: 2/17 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 8, Reason: Had to be transferred to local hospitals once specialist stroke unit treatment not required (only occurred in delayed group because length of stay had been increased according to the study protocol)	
Protocol outcomes not reported by the study	Recurrent stroke at 90 days; Quality of life at 90 days and 1 year

Study	Poletto 2015[72]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=39)
Countries and setting	Conducted in Brazil; Setting: Single centre (large urban emergency department of a public university hospital)
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 14 days intervention and 90 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CT- or MRI-confirmed ischemic stroke
Stratum	Overall: All severities
Subgroup analysis within study	Not applicable:
Inclusion criteria	Adult patients with CT- or MRI-confirmed ischemic stroke within 48 h of symptom onset who were admitted on weekdays to the acute vascular unit (AVU) or general emergency unit of an emergency department (ED). Clinical and hemodynamic stability (systolic blood pressure 120-220 mm Hg, SaO2 >92% with or without supplementation, heart rate 60-100 bpm, body temperature <38°C, and respiratory rate <25); Glasgow Coma Scale score >8; mRS score ≤3, and motor deficit and/or ataxia as measured by the National Institutes of Health Stroke Scale (NIHSS).
Exclusion criteria	Haemorrhagic stroke or transient ischemic attack, history of progressive neurological disease, acute coronary disease, decompensated cardiac disease, or respiratory failure.
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Mean (SD): Intervention: 64 (18); control: 66 (16) years. Gender (M:F): 35/65%. Ethnicity: 94% white
Further population details	1. Ischaemic/haemorrhagic stroke: Ischaemic stroke 2. Thrombolysis/no thrombolysis: No thrombolysis (35% had thrombolysis).

Extra comments	Mean (SD) NIHSS at baseline: intervention - 10 (7); control - 11 (6).
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Early mobilisation (within 72 hours) - Early mobilisation (low intensity: <3 sessions per day). Mobilisation started within 48 h of stroke symptom onset. Trained physical therapists managed the therapy, and focused on sitting out of bed in a chair or standing (whenever and as soon as possible) and conducting functional training and motor relearning (in line with the Bobath concept). Exercises were performed bilaterally with at least 5 repetitions for each joint and each exercise and emphasis on deficits in the impaired side. Mobilisation was once a day, 5 times a week, for approximately 30 min per session, in addition to sitting out of bed for at least 30 min whenever possible. Duration 14 days (or until discharge if earlier). Concurrent medication/care: Not stated. Indirectness: No indirectness Comments: Median (IQR) time from stroke onset to first mobilisation: 43 (28-48 hours); Median (IQR) duration of mobilisation: 135 (85-213) minutes Mean (SD): number of out-of-bed activities: 4.2 (2.3) (n=19) Intervention 2: Usual Care. Conventional physical therapy performed when requested by the staff according to the patients' needs and the availability of physical therapists. This included global motor exercises and respiratory therapy (ordinarily in bed). The duration of standard-care therapy sessions was approximately 15 min and most did not leave their beds. Duration 14 days (or until discharge if earlier). Concurrent medication/care: Not stated. Indirectness: No indirectness Comments: Median (IQR) time from stroke onset to first mobilisation: 72 (61-108 hours); Median (IQR) duration of mobilisation: 0 (0-50) minutes Mean (SD): number of out-of-bed activities: 0.26 (0.73)
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EARLY MOBILISATION (LOW INTENSITY: <3 SESSIONS PER DAY) versus USUAL CARE

Protocol outcome 1: Mortality at 7 days, 90 days and 1 year
- Actual outcome: Mortality at 90 days; Group 1: 2/16, Group 2: 2/17
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: 2, Reason: 3 month follow-up not completed at time of publication; Group 2 Number missing: 2,

Reason: 3 month follow-up not completed at time of publication Protocol outcome 2: Adverse events (PE, DVT, pressure sores, pneumonia, falls) at 90 days - Actual outcome: PE, DVT, pneumonia or falls at 90 days; Group 1: 3/16, Group 2: 2/17; Comments: All events were pneumonia, no other adverse events recorded 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: 2, Reason: 3 month follow-up not completed at time of publication; Group 2 Number missing: 2, Reason: 3 month follow-up not completed at time of publication Protocol outcome 3: Length of stay at Hospitalisation - Actual outcome: Length of hospital stay at 90 days; ; median (IQR) Group 1: 8 (5 to 14); Group 2: 10 (4 to 25) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 3 month follow-up not completed at time of publication; Group 2 Number missing: 2, Reason: 3 month follow-up not completed at time of publication Protocol outcome 4: Degree of disability or dependence in daily activities (mRS or Barthel) at 7 days, 90 days and 1 year - Actual outcome: mRS 0-2 at 90 days; Group 1: 8/16, Group 2: 9/17 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 3 month follow-up not completed at time of publication; Group 2 Number missing: 2, Reason: 3 month follow-up not completed at time of publication Protocol outcome 5: Acute neurological deterioration (worsening of NIHSS) at 7 days and 90 days - Actual outcome: Neurological deterioration at 90 days; Group 1: 0/16, Group 2: 0/17 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: 3 month follow-up not completed at time of publication; Group 2 Number missing: 2, Reason: 3 month follow-up not completed at time of publication	
Protocol outcomes not reported by the study	Recurrent stroke at 90 days; Quality of life at 90 days and 1 year

Study	**SEVEL (Stroke and Early Vertical Positioning) trial: Herisson 2016[47]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=167)
Countries and setting	Conducted in France; Setting: 11 centers in the north-west France
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosed by a neurologist defined by sudden onset of neurological deficit without sign of bleeding on CT scan or MRI.
Stratum	Overall: NIHSS ≤22
Subgroup analysis within study	Not applicable
Inclusion criteria	Above 18 year old, exhibiting neurological deficits at the time of inclusion, were kept in bed (30° maximum) until inclusion time, and if they were enrolled in a healthcare plan (French social security).
Exclusion criteria	Stroke severity (malignant infarction, NIHSS >22, alteration of consciousness with a Glasgow Coma Score < 13); fluctuation of the neurological signs before admission (history of worsening linked to an upright positioning); known intra-cranial stenosis > 50%, symptomatic of the current episode; minor neurological deficit (isolated facial palsy, isolated hemianopia, isolated sensory impairment); iterative vomiting or difficulty in breathing; contra-indication for sitting, e.g. deep vein thrombosis (diagnosed or suspicion) or lower limb fracture; pre-admission Rankin score [3–6]; anticipated difficult follow up (e.g. not speaking French, living in another region); pregnant women; and enrolment in another trial or refusal to participate.

Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Early: 68.1 (13.7); progressive: 71.2 (13.3) years. Gender (M:F): Early: 76.2/23.8%; progressive: 54.7/45.3%. Ethnicity: Not stated
Further population details	1. Ischaemic/haemorrhagic stroke: Ischaemic stroke 2. Thrombolysis/no thrombolysis: Not stated / Unclear
Extra comments	Mean (SD) NIHSS at baseline: early - 7.2 (3.9); progressive - 7.8 (5.6). Enrolment was at the earliest possible time and no later than 1 calendar day after stroke onset.
Indirectness of population	No indirectness
Interventions	(n=82) Intervention 1: Very early mobilisation (within 24 hours) - Very early mobilisation (intensity unclear). Seated out of bed at the earliest time possible, but no later than the calendar day after stroke onset . Duration The minimum duration of first sitting was 15 minutes, with duration determined by patient fatigue and tolerance (return to bed for any of the following: neurological worsening, vagal reaction >40 mmHg increase in blood pressure exceeding 180/100 mmHg, or symptomatic decrease in blood pressure) Concurrent medication/care: Blood pressure and heart rate were closely monitored. Indirectness: No indirectness (n=85) Intervention 2: Early mobilisation (within 72 hours) - Early mobilisation (intensity unclear). Day 0: the patient would be positioned in bed at 30°; day 1: 45°; day 2: 60°; day 3: sitting out of bed Duration The minimum duration of first sitting was 15 minutes, with duration determined by patient fatigue and tolerance (return to bed for any of the following: neurological worsening, vagal reaction >40 mmHg increase in blood pressure exceeding 180/100 mmHg, or symptomatic decrease in blood pressure). Concurrent medication/care: Blood pressure and heart rate were closely monitored. Indirectness: No indirectness
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: VERY EARLY MOBILISATION (INTENSITY UNCLEAR) versus EARLY MOBILISATION/PROGRESSIVE SITTING (INTENSITY UNCLEAR)	

Protocol 1: Mortality at 7 days, 90 days and 1 year - Actual outcome: Mortality at 90 days; Group 1: 3/63, Group 2: 6/75 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: 17, Reason: 1 withdrew consent; 5 primary outcome not assessed; 11 follow-up visit not done; Group 2 Number missing: 7, Reason: 1 primary outcome not assessed; 6 follow-up visit not done Protocol outcome 2: Adverse events (PE, DVT, pressure sores, pneumonia, falls) at 90 days - Actual outcome: Pulmonary infection; DVT; pressure ulcer or fall at 90 days; Group 1: 2/63, Group 2: 1/75; Comments: Falls: 1 vs 1; DVT: 1 vs 0; pressure ulcer 0 vs 0 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: 17, Reason: 1 withdrew consent; 5 primary outcome not assessed; 11 follow-up visit not done; Group 2 Number missing: 7, Reason: 1 primary outcome not assessed; 6 follow-up visit not done Protocol outcome 3: Length of stay at Hospitalisation - Actual outcome: Length of stay at 90 days; Group 1: mean 9.78 days (SD 4.85); n=58, Group 2: mean 10.53 days (SD 6.11); n=66 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: 17, Reason: 1 withdrew consent; 5 primary outcome not assessed; 11 follow-up visit not done; Group 2 Number missing: 7, Reason: 1 primary outcome not assessed; 6 follow-up visit not done Protocol outcome 4: Degree of disability or dependence in daily activities (mRS or Barthel) at 7 days, 90 days and 1 year - Actual outcome: mRS 0-2 at 7 days; Group 1: 39/63, Group 2: 53/75 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: 17, Reason: 1 withdrew consent; 5 primary outcome not assessed; 11 follow-up visit not done; Group 2 Number missing: 7, Reason: 1 primary outcome not assessed; 6 follow-up visit not done - Actual outcome: mRS 0-2 at 90 days; Group 1: 48/63, Group 2: 58/75 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: 17, Reason: 1 withdrew consent; 5 primary outcome not assessed; 11 follow-up visit not done; Group 2 Number missing: 7, Reason: 1 primary outcome not assessed; 6 follow-up visit not done Protocol outcome 5: Acute neurological deterioration (worsening of NIHSS) at 7 days and 90 days - Actual outcome: Neurological deterioration at 90 days; Group 1: 1/63, Group 2: 0/75 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: 17, Reason: 1 withdrew consent; 5 primary outcome not assessed; 11 follow-up visit not done; Group 2 Number missing: 7, Reason: 1 primary outcome not assessed; 6 follow-up visit not done	
Protocol outcomes not reported by the study	Recurrent stroke at 90 days; Quality of life at 90 days and 1 year

Study	VERITAS - very early rehabilitation or intensive telemetry after stroke trial: Langhorne 2010[57]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=32)
Countries and setting	Conducted in United Kingdom; Setting: Stroke unit
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 90 days
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall: No exclusions based on severity but modified NIHSS baseline scores appear mild-to-moderate
Subgroup analysis within study	Not applicable:
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Median (IQR): Early: 64 (60-12); control: 71 (53-76) years. Gender (M:F): 50/50%. Ethnicity: Not stated
Further population details	1. Ischaemic/haemorrhagic stroke: Ischaemic stroke (Only 1 case of cerebral haemorrhage). 2. Thrombolysis/no thrombolysis: Not stated / Unclear
Extra comments	Median (IQR) modified NIH score (range:0-31) at baseline: early - 4 (2-6); control - 6 (4-10)
Indirectness of population	No indirectness

Interventions	(n=16) Intervention 1: Early mobilisation (within 72 hours) - Early mobilisation (high intensity: >3 sessions per day). Standard care plus early mobilisation based on AVERT trial - aim to get patients to sit stand and walk within 24 hours of stroke and continue this at least 4 times a day. However, in practice time from symptom onset to first mobilisation was median (IQR) 27.3 (26.0-29.0) . Duration Unclear. Concurrent medication/care: With or without automated monitoring. Indirectness: Serious indirectness; Indirectness comment: Included 8 patients with automated monitoring in addition to the intervention (n=16) Intervention 2: Early mobilisation (within 72 hours) - Early mobilisation (low intensity: <3 sessions per day). Standard care: immediate transfer to a multidisciplinary stroke unit where the aim was to get patients to sit, stand and walk from the day of admission. In practice the median (IQR) time to first mobilisation was 32.0 (22.5-47.3) hours.. Duration Unclear. Concurrent medication/care: With or without automated monitoring. Indirectness: Serious indirectness; Indirectness comment: Included 8 patients with automated monitoring in addition to the intervention
Funding	Equipment / drugs provided by industry (Welch Allyn provided monitoring equipment; funding from Chest, Heart and Stroke Scotland)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EARLY MOBILISATION (HIGH INTENSITY: >3 SESSIONS PER DAY) versus EARLY MOBILISATION (LOW INTENSITY: <3 SESSIONS PER DAY)

Protocol outcome 1: Mortality at 7 days, 90 days and 1 year
- Actual outcome: Mortality at 90 days; Group 1: 0/16, Group 2: 1/16
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Length of stay at Hospitalisation
- Actual outcome: Length of hospital stay at 90 days; median (IQR): Group 1: 10 (5 to 14) ; Group 2: 12 (6 to 16)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Degree of disability or dependence in daily activities (mRS or Barthel) at 7 days, 90 days and 1 year
- Actual outcome: mRS 0-2 at 90 days; Group 1: 12/16, Group 2: 7/16
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Recurrent stroke at 90 days; Adverse events (PE, DVT, pressure sores, pneumonia, falls) at 90 days; Quality of life at 90 days and 1 year; Acute neurological deterioration (worsening of NIHSS) at 7 days and 90 days

Appendix E: Forest plots

E.1 Very early mobilisation versus usual care

Figure 2: Mortality at 7 days

Study or Subgroup	Very early mobilisation Events	Total	Usual care Events	Total	Risk Ratio M-H, Fixed, 95% CI
AVERT II 2009	4	38	1	33	3.47 [0.41, 29.56]

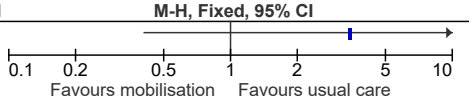


Figure 3: Mortality at 90 days

Study or Subgroup	Very early mobilisation Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
AKEMIS 2012	7	27	2	29	9.7%	3.76 [0.85, 16.54]
AVERT II 2009	8	38	3	33	13.2%	2.32 [0.67, 8.02]
AVERT III 2016	88	1048	72	1050	63.2%	1.22 [0.91, 1.65]
Chippala 2016	0	40	0	40		Not estimable
SEVEL 2012	3	63	6	75	11.5%	0.60 [0.16, 2.28]
VERITAS 2010	0	16	1	16	2.4%	0.33 [0.01, 7.62]
Total (95% CI)		**1232**		**1243**	**100.0%**	**1.32 [0.81, 2.17]**
Total events	106		84			

Heterogeneity: Tau² = 0.08; Chi² = 4.94, df = 4 (P = 0.29); I² = 19%
Test for overall effect: Z = 1.12 (P = 0.26)

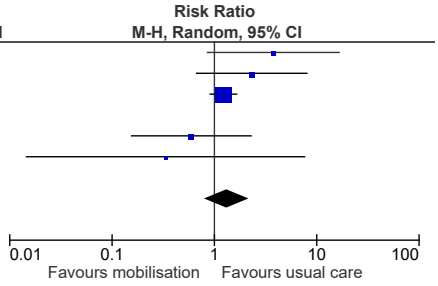


Figure 4: Mortality at 12 months

Study or Subgroup	Very early mobilisation Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AVERT II 2009	11	36	6	33	5.0%	1.68 [0.70, 4.03]
AVERT III 2016	139	1038	118	1042	95.0%	1.18 [0.94, 1.49]
Total (95% CI)		**1074**		**1075**	**100.0%**	**1.21 [0.97, 1.51]**
Total events	150		124			

Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.66 (P = 0.10)

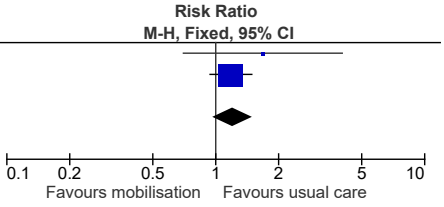


Figure 5: Modified Rankin Scale 0 to 2 at 7 days

Study or Subgroup	Very early mobilisation Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AKEMIS 2012	10	25	17	28	24.9%	0.66 [0.37, 1.16]
SEVEL 2012	39	63	53	75	75.1%	0.88 [0.69, 1.12]
Total (95% CI)		**88**		**103**	**100.0%**	**0.82 [0.66, 1.03]**
Total events	49		70			

Heterogeneity: Chi² = 0.85, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 1.70 (P = 0.09)

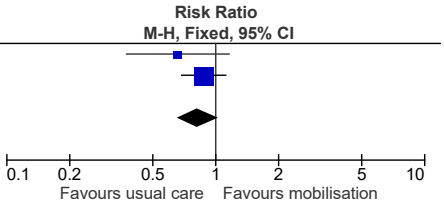


Figure 6: Modified Rankin Scale 0 to 2 at 90 days

Study or Subgroup	Very early mobilisation Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AKEMIS 2012	10	25	17	28	2.6%	0.66 [0.37, 1.16]
AVERT II 2009	15	38	10	33	1.8%	1.30 [0.68, 2.50]
AVERT III 2016	480	1038	525	1045	85.8%	0.92 [0.84, 1.01]
SEVEL 2012	48	63	58	75	8.7%	0.99 [0.82, 1.18]
VERITAS 2010	12	16	7	16	1.1%	1.71 [0.92, 3.20]
Total (95% CI)		**1180**		**1197**	**100.0%**	**0.94 [0.86, 1.01]**
Total events	565		617			

Heterogeneity: Chi² = 6.53, df = 4 (P = 0.16); I² = 39%
Test for overall effect: Z = 1.64 (P = 0.10)

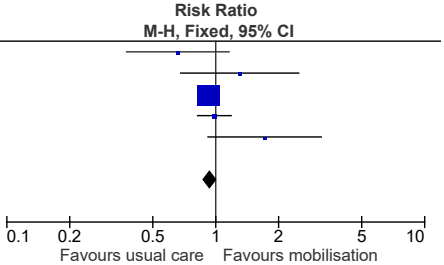


Figure 7: Modified Rankin Scale 0 to 2 at 1 year

Study or Subgroup	Very early mobilisation Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
AVERT II 2009	14	36	8	33	28.0%	1.60 [0.77, 3.33]
AVERT III 2016	480	1038	525	1045	72.0%	0.92 [0.84, 1.01]
Total (95% CI)		**1074**		**1078**	**100.0%**	**1.08 [0.66, 1.75]**
Total events	494		533			

Heterogeneity: Tau² = 0.08; Chi² = 2.20, df = 1 (P = 0.14); I² = 55%
Test for overall effect: Z = 0.29 (P = 0.77)

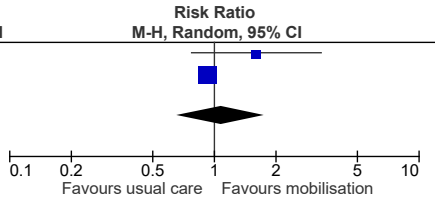


Figure 8: Recurrent stroke at 90 days

Study or Subgroup	Very early mobilisation Events	Total	Usual care Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
AVERT II 2009	1	38	0	33	6.48 [0.13, 329.67]

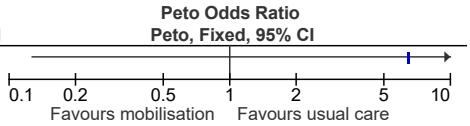


Figure 9: Neurological deterioration at 90 days

Study or Subgroup	Very early mobilisation Events	Total	Usual care Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
SEVEL 2012	1	63	0	75	8.94 [0.17, 457.29]

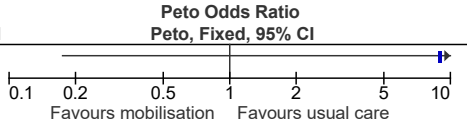


Figure 10: Adverse events at 90 days

Study or Subgroup	Very early mobilisation Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AVERT II 2009	30	38	31	33	97.3%	0.84 [0.70, 1.01]
SEVEL 2012	2	63	1	75	2.7%	2.38 [0.22, 25.65]
Total (95% CI)		**101**		**108**	**100.0%**	**0.88 [0.72, 1.08]**
Total events	32		32			

Heterogeneity: Chi² = 0.93, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)

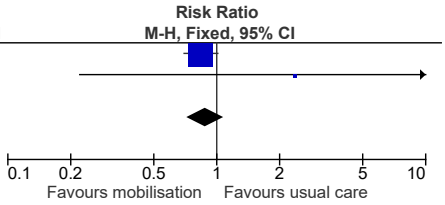


Figure 11: Length of hospital stay

Study or Subgroup	Very early mobilisation Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
SEVEL 2012	9.78	4.85	58	10.53	6.11	66	-0.75 [-2.68, 1.18]

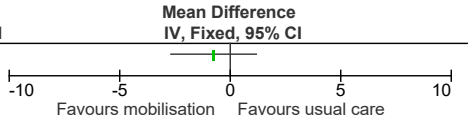


Figure 12: Barthel index at discharge

Study or Subgroup	Favours usual care Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Chippala 2016	76.25	16.16	40	68.25	14.34	50	8.00 [1.61, 14.39]

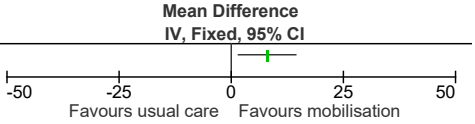
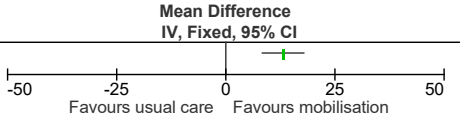


Figure 13: Barthel index at 90 days

Study or Subgroup	Very early mobilisation Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Chippala 2016	88.37	10.08	40	75.25	11.53	40	13.12 [8.37, 17.87]



E.2 Early mobilisation versus usual care

Figure 14: Mortality at 90 days

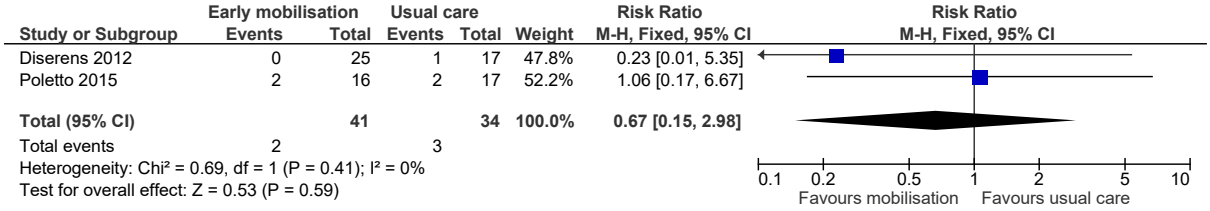


Figure 15: Modified Rankin Scale 0 to 2 at 90 days

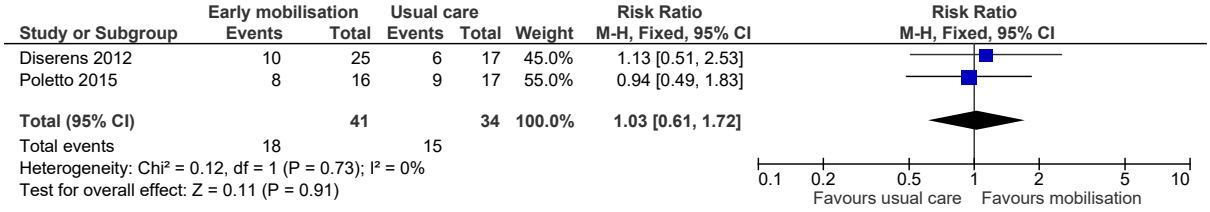


Figure 16: Neurological deterioration at 90 days

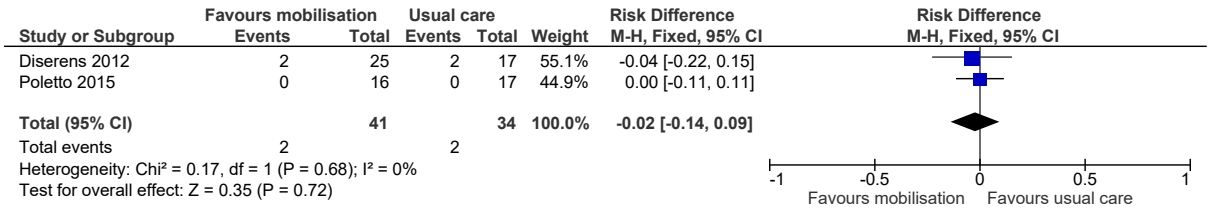


Figure 17: Adverse events at 90 days

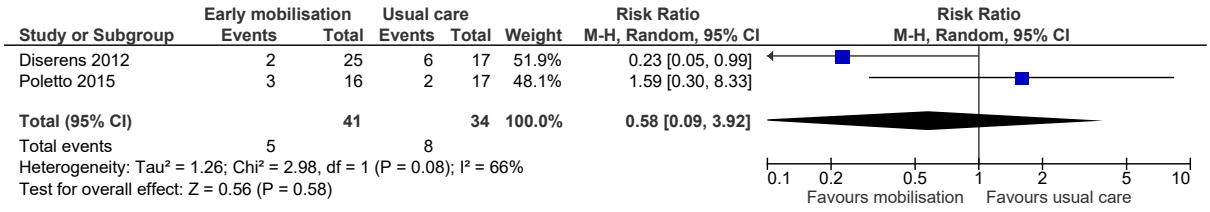


Figure 18: Length of hospital stay

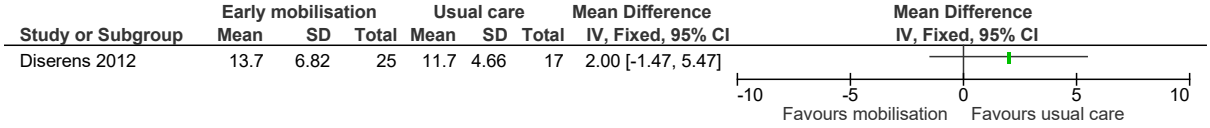
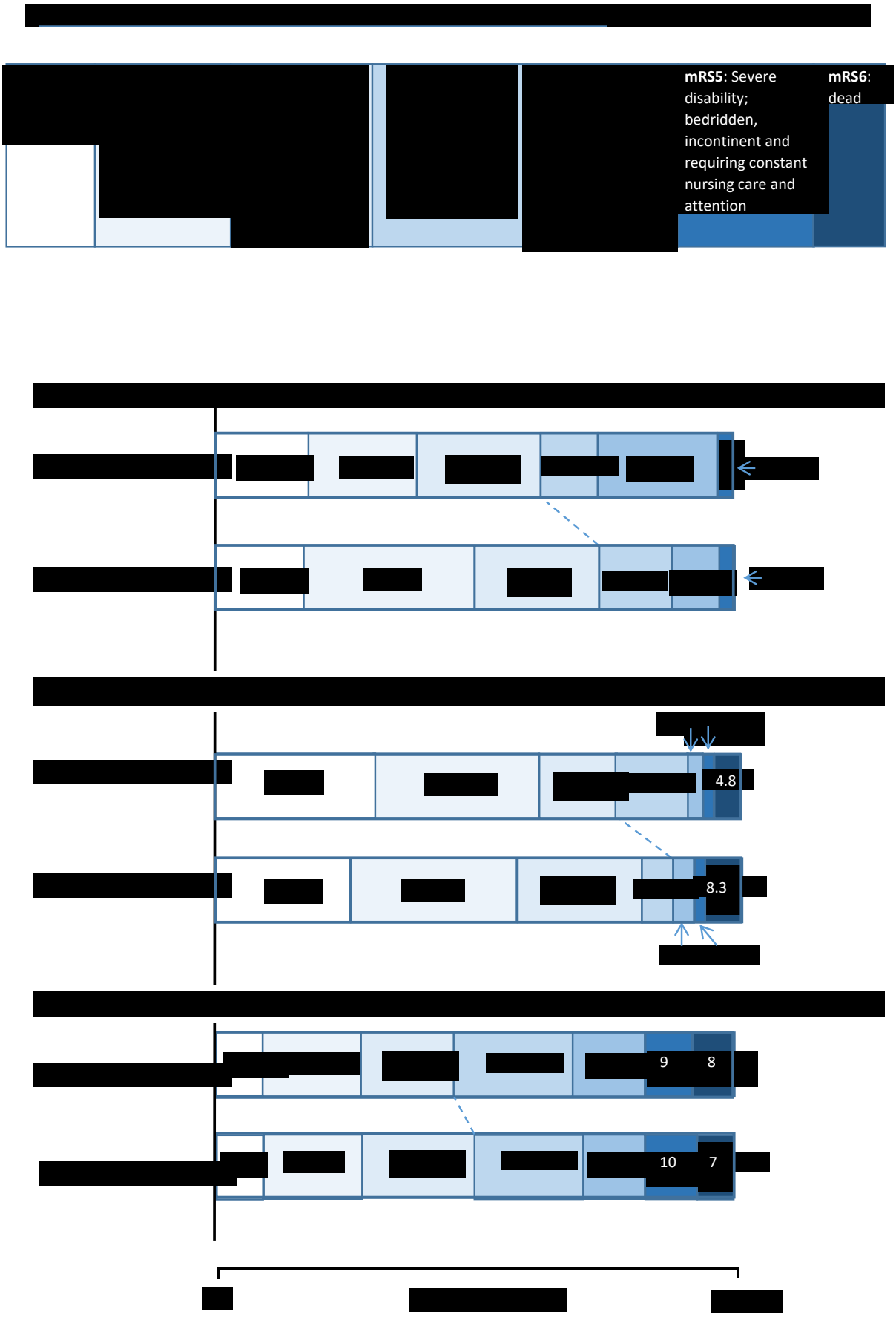


Figure 19: Modified Rankin Scale at 7 and 90 days (ordinal shift graphs)



Appendix F: GRADE tables

Table 12: Clinical evidence profile: very early mobilisation versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Very early mobilisation	Standard care - subgroups	Relative (95% CI)	Absolute		
Mortality at 7 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/38 (10.5%)	3%	RR 3.47 (0.41 to 29.56)	74 more per 1000 (from 18 fewer to 857 more)	⊕⊕OO LOW	CRITICAL
Mortality at 90 days												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	106/1232 (8.6%)	6.9%	RD 0.01 (-0.03 to 0.05)	11 more per 1000 (from 30 fewer to 51 more)[2]	⊕⊕⊕O MODERATE	CRITICAL
Mortality at 12 months												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	150/1074 (14%)	14.8%	RR 1.21 (0.97 to 1.51)	31 more per 1000 (from 4 fewer to 75 more)	⊕⊕⊕O MODERATE	CRITICAL
mRS at 0 to 2 at 7 days												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	49/88 (55.7%)	65.7%	RR 0.82 (0.66 to	118 fewer per 1000 (from 223	⊕⊕OO	CRITICAL

									1.03)	fewer to 20 more)	LOW	
mRS 0 to 2 at 90 days												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	565/1180 (47.9%)	43.8%	RR 0.94 (0.86 to 1.01)	26 fewer per 1000 (from 61 fewer to 4 more)	⊕⊕⊕⊕ HIGH	CRITICAL
mRS 0 to 2 at 12 months												
2	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	none	494/1074 (46%)	37.2%	RR 0.93 (0.85 to 1.02)	26 fewer per 1000 (from 56 fewer to 7 more)	⊕⊕⊕O MODERATE	CRITICAL
Recurrent stroke at 90 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/38 (2.6%)	0%	OR 6.48 (0.13 to 329.67)	30 more per 1000 (from 50 fewer to 100 more)[2]	⊕⊕OO LOW	IMPORTANT
Neurological deterioration (worsening NIHSS >4 points) at 90 days												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/63 (1.6%)	0%	OR 8.94 (0.17 to 457.29)	20 more per 1000 (from 30 fewer to 60 more)[2]	⊕OOO VERY LOW	IMPORTANT
Adverse events at 90 days												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32/101 (31.7%)	47.6%	RR 0.88 (0.72 to 1.08)	57 fewer per 1000 (from 133 fewer to 38 more)	⊕⊕⊕O MODERATE	IMPORTANT
Barthel index at discharge (Better indicated by higher values)												

1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	50	-	MD 8 higher (1.61 to 14.39 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Barthel index at 90 days (Better indicated by higher values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	MD 13.12 higher (8.37 to 17.87 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Length of hospital stay (Better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	58	66	-	MD 0.75 lower (2.68 lower to 1.18 higher)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Calculated from risk difference
[3] 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
[4] Heterogeneity, I2=55%, unexplained by subgroup analysis because only 2 studies were in the analysis

Table 13: Clinical evidence profile: early mobilisation versus usual care

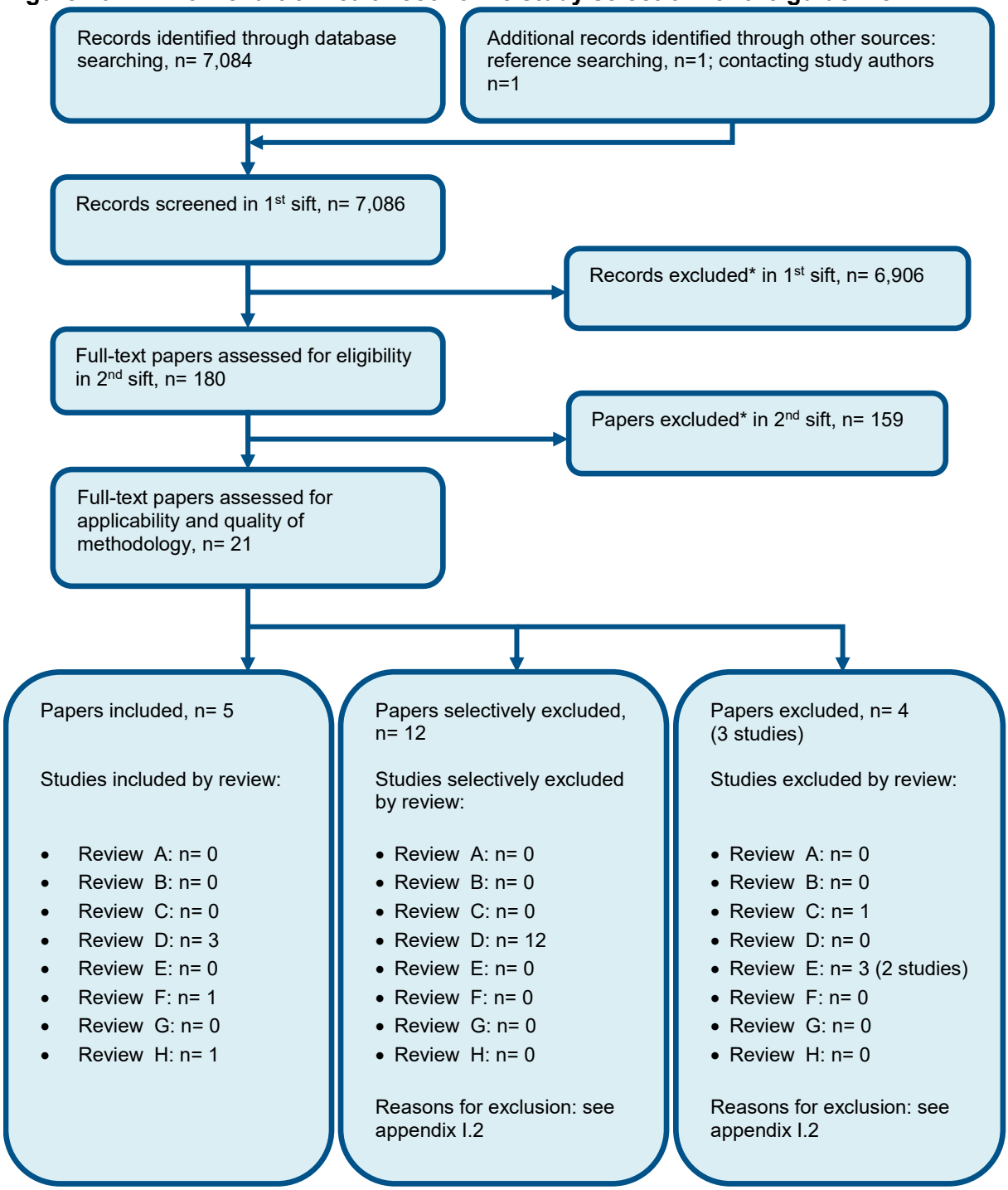
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early mobilisation**	**Standard care**	**Relative (95% CI)**	**Absolute**		
Mortality at 90 days												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/41 (4.9%)	8.8%	RR 0.67 (0.15 to 2.98)	29 fewer per 1000 (from 75 fewer to 174	⊕OOO VERY	CRITICAL

										more)	LOW	
mRS 0 to 2 at 90 days												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/41 (43.9%)	44.1%	RR 1.03 (0.61 to 1.72)	13 more per 1000 (from 172 fewer to 318 more)	⊕OOO VERY LOW	CRITICAL
Neurological deterioration (worsening NIHSS >4 points) at 90 days												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/41 (4.9%)	5.9%	RD 0 (-0.14 to 0.09)	21 fewer per 1000 (from 140 fewer to 90 more)[3]	⊕OOO VERY LOW	IMPORTANT
Adverse events at 90 days												
2	randomised trials	very serious[1]	serious[4]	no serious indirectness	very serious[2]	none	5/41 (12.2%)	23.5%	RR 0.58 (0.09 to 3.92)	99 fewer per 1000 (from 214 fewer to 686 more)	⊕OOO VERY LOW	IMPORTANT
Length of hospital stay (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	17	-	MD 2 higher (1.47 lower to 5.47 higher)	⊕OOO VERY 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] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Calculated from risk difference
[4] Heterogeneity, I2=66%, unexplained by subgroup analysis because only 2 studies were in the analysis

Appendix G: Health economic evidence selection

Figure 20: Flow chart of health economic study selection for the guideline



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

Appendix H: Health economic evidence tables

Study	Tay-Teo 2008 [85]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome: dichotomised mRS at 3 months: good (mRS ≤2) and poor (mRS ≥3) **Study design:** Within-trial analysis of AVERT II RCT **Approach to analysis:** Resource items used within 12 months of stroke obtained from previous literature. Resource use data determined from medical records and 3-, 6- and 12-month patient/next-of-kin interviews. Unit costs applied to resource items. Costs of hospitalisations due to stroke obtained by categorising by stroke severity and length of stay. The same daily cost was applied for the first two days, irrespective of stroke severity. **Perspective:** Australian societal perspective/ hospital perspective (only hospital perspective is presented here) **Follow-up:** Health outcomes and costs: 3 months, costs: 12 months **Discounting:** Costs:n/a;	**Population:** Ischaemic or haemorrhagic strokes within 24 hours of stroke onset **Patient characteristics:** Mean age: 74.7 years Male: 64% **Intervention 1:** Standard care, delivered by ward therapists and nurses. Expected dose half dose of intervention 2. **Intervention 2:** Very early mobilisation: upright and out of bed, either sitting or standing, dependent on ability. Implemented in addition to standard care. Twice per day for 6 days per week, for 14 days or until discharge. Delivered by nurse/physiotherapist team	**Hospital perspective:** **Three month total costs (mean per patient):** Intervention 1: £16,276 Intervention 2: £13,617 Incremental (2−1): Saves £2,659 (95% CI: NR; p=NR) **Twelve month total costs (mean per patient):** Intervention 1: £18,159 Intervention 2: £15,666 Incremental (2−1): Saves £2,493 (95% CI: NR; p=NR) **Currency & cost year:** 2004 AUD (presented here as 2004 UK pounds[(b)]) **Cost components incorporated:** Hospital perspective: Time cost for implementing very early mobilisation, acute-phase hospitalisation, interim care arrangement, emergency attendance, rehospitalisation, inpatient rehabilitation, outpatient	**Adjusted OR (mRS 0-2 at 3 months):** 4.10 (95% CI: 0.99-16.88; p=0.051)	**Three month ICER (Intervention 2 versus Intervention 1) (Hospital perspective):** Dominant (da)

Outcomes: n/a		rehabilitation		

Data sources

Health outcomes: AVERT II[24, 25, 36, 37, 79, 86] **Quality-of-life weights:** n/a **Cost sources:** National Hospital Cost Data Collection, Medicare Benefits Schedule, local costs where not obtainable from national sources

Comments

Source of funding: National Heart Foundation of Australia, Affinity Health, Austin Health Medical Research Fund, Australian National Health and Medical Research Council **Limitations:** High recruitment of moderate to severe strokes to AVERT II could limit generalisability**.** Health outcomes and resource use are based on the AVERT phase II trial only. Health effects not expressed as QALYs, diverging from NICE reference case. mRS score is dichotomised; ordinal shift not used. Medications and diagnostic investigations not included in resource use. Aspects of resource use obtained through patient/next-of-kin interviews could be subject to recall bias. Potential conflicts of interest are not reported. **Other:**

Overall applicability: Partially applicable(c) **Overall quality:** Potentially serious limitations(d)

Abbreviations: CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; mRS: modified Rankin Scale; n/a: not applicable; NR: not reported; pa: probabilistic analysis; OR: odds ratio; QALY: quality-adjusted life year; RCT: randomised controlled trial

(a) Converted using 2004 purchasing power parities[71]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 14: Studies excluded from the clinical review

Study	Exclusion reason
Ada 2009[1]	Conference abstract: unavailable
Ada 2010[2]	Conference abstract
Ada 2010[3]	Not review population
Adeolu 2012[4]	Not review population
Aries 2012[5]	Incorrect study design
Armstrong 2012[6]	Not review population
Arnold 2015[7]	Incorrect study design
Asberg 1989[8]	Incorrect interventions
Awad 2016[9]	Commentary
Bagley 2005[10]	Incorrect interventions
Baltz 2013[11]	Incorrect study design
Bayley 2017[12]	Narrative review
Bernhardt 2016[13]	Conference abstract
Bernhardt 2007[20]	Conference abstract: unavailable
Bernhardt 2008[21]	HE study
Bernhardt 2011[19]	Conference abstract
Bernhardt 2015[16]	Commentary
Bernhardt 2015[14]	Conference abstract: unavailable
Braun 2016[26]	Not review population
Brauser 2015[27]	Commentary
Britton 2008[28]	Not review population
Cabanas-Valdés 2016[29]	Not review population
Collier 2007[32]	Conference abstract: unavailable
Collier 2008[33]	Conference abstract: unavailable
Craig 2010[34]	IPD of only 2 RCTs
Cuesy 2010[35]	Incorrect interventions
Cumming 2011[37]	No outcomes of interest
Dagonnier 2013[38]	Conference abstract: unavailable
Dean 2007[41]	Not review population
Dean 2009[40]	Conference abstract: unavailable
Dean 2010[39]	Not review population
Diserens 2010[43]	Conference abstract: unavailable
Forster 2015[44]	Narrative review
Fuest 2018[45]	Narrative review
Hargroves 2008[46]	Incorrect study design
Hokstad 2016[48]	Incorrect study design

Study	Exclusion reason
Hunter 2011[49]	Not review population
Indredavik 1999[50]	Incorrect interventions
Karic 2016[51]	Incorrect study design
Karic 2017[52]	Incorrect study design
Keating 2012[53]	Narrative review
Kosak 1998[54]	Conference abstract
Kosak 2000[55]	Not review population
Kurabe 2010[56]	Incorrect study design
Li 2018[59]	Systematic review: quality assessment is inadequate
Liu 2014[60]	Incorrect interventions
Lynch 2016[61]	Conference abstract: unavailable
Lynch 2017[62]	Commentary
Ma 2013[63]	Systematic review: quality assessment is inadequate
Morreale 2016[64]	Incorrect interventions
Muhl 2013[65]	Conference abstract
Muhl 2014[66]	Conference abstract: unavailable
Muhl 2014[67]	Incorrect study design
Olkowski 2013[70]	Incorrect study design
Olkowski 2015[69]	Incorrect study design
Pollock 2014[73]	Incorrect interventions
Rocca 2016[74]	Not review population
Ronning 2009[75]	Clinical trial webpage only
Sankara Kumaran 2013[76]	Incorrect study design
Silva 2013[77]	Foreign language, Portuguese
Sorbello 2007[78]	Conference abstract: unavailable
Stokelj 2010[80]	Systematic review: quality assessment is inadequate
Sundseth 2008[81]	Conference abstract: unavailable
Sundseth 2012[82]	Conference abstract: unavailable
Tay-teo 2008[85]	No outcomes of interest
Wijk 2009[88]	Conference abstract: unavailable
Wijk 2012[87]	No outcomes of interest
Xu 2017[89]	Systematic review: quality assessment is inadequate
Zeng 2007[90]	Clinical trial webpage only