National Institute for Health and Care Excellence

Draft for consultation

Stroke Rehabilitation in adults (update)

[E] Evidence reviews for intensity of rehabilitation - Health economics

NICE guideline GID-NG10175

Evidence reviews underpinning recommendations 1.2.15 to 1.2.19 and research recommendations in the NICE guideline

April 2023

Draft for Consultation

These evidence reviews were developed by the Guideline Development Team at NICE

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ISBN:

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1 Efficacy of intense rehabilitation (quantitative evidence – economic sections only)

1.1 Review question

In people after stroke, what is the clinical and cost effectiveness of more intensive rehabilitation compared with standard rehabilitation?

1.1.4 Economic evidence

1.1.4.1 Included studies

Eight health economic studies with relevant comparisons about intensity of rehabilitation were included in this review.[16 7, 10 9, 12, 15, 21, 22]

This included:

- Three studies categorised as multidisciplinary rehabilitation[15, 16, 21] (with or without communication difficulties)
- Three studies categorised as physiotherapy[7, 9, 10] (without communication difficulties)
- One study categorised as psychology/neuropsychology therapy[12] (with communication difficulties)
- One study categorised as occupational therapy[22] (without communication difficulties).

These are summarised in the health economic evidence profiles below (Table 1, Table 2 Table 3 and Table 4) and the health economic evidence tables in Appendix D.

See also the health economic study selection flow chart in Appendix C.

1.1.4.2 Excluded studies

One health economic study was identified but excluded due to a combination of limited applicability and methodological limitations.[14] This is listed in Appendix F, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix C.

1.1.5 Summary of included economic evidence

Table 1: Health economic evidence profile: more intensive versus less intensive rehabilitation therapy – multidisciplinary rehabilitation (with and without communication difficulties)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Nagayama 2022[15] (Japan)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Within-trial analysis of a natural experiment study (n=405 – same study) with no modelled extrapolation. • Comparative-cost analysis (no health outcomes) • Population: Adults who were hospitalised with acute stroke in a convalescent rehabilitation unit for more than 1 month, who returned home post-discharge. • Comparators: 1) Low-Intensity rehabilitation (n=36). Mean (SD) therapy time was 89.7 (39.7) minutes per day. Mean (SD) length of hospital stay was 93.5 (39.9) days. 2) High-intensity rehabilitation (n=369). Mean (SD) therapy time was 135.3 (30.9) minutes per day. Mean (SD) length of hospital stay was 96.3 (47.4) days. • Follow-up: 1-year post-discharge from hospital.	2-1: £812[(c)]	NA	No significant differences were reported for the medical costs between groups during the year after discharge (p=0.653)	NA

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
National Institute for Health and Care Excellence, CG162 P.159, 2013[16] (UK)	Partially applicable[(d)]	Potentially serious limitations[(e)]	• Simple lifetable model based on Ryan 2006 RCT[24] • Cost-utility analysis (QALYs) • Population: adults and young people (16+) who have had a stroke and need rehabilitation • Comparators: - Less intensive multidisciplinary rehabilitation (three or less face-to-face contacts per week, for 12 weeks maximum) - More intensive multidisciplinary rehabilitation (six or more face-to-face contacts per week, for 12 weeks maximum) • Time horizon: Lifetime • Utility difference scenarios, 12 week difference is: 1. Maintained over lifetime. 2. Disappears over time: a) 3-months; b) 1-year; c) 5-years	Scenario 1: £226[(f)] Scenario 2a: £228[(f)] Scenario 2b: £228[(f)] Scenario 2c: £226[(f)]	Scenario 1: 0.70 QALYs Scenario 2a: 0.03 QALYs Scenario 2b: 0.08 QALYs Scenario 2c: 0.29 QALYs	Scenario 1: £324 per QALY gained Scenario 2a: £6,722 per QALY gained Scenario 2b: £2,751 per QALY gained Scenario 2c: £776 per QALY gained	Probability of more intensive MDT rehabilitation cost effective (£20K threshold): 1) 99%/ 2a) 95% / 2b) 99% / 2c) 100% Results were not sensitive to changes to the initial cohort age or length of rehabilitation session. Threshold analyses: • Cost difference where no longer cost effective: £685 (2a) to £13,433 (1) • QALY difference no longer cost effective: (see economic evidence table in Appendix D for details).
Oyanagi 2021[21] (Japan)	Partially applicable[(g)]	Potentially serious limitations[(h)]	• Within-trial analysis of a retrospective study (same paper) with no modelled extrapolation. • Cost-effectiveness analysis (health outcome: mRS) • Population: Adults (≥18 years old) diagnosed with stroke in the acute phase (72 hours – 7 days) receiving inpatient rehabilitation.	2−1: £83[(i)]	(2-1) mRS score of 0-2 at discharge[(j)]: -13%	£638 per case of mRS>2 averted. No significant differences were observed between the two groups for total medical expenses during	NA

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			• Comparators: 1) Normal-frequency intervention (n=654). Mean (SD) rehabilitation time was 43.6 (12.6) minutes per day delivered over a length hospital stay of 20.9 (16.0) days. • 2) High-frequency intervention (n=1105). Mean (SD) rehabilitation time was 66.3 (16.4) minutes per day delivered over a length hospital stay of 24.1 (14.2) days. • Follow-up: End of hospitalisation (maximum observed was 25 days).			hospitalisation, despite the higher-frequency rehabilitation group having a higher disease severity (median NIHSS score at admission was 5 (IQR: 3-13), compared to 4 (IQR: 2-12) for normal-intensity rehabilitation (p<0.001).	

Abbreviations: 95% CI= 95% confidence interval; ICER= incremental cost-effectiveness ratio; IQR= interquartile range; MDT= multi-disciplinary team; mRS= modified Rankin scale (scale 0-6, lower values are better); NA= not applicable; NIHSS= National Institute of Health Stroke Scale (scale 0-42, lower values are better); NR= not reported; QALYs= quality-adjusted life years; RCT= randomised controlled trial.

(a) Within-trial analysis based on a retrospective natural experiment study not the wider evidence based identified in the clinical review. References for unit costs were not reported which limits interpretation of results for UK context. No probabilistic sensitivity analyses were performed.

(b) QALYs (and cost per QALY gained) were not presented. Japanese healthcare perspective and 2005-2017 resource use estimates may not reflect current UK context.

(c) 2020 Japanese Yen (¥) converted to UK pounds (£) converted to UK pounds using purchasing power parities.[20] No significant differences in the medical costs reported between groups during the year after discharge (p=0.653). References for unit costs were not reported but 2020-unit costs were assumed based on costs reported in Japanese Yen that were converted to US dollars ($) using average currency conversion rates in March 2020. Cost components incorporated: Medical costs including length total rehabilitation time, clinic visits and length of hospital stay.

(d) Resource use (2000-2002) and unit costs (2013) may not reflect current UK NHS context; intensity of multidisciplinary rehabilitation in both the intervention and comparator arms of Ryan are well below current UK levels.

(e) Model is based on Ryan 2006 RCT[24] and so only reflects this study and not the wider evidence base identified in the clinical review. Ryan 2006 was not included in updated clinical review because it was judged that there was insufficient information to categorise the study in line with the new review protocol strata; however as the economic evaluation compared higher versus lower intensity multidisciplinary rehabilitation and it is the model from previous guideline it has not been excluded. Base-case analysis assumed no difference in post-rehabilitation costs; however, greater functional ability could plausibly result in lower dependency and potentially lower social care costs however, this would further favour more intensive rehabilitation and so would not change conclusions.

(f) 2013 UK pounds. Cost components incorporated: rehabilitation costs, which consisted of total number/length of rehabilitation sessions and cost per hour home visit for both a rehabilitation professional and rehabilitation assistant.

(g) QALYs (and cost per QALY gained) were not presented. Japanese healthcare perspective and 2013-2016 resource use estimates may not reflect UK NHS context.
(h) Within-trial analysis based on a retrospective study not the wider evidence based identified in the clinical review. Follow-up data was only collected until discharge from hospital which may not sufficiently assess the full costs and benefits. Median (not mean) outcomes reported. Intervention costs associated with increased frequency of rehabilitation were not incorporated into costs differences between groups. References for unit costs (including costs year) were not reported which limits interpretation of results for UK context. No probabilistic sensitivity analyses were performed.
(i) 2020 Japanese Yen (¥) converted to UK pounds (£)[20] Total costs were not statistically significant between groups (p=0.06). References for unit costs were not reported but 2020 was assumed based on year prior to the date study was submitted (11/01/2021). Cost components incorporated: Medical costs during hospitalisation (drugs, injections, treatment, inspection, and imaging).
(j) Differences between preadmission mRS scores were not statistically significant between the groups (p<0.007), while mRS discharge scores were statistically different between groups (<0.001) NIHSS discharge scores were not reported as NIHSS scores at admission were significantly higher in the high-frequency intervention group than in the normal frequency group (p< 0.001).

Table 2: Health economic evidence profile: more intensive versus less intensive rehabilitation therapy – physiotherapy (without communication difficulties)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Chan 2015 [7] (Canada)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Simple lifetable model based on Cooke 2010 RCT[8] • Cost-utility analysis (QALYs) • Population: adults who have had a recent stroke and need physiotherapy while receiving inpatient rehabilitation. • Comparators: 1. Conventional physiotherapy (CPT) (RCT reported 9.2 hours over 6 weeks) 2. Higher-intensity physiotherapy (CPT + CPT) up to 1 extra hour of therapy, 4 days a week for 6 weeks. (mean 23hrs) 3. Functional strength training (FST) plus CPT up to 1	2-1: saves £1,520[(c)] 3-1: saves £1,369[(c)] 3-2: £151[(c)]	2-1: 0.05 QALYs 3-1: 0.12 QALYs 3-2: 0.07 QALYs	Lower intensity physiotherapy was dominated by both higher intensity physiotherapy interventions. 3-2: £2,147 per QALY gained	Probability of either of the higher intensity interventions being cost effective compared to lower intensity (£20K threshold): ~55% The dominance of the two increased-intensity interventions remained for most one-way sensitivity analyses. One exception was when the 6-week utility values observed in the RCT were replaced with the 18-week follow-up values (CPT+CPT had lower costs, but also lower QALYs compared with CPT). Setting inpatient rehabilitation length of stay to ‘no reduction’ made both of

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			extra hour of therapy, 4 days a week for 6 weeks. (mean 23.5 hours). • Time horizon: Lifetime (difference in quality of life at 6 weeks assumed to disappear over two years.				the higher-intensity interventions lose dominance but still remain cost-effective compared to CPT.
Dohl 2020 [9] (Norway)	Partially applicable[(d)]	Potentially serious limitations[(e)]	• Within-trial analysis of LAST RCT[1] • Cost-consequence analysis (various health outcomes) • Population: Adults with post-stroke aphasia • Comparators: 1. Standard care; Physiotherapy (</= 45 minutes, <5 days a week). 2. Individualized regular coaching: Physiotherapy (≤45 minutes, <5 days a week) • Time horizon: 18 months	£1,957[(f)]	From clinical review (2 vs 1) at ≥6 months [1] HrQoL (SIS): -0.70 (95% CI: -7.98, 6.58) Activities of daily living (Barthel Index) at ≥6 months: 0.00 (95% CI: -0.47,0.47) Modified Rankin scale: -0.05 (95% CI: -0.37, 0.27) EQ-5D-5L: no difference[(g)]	NA	No sensitivity analyses undertaken.
Fernandez-Garcia	Directly applicable	Minor limitations[(h)]	• Within-trial analysis of RATULS RCT[23] • Cost-utility analysis (QALYs)	2-1: £1601[(i)] 3-1: £741[(i)]	2-1: 0.00 QALYs	More intensive rehabilitation (robot arm	Probability cost effective (£20K threshold): • usual care 81%

<table>
<tr><th>Study</th><th>Applicability</th><th>Limitations</th><th>Other comments</th><th>Incremental cost</th><th>Incremental effects</th><th>Cost effectiveness</th><th>Uncertainty</th></tr>
<tr><td>2021[4] (UK)</td><td></td><td></td><td>• Population: adults with moderate or severe upper limb functional limitation as a result of first-ever stroke that had occurred between 1 week and 5 years before randomisation
• Comparators:
1. Usual care (45 minutes with a physiotherapist or occupational therapist, 5 days a week)
2. More intensive – robot-assisted training (45 minutes per day, 3 times per week) plus usual care
3. More intensive – enhanced upper limb therapy (EULT) (45 minutes with a physiotherapist, 3 times per week) plus usual care.
• Time horizon: 6 months</td><td></td><td>3-1: 0.01 QALYs</td><td>training) was dominated by usual care.

More intensive (EULT) vs usual care: £74,100 per QALY gained</td><td>• more intensive (robot) 0%
• more intensive (EULT) 19%

Sensitivity analyses around missing data and robot costs did not change conclusions.

Extrapolation of data to 12 month time horizon made more intensive rehabilitation (EULT) cost effective compared to usual care (£6,095; probability cost effective 55%). More intensive (robot) remained dominated by usual care.</td></tr>
<tr><td>National Institute for Health and Care Excellence[(j)] 2023 (UK)</td><td>Directly applicable</td><td>Minor limitations[(k)]</td><td>• Markov model with 4 alternative base case scenarios based on 8 RCTs from the clinical review.
• Cost-utility analysis (QALYs)
• Population: adults who have had a stroke and require physiotherapy as part of their rehabilitation and who can tolerate more than 45 minutes of therapy in a day
• Comparators:</td><td colspan="4"><table>
<tr><th>Base case analysis</th><th>Incremental cost[(l)]</th><th>QALYs gained</th><th>Cost per QALY gained</th><th>Probability CE @£20K</th><th>Sensitivity analyses where results changed significantly</th></tr>
<tr><td colspan="6">Scenario 1: post-rehabilitation, weekly reduction of EQ-5D mean difference until no difference between was seen between higher and lower intensity groups, meaning higher intensity leads to faster stroke recovery</td></tr>
<tr><td>a) intervention costs only</td><td>£2,279</td><td>0.05</td><td>£48,539</td><td>7%</td><td>Higher was not cost effective in any sensitivity analysis</td></tr>
<tr><td>b) with post-rehab care savings</td><td>-£3,312</td><td>0.05</td><td>Higher dominant</td><td>76%</td><td>• an 18-week time horizon, (£73,059 per QALY gained),
• alternative data for post-rehabilitation care cost</td></tr>
</table></td></tr>
</table>

Study	Applicability	Limitations	Other comments	Incremental cost		Incremental effects	Cost effectiveness		Uncertainty
			1. Less intensive physiotherapy: >45 mins – 1 hour physiotherapy, 5 days a week 2. More intensive physiotherapy: 1 to 2 hours of physiotherapy, 5 days a week • Time horizon: Lifetime						savings - higher intensity had a 43% probability of being <£20,000 per QALY gained but mean of £233 per QALY gained.
				Scenario 2: post-rehabilitation, 3-month weekly reduction applied before the difference was maintained, meaning higher intensity leads to permanent health gains					
				a) intervention costs only	£2,286	0.24	£9,676	83%	•the 18-week time horizon (£181,443 per QALY gained), •2-year time horizon (£36,382 per QALY gained), •an initial cohort age of 90 years (£38,472 per QALY gained).
				b) with post-rehab care savings	-£29,487	0.24	Higher dominant	96%	•an 18-week time horizon, (£88,543 per QALY gained).

Abbreviations: BI= Barthel index (scale 0-100, higher values are better); CE= cost effective; ICER= incremental cost-effectiveness ratio; mRS= modified Rankin scale (scale 0-6, lower values are better); NA= not applicable; SIS= Stroke Impact Scale (scale 0-59, higher values are better); QALYs= quality-adjusted life years; RCT= randomised controlled trial.

(a) *2010 resource use and 2013 Canadian unit costs may not reflect current UK NHS context. Applied a 5% discount rate for costs and outcomes when 3.5% is the preferred rate by NICE.*

(b) *Model is based on Cooke 2010 RCT [8] (in terms of comparators and quality of life benefit) and so only reflects this study and not the wider evidence base identified in the clinical review. Bed-days saved with higher intensity interventions was based on expert opinion and was what drove the cost savings.*

(c) *2013 Canadian dollars converted to 2018 UK pounds (£)Organisation for Economic Co-operation and Development (OECD). Purchasing power parities (PPP). 2012. Available from: http://www.oecd.org/std/ppp}. Cost components incorporated included physiotherapist wage and length of stay for inpatient rehabilitation.*

(d) *2014 Norwegian healthcare system may not reflect current UK NHS context. Discounting was not applied but given only 18 months cost analysis this is not considered likely to impact results greatly. QALYs were not used as the health outcome measure. EQ-5D 5L, UK tariff, was collected and analysed in trial but numerical results not reported; authors report no difference was found*

(e) *Within-trial analysis of the LAST RCT included in the clinical review and so by definition only reflects one of a number of studies identified in the clinical review relating to intensity of rehabilitation. No sensitivity analyses are reported.*

(f) *2014 Norwegian Kroner converted to UK pounds (£). Cost components incorporated included general practitioner (GP) services, physiotherapy services (private and public), primary care services (mainly home health care and rehabilitation/ nursing homes) and hospital care. Indirect costs as e.g. travel expenses were not included. Resource use estimates were taken from the Norwegian health economics administration (HELFO), participating municipalities of Trondheim and the Norwegian patient registry.*

(g) *EQ-5D-5L results were not presented numerically but authors reported that there was no differences between the groups.*

(h) *Within-trial analysis based on RATULS RCT and so only reflects this study and not the wider evidence base identified in the clinical review.*

(i) 2018 UK pounds. Cost components incorporated: intervention costs, follow-up costs, primary care, therapy and community-based, services, secondary care, residential and nursing home care, social services, medication costs. Unit costs were taken from 2017/18 NHS reference costs and 2017 PSSRU unit costs (which were inflated to 2018 prices using the Bank of England inflator [2].
(j) An original economic model was developed as part of this guideline update. For details, see Evidence review E – Intensity of rehabilitation F model write-up.
(k) Only 12 of 32 studies included in the clinical review reported the same intensity of physiotherapy that could be used in the cost effectiveness analysis, with only 8 studies reporting the same for levels of higher and lower intensity. Evidence of treatment effect was informed using trials that were heterogeneous in nature. Lack of evidence created uncertainty towards duration of treatment effect, carer-specific treatment effects and downstream cost-savings.
(l) 2021 UK pounds (£). Cost components incorporated included: Staff time for physiotherapy and rehabiliation assistant (hospital and community-based) was applied to all scenarios while ongoing care cost-savings were applied to scenarios 1b and 2b.

Table 3: Health economic evidence profile: more intensive versus less intensive rehabilitation - psychology/neuropsychology (with communication difficulties)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Humphreys 2015[12] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Within-trial analysis of Thomas 2013 RCT[27] • Cost-effectiveness analysis (SADQH21 score) • Population: post-stroke adults with aphasia, living in the community identified as having low mood • Comparators: 1. Usual care 2. Usual care + behavioural therapy (up to 20 treatment sessions over three months, with sessions lasting approximately one hour delivered by an assistant psychologist; mean 9.3 sessions) • Time horizon: 6 months	£1833[(c)]	7.3 reduction in SADQH21[(d)]	£263 per point reduction in the SADQH21[(e)]	Bootstrapping undertaken to estimate uncertainty in ICER.

Abbreviations: ICER= incremental cost-effectiveness ratio; SADQH21 = Stroke Aphasic Depression Questionnaire Hospital version 21 (scale 0-30, lower values are better); QALY=quality-adjusted life year.
(a) 2011 resource use and unit costs may not reflect current UK NHS context. QALYs not used as health outcome.
(b) Within-trial analysis of Thomas 2013 RCT and so only reflects this study and not the wider evidence base identified in the clinical review. Analysis of cost compare resource use collected at 6 months to that at 3 months; unclear if this is appropriate and justification not discussed. Health outcomes may not be fully captured by only considering impact on SADQH21. Limited sensitivity analysis.

(c) 2011 UK pounds. Cost components incorporated: Intervention costs (behavioural therapy delivered by assistant psychologist with supervision from a clinical psychologist) and visits to or from SLT, occupational therapist, physiotherapist, GP, mental health nurse, practice nurse and home help contacts. Antidepressant medication costs were not included. Resource use was measured using a self-reported questionnaire with simplified response categories (never, sometimes, often) to facilitate completion by participants with aphasia.
(d) As reported in economic analysis paper. Clinical review for guideline reports mean difference of 3.1.
(e) As reported in economic analysis paper. Reason for minor discrepancies with incremental costs and health outcomes unclear; may be due to rounding.

Table 4: Health economic evidence profile: more intensive versus less intensive rehabilitation – occupational therapy (without communication difficulties)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Pila 2022[22] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Within-trial analysis of a retrospective study (n=36) - same paper) with no modelled extrapolation. • Comparative cost analysis (No health outcomes) • Population: Adults diagnosed with stroke in the subacute phase (3 weeks to 5 months) pre- and post-rehabilitation program Fugl-Meyer Assessment (FMA) scale ratings. • Comparators: 1. Lower dose group (n=22) received a mean (SD) number of 29 (3) sessions of OT and 26 (2) sessions of RT, lasting 30 minutes each over a 17-week period. 2. Higher dose group (n=14) received a mean (SD) number of 31 (2) sessions of both OT and RT, with both sessions lasting 35 minutes each over a 17-week period. • Follow-up: Up to 17 weeks	£796 [(c)]	NA[(d)]	NA The total cost of the combined program was higher for the higher dose group ($p = 6.10E^{-25}$).	NR

Abbreviations: FMA= Fugl-Meyer Assessment (scale 0-66, higher scores are better); NA= not applicable; NR= not reported; OT= occupational therapy; QALYs= quality-adjusted life years; RT= robot-assisted therapy; RCT= randomised controlled trial.

(a) QALYs (and cost per QALY) were not calculated. French healthcare perspective including 2009-2019 resource use estimates may not reflect current UK NHS context.
(b) Baseline outcomes and intervention effects for the higher dose group were based on single non-randomised retrospective study excluded from clinical review. Estimates of resource use were based on data from the study population and not a systematic review. Follow-up period was vaguely reported and may not sufficiently assess the full costs and benefits. Only intervention-related healthcare costs and resource use were incorporated into the analysis; no downstream resource use included. References for unit costs (including cost year) were not reported. References for unit costs (including cost year) were not reported. No probabilistic sensitivity analyses were performed.
(c) 2019 Euros (€) converted to UK pounds (£)[20] References for unit costs were not reported but 2019 was assumed based on year prior to the date study was submitted (03/09/2021). Cost components incorporated: Hourly staff cost of an occupational therapist and the hourly cost of Robot-assisted therapy (including daily working hours, effective working days per year and operating costs for the Robot).
(d) Mean increase in FMA score was 16 ± 13% for the higher dose group and 11 ± 8% for the lower dose group with no between group difference in change (p = 0.28).

1.1.6 Economic model

An original economic model was developed because the published health economic evidence is limited and there is potential for a significant resource impact. For details, see Evidence review E – Intensity of rehabilitation F model write-up.

1.1.7 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 5: Unit costs: rehabilitation professionals

Resource	Cost per working hour[(a)]		Source
	Hospital	Community	
Band 6/7 PT, OT, SLT or dietitian	£53/£64	£55/£67	PSSRU 2021[13]
Band 6/7 Nurse	£54/£64	£58/£69	
Band 7 psychologist	£64	£67	PSSRU 2021[13], assumed to be the same as dietitian[(b)]
Band 3 Clinical support worker higher level (physiotherapy)	£33	£32	PSSRU 2021[13], estimated based on agenda for change band 3 salary[(c)]

Abbreviations: OT= occupational therapist; PT= physiotherapist; SLT= speech and language therapist
(a) Note: Costs per working hour include salary, salary oncosts, overheads (management and other non-care staff costs including administration and estates staff), capital overheads and qualification costs
(b) Same assumption was used in the NICE chronic pain guideline[17]
(c) Band 3 PT not in PSSRU 2021 so salary was assumed to equal Band 3 Mean annual basic pay per FTE for administration and estates staff, NHS England (PSSRU2021 p.149).

1.18 Evidence statements

Multidisciplinary rehabilitation

- One cost-effectiveness analysis found that high-frequency multidisciplinary rehabilitation would cost £638 per case of mRS>2 averted. This analysis was assessed as partially applicable with potentially serious limitations.
- One comparative cost analysis found that high-intensity multidisciplinary rehabilitation was not statistically more costly than normal-frequency rehabilitation (cost difference: £812 per patient (p=0.0653). This analysis was assessed as partially applicable with potentially serious limitations.

Physiotherapy

- One cost-utility analysis found more intensive physiotherapy (for both higher intensity and functional strength-training groups) dominated usual care (lower costs and higher quality of life). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found more intensive physiotherapy was not cost-effective compared to usual care (£74,100 per QALY gained), with only a 19% probability of being cost-effective at a £20,000 willingness-to-pay threshold. This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-consequences analysis found more intensive physiotherapy (i.e., individualised regular coaching) during rehabilitation incurred higher costs (£1,957 more patient) compared to usual care, with no significant difference in terms of health outcomes. This analysis was assessed as partially applicable with potentially serious limitations.
- An original cost-utility analysis found that higher intensity physiotherapy (1-2 hours vs <45minutes) was:

    - not cost effective (£49,000 per QALY gained) in Scenario 1a where there were no care cost-savings and the utility improvement diminished to zero over time.
    - dominant in Scenario 1b where there were care cost-savings and the utility improvement diminished to zero over time
    - cost effective (£9,700 per QALY gained) in Scenario 2a where there were no care cost-savings and the utility improvement is maintained
    - dominant in Scenario 2b where there were care cost-savings and the utility improvement is maintained.

  This analysis was assessed as directly applicable with potentially serious limitations.

Psychological therapy

- One cost-effectiveness analysis found that in people with communication difficulties, cognitive behavioural therapy during rehabilitation would cost £263 for a 1-point reduction in Stroke Aphasic Depression Questionnaire Hospital version 21 (SADQH21) compared to usual care. This analysis was assessed as partially applicable with potentially serious limitations.

Occupational therapy

- One comparative cost analysis found that the more intensive occupational therapy during stroke rehabilitation had higher total costs (£796 more per patient) compared to usual care, with no significant no significant difference in terms of health outcomes. This analysis was assessed as partially applicable with potentially serious limitations.

Included original economic analysis from the previous guideline (CG162) 2013:

- More intensive rehabilitation was found to be cost effective compared to less intensive rehabilitation, based on a modelled analysis using levels of intervention and outcomes from the Ryan et al. 2006 study (24 versus 18 rehabilitation sessions; EQ5D difference 0.14 at 3 months) and a range of long-term utility assumptions. However, these conclusions are limited by concerns regarding the applicability of the study reported by Ryan and colleagues to current UK practice. Exploratory threshold analyses found:
    - Under the most conservative long-term utility assumption (where the utility difference observed at the end of rehabilitation had disappeared over 3 months), more intensive rehabilitation would no longer be cost effective if the difference in rehabilitation cost was more than £685 (equivalent to a difference of about 17 sessions, of 45 minutes, with a rehabilitation professional).
    - Under the most favourable long-term utility assumption (where the difference observed at the end of rehabilitation was maintained indefinitely), more intensive rehabilitation remained cost effective until the difference in rehabilitation costs exceeded £13,433 (equivalent to a difference of over 300 sessions with a rehabilitation professional).
    - Assuming a difference of 60 sessions between more and less intensive rehabilitation: a utility difference of 0.14 would need to be maintained for 9 months for more intensive to be cost effective; a difference of 0.24 for 5 months; and a difference of 0.02 for 64 months (about 4 years).

1.1.9 References

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Appendices

Appendix A – Review protocols

See C1 for main review protocol defining population, intervention and comparators and stratification.

Review protocol for health economic literature review

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see Appendix B below. For questions being updated, the search will be run from 2014, which was the cut-off date for the searches conducted for NICE guideline CG186. Databases searched: • Centre for Reviews and Dissemination NHS Economic Evaluations Database (NHS EED) – all years (closed to new records April 2015) • Centre for Reviews and Dissemination Health Technology Assessment database – all years (closed to new records March 2018)

	• International HTA database (INAHTA) – all years Medline and Embase – from 2014 (due to NHS EED closure)
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2005 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)[18]. **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 in the excluded health economic studies appendix below. 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 2005 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 2005 will be rated as 'Not applicable'. • Studies published before 2005 (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 – Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Stroke Rehabilitation population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies. Additional searches were run in CINAHL and PsycInfo looking for health economic evidence.

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 08 January 2023 Quality of Life 1946 – 08 January 2023	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports,) English language
Embase (OVID)	Health Economics 1 January 2014 – 08 January 2023 Quality of Life 1974 – 08 January 2023	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 08 January 2023	English language
PsycINFO (OVID)	1 January 2014 – 08 January 2023	Health economics studies Exclusions (animal studies, letters, case reports) Human

Database	Dates searched	Search filters and limits applied
		English language
Current Nursing and Allied Health Literature - CINAHL (EBSCO)	1 January 2014 – 08 January 2023	Health economics studies Exclusions (Medline records, animal studies, letters, editorials, comments, theses) Human English language

1 **Medline (Ovid) search terms**

1.	exp Stroke/
2.	exp Cerebral Hemorrhage/
3.	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
4.	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident*)).ti,ab.
5.	"brain attack*".ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/17-23
25.	6 not 24
26.	Economics/
27.	Value of life/
28.	exp "Costs and Cost Analysis"/
29.	exp Economics, Hospital/

30.	exp Economics, Medical/
31.	Economics, Nursing/
32.	Economics, Pharmaceutical/
33.	exp "Fees and Charges"/
34.	exp Budgets/
35.	budget*.ti,ab.
36.	cost*.ti.
37.	(economic* or pharmaco?economic*).ti.
38.	(price* or pricing*).ti,ab.
39.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
40.	(financ* or fee or fees).ti,ab.
41.	(value adj2 (money or monetary)).ti,ab.
42.	or/26-41
43.	quality-adjusted life years/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/43-61
63.	25 and 42
64.	25 and 62
65.	limit 63 to English language
66.	limit 64 to English language

Embase (Ovid) search terms

1.	exp Cerebrovascular accident/
2.	exp Brain infarction/

3.	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
4.	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident*)).ti,ab.
5.	"brain attack*".ti,ab.
6.	Intracerebral hemorrhage/
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	"quality of life index"/
41.	short form 12/ or short form 20/ or short form 36/ or short form 8/
42.	sickness impact profile/
43.	(quality adj2 (wellbeing or well being)).ti,ab.

44.	sickness impact profile.ti,ab.
45.	disability adjusted life.ti,ab.
46.	(qal* or qtime* or qwb* or daly*).ti,ab.
47.	(euroqol* or eq5d* or eq 5*).ti,ab.
48.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
49.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
50.	(hui or hui1 or hui2 or hui3).ti,ab.
51.	(health* year* equivalent* or hye or hyes).ti,ab.
52.	discrete choice*.ti,ab.
53.	rosser.ti,ab.
54.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
55.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
56.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
57.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
58.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
59.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
60.	or/39-59
61.	limit 24 to English language
62.	38 and 61
63.	60 and 61

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Stroke EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Cerebral Hemorrhage EXPLODE ALL TREES
#3.	(stroke* or cva or poststroke* or apoplexy or "cerebrovascular accident")
#4.	(((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident*)))
#5.	("brain attack*")
#6.	#1 OR #2 OR #3 OR #4 OR #5

INAHTA search terms

1.	(brain attack*) OR (((cerebro* or brain or brainstem or cerebral*) and (infarct* or accident*))) OR ((stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident")) OR ("Cerebral Hemorrhage"[mhe]) OR ("Stroke"[mhe])

CINAHL search terms

1.	MH "Economics+"
2.	MH "Financial Management+"
3.	MH "Financial Support+"
4.	MH "Financing, Organized+"
5.	MH "Business+"
6.	S2 OR S3 or S4 OR S5
7.	S1 not S6
8.	MH "Health Resource Allocation"
9.	MH "Health Resource Utilization"
10.	S8 OR S9
11.	S7 OR S10

12.	(cost or costs or economic* or pharmacoeconomic* or price* or pricing*) OR AB (cost or costs or economic* or pharmacoeconomic* or price* or pricing*)
13.	S11 OR S12
14.	PT editorial
15.	PT letter
16.	PT commentary
17.	S14 or S15 or S16
18.	S13 NOT S17
19.	MH "Animal Studies"
20.	(ZT "doctoral dissertation") or (ZT "masters thesis")
21.	S18 NOT (S19 OR S20)
22.	PY 2014-
23.	S21 AND S22
24.	MW Stroke or MH Cerebral Hemorrhage
25.	stroke* or cva or poststroke* or apoplexy or "cerebrovascular accident"
26.	(cerebro* OR brain OR brainstem OR cerebral*) AND (infarct* OR accident*)
27.	"brain attack*"
28.	S24 OR S25 OR S26 OR S27
29.	S23 AND S28

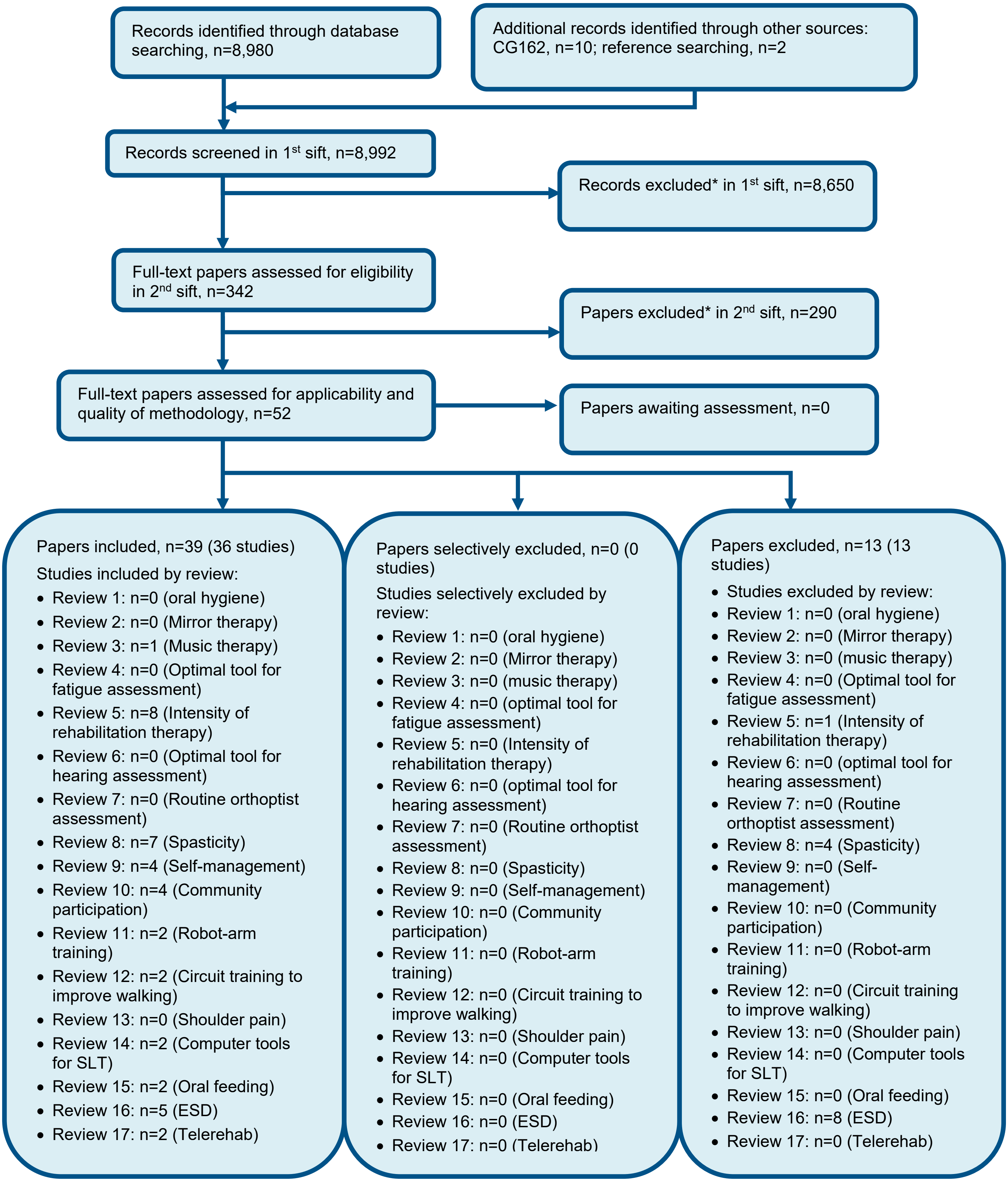
1 **PsycINFO search terms**

1.	exp Stroke/
2.	exp Cerebral hemorrhage/
3.	(stroke or strokes or cva or poststroke* or apoplexy or "cerebrovascular accident").ti,ab.
4.	((cerebro* or brain or brainstem or cerebral*) adj3 (infarct* or accident*)).ti,ab.
5.	"brain attack*".ti,ab.
6.	Cerebrovascular accidents/
7.	exp Brain damage/
8.	(brain adj2 injur*).ti.
9.	or/1-8
10.	Letter/
11.	Case report/
12.	exp Rodents/
13.	or/10-12
14.	9 not 13
15.	limit 14 to (human and english language)
16.	First posting.ps.
17.	15 and 16
18.	15 or 17
19	"costs and cost analysis"/
20.	"Cost Containment"/
21.	(economic adj2 evaluation$).ti,ab.
22.	(economic adj2 analy$).ti,ab.

23.	(economic adj2 (study or studies)).ti,ab.
24.	(cost adj2 evaluation$).ti,ab.
25.	(cost adj2 analy$).ti,ab.
26.	(cost adj2 (study or studies)).ti,ab.
27.	(cost adj2 effective$).ti,ab.
28.	(cost adj2 benefit$).ti,ab.
29.	(cost adj2 utili$).ti,ab.
30.	(cost adj2 minimi$).ti,ab.
31.	(cost adj2 consequence$).ti,ab.
32.	(cost adj2 comparison$).ti,ab.
33.	(cost adj2 identificat$).ti,ab.
34.	(pharmacoeconomic$ or pharmaco-economic$).ti,ab.
35.	or/19-34
36.	(0003-4819 or 0003-9926 or 0959-8146 or 0098-7484 or 0140-6736 or 0028-4793 or 1469-493X).is.
37.	35 not 36
38.	18 and 37

Appendix C – Economic evidence study selection

Figure 1: Flow chart of health economic study selection for the guideline



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

Appendix D – Economic evidence tables

Study	Chan 2015[7]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (CUA) (health outcome: QALYs) **Study design:** 2-state Markov model based on RCT included in the clinical review Cooke et al. 2010.[8] **Approach to analysis:** Markov model used hypothetical patient cohort where participants could only transition from alive to dead in terms of health states due to clinical literature showing that the functional improvements associated with higher-intensity PT were not linked to any downstream improvements.	**Population:** Adults who have had a recent stroke and need physiotherapy while receiving inpatient rehabilitation. **Cohort settings:** Start age: 73 years Male: 50% **Intervention 1:** Conventional physiotherapy (CPT) (RCT reported 9.2 hours over 6 weeks) **Intervention 2:** Higher-intensity physiotherapy (CPT + CPT) up to 1 extra hour of therapy, 4 days a week for 6 weeks. (mean 23hrs) **Intervention 3:** Functional strength training (FST) plus CPT up to 1 extra hour of	**DA Total costs (mean per patient):** **Intervention 1:** £12,439 **Intervention 2:** £10,973 **Intervention 3:** £10,963 **DA incremental (Intervention 2 versus 1):** -£1,466 **DA incremental (Intervention 3 versus 1):** -£1,476 **DA incremental (Intervention 3 versus 2):** -£10 **PA Incremental (Intervention 2 versus 1) (SD):** -£1,486 (£11,82)	**QALYs (mean per patient):** NR **Incremental (CPT + CPT versus CPT) (SD):** 0.05 (0.69) **Incremental (FST + CPT versus CPT) (SD):** 0.12 (0.68)	**ICER (Intervention 2 versus 1):** Dominates Intervention 1 (CPT) **ICER (Intervention 3 versus 1):** Dominates Intervention 1 (CPT) Probability Intervention 1 is cost effective (£20K threshold): ~50% or higher. **Analysis of uncertainty:** Several one-way sensitivity analyses were conducted which included changing the duration of effect, PT wage, Involvement of physiotherapy assistant, discount rate applied, utility values (18-week values instead of 6-week values) and Inpatient rehabilitation length of stay. The dominance of the two increased-intensity interventions remained for most one-way sensitivity analyses. One exception was when the 6-week utility values observed in the RCT were replaced with the 18-week follow-up values. In this scenario, higher intensity PT had lower costs, but also lower QALYs compared with conventional PT. The only other exception was when the inpatient rehabilitation length of stay was

Perspective: Canadian single-payer healthcare system **Time horizon:** Lifetime **Treatment effect duration:**[(a)] Assumed that the utility differences at 6 weeks would last for two years, with the difference in values gradually decreasing to 0 over this period. **Discounting:** 5% applied to costs and outcomes.	therapy, 4 days a week for 6 weeks. (mean 23.5 hours).	**PA Incremental (Intervention 3 versus 1) (SD):** -£1,338 (£11,980) **Currency & cost year:** 2013 Canadian dollars converted to UK pounds (£). **Cost components incorporated:** Physiotherapist wage and average bed day cost for inpatient rehabilitation.		set to 'no reduction', which produced ICERs of £8,135 for higher-intensity PT and £4,939 for FST plus conventional PT. Results of the cost-effectiveness acceptability curves that show both higher-intensity PT and the FST intervention as having a 50% or lower probability of being cost-effective, compared with conventional treatment, at all levels of willingness to pay.
Data sources				
Health outcomes: Primary clinical outcome (QALYs) was calculated using EQ-5D scores taken from Phase I RCT (n=109) included in the clinical review Cooke et al. 2010 [8]. The starting mean age of the hypothetical model cohort was taken from taken from Ontario stroke audit (2009)[11] and the model cohort gender split (50% female) was taken from Canadian Stroke Network (2011) [6]. Lifetime mortality was incorporated into the model using life tables from Statistics Canada (2013)[26] and standardized mortality ratios from Danish cohort study by Bronnum-Hansen (2001)[5]. **Quality-of-life weights:** EQ-5D measurement was taken at baseline, 6 weeks, and at follow-up (18 weeks from baseline). Expert opinion was used to estimate the duration of effect of higher-intensity PT, which was agreed to be incorporated as 2 years of higher utility values, with the difference in values gradually decreasing to 0 over this period. CUA only included scores collected at 6 weeks due to concerns that the 18-week utilities might not be representative, since a greater number of participants were lost to follow-up in the conventional PT arm. It was assumed that the differences at 6 weeks would be sustained at 1 year and then gradually decline. **Cost sources:** Total mean time spent by physiotherapists for each intervention was taken from Cooke et al. 2010 [8]. Expert opinion was also used to corroborate total number of hours for each intervention was similar to clinical practice in Ontario. Mean length of stay was taken from Ontario Stroke Evaluation Report (2013). Physiotherapist wage was taken from federal government's Workplace Partnerships Directorate (2013). Average cost per bed day was taken from Meyer and Colleagues report (2012) for the Ontario Stroke Network which was inflated to 2013 Canadian dollars from 2008 prices using the Consumer Price Index for medical and personal care as reported by Statistics Canada (2014). It was assumed that there were no downstream cost differences between intervention and comparator.				
Comments				

Source of funding: Health Quality Ontario **Limitations:** Canadian healthcare costs may not reflect UK NHS context. No long-term follow-up utility data despite lifetime horizon. Primary clinical outcome taken from a single RCT. The RCT lost a greater number of participants to follow-up in the CPT arm which could introduce bias. There is a high level of uncertainty in this analysis due to the uncertainty in model inputs, with some of the major inputs based on expert panel consensus or expert opinion. **Other:** Study also included a literature review which did not identify any published studies on the cost-effectiveness of increased PT intensity for stroke rehabilitation. No published studies observing additional cost impacts of higher-intensity PT beyond physiotherapist time, downstream cost impacts, and duration of PT effect were found by the authors.
Overall applicability:(b) Partially applicable **Overall quality:**(c) Potentially serious limitations

Abbreviations: SD = standard deviation; NR = not reported; QALY=quality-adjusted life year; EULT = Enhanced upper limb therapy; IQR = Interquartile range.

a) *For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.*
b) *Directly applicable / Partially applicable / Not applicable*
c) *Minor limitations / Potentially serious Limitations / Very serious limitations*

Study	**Dohl 2020**[9]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA **Study design:** Within-trial RCT analysis **Approach to analysis:** Health care costs were estimated for each person in the LAST study [1] based on individual information of health care use. Multivariate regression analysis was used to analyse cost differences between the groups and the relationship between individual costs and	**Population:** Adults, above 18 years old, living at home, with first-ever or recurrent stroke, no serious comorbidities and with modified Rankin Scale (mRS) less than five. **Cohort settings:** Start age: 72 Male: 61% **Intervention 1:** Standard care; Physiotherapy (</= 45 minutes, <5 days a week). Usually consisted of less than 1 h physiotherapy	**Total costs (mean per patient) (SD):** Intervention 1: £14,720 (£23,159) Intervention 2: £16,677 (£22,197) **Incremental (2-1):** £1,957 **Currency & cost year:** 2014 converted to UK pounds (£) **Cost components incorporated:**	From clinical review (2 vs 1) – Askim, 2018: [1] HrQoL (Stroke Impact Scale) at ≥6 months(b): -0.70 (95% CI: -7.98, 6.58) Activities of daily living (Barthel Index) at ≥6 months(b): 0.00 (95% CI: -0.47,0.47) Modified Rankin scale at at ≥6 months(b): -0.05 (95% CI: -0.37, 0.27) EQ-5D-5L results were not presented numerically but authors	**ICER (Intervention 2 versus Intervention 1):** n/a Probability Intervention 2 is cost effective (£20K threshold): n/a **Analysis of uncertainty:** None

determinants of health care utilisation. **Perspective:** Norwegian public health care system **Follow-up:** 18 months **Treatment effect duration:**[(a)] n/a **Discounting:** Costs: n/a Outcomes: n/a	per week, often limited to the first 3 months for patients with mild to moderate strokes but could last for up to 6 months for patients with the most severe strokes and for selected patients even longer. **Intervention 2:** Individualized regular coaching on physical activities and exercise (exercise for 45-60 minutes 2-3 times a week, physical activity for at least 30 minutes 7 days a week)	• General practitioner (GP) services, physiotherapy services (private and public), primary care services (mainly home health care and rehabilitation/ nursing homes) and hospital care. Indirect costs as e.g. travel expenses were not included.	reported that there was no differences between the groups.	

Data sources
Health outcomes: Within-RCT analysis (reported separately in Askim, 2018 study [1] included in clinical review). There were no differences reported between the groups on health-related quality of life (EQ-5D-5L), Barthel Index, modified Rankin Scale, or the Berg Balance Scale. **Cost sources:** Information about GP services and private physiotherapy services were taken from the Norwegian health economics administration (HELFO). Use of public physiotherapy services, home health care and rehabilitation/nursing homes were provided by the participating municipalities. Use of specialized health care (hospital inpatient, day-care and outpatient) was obtained from the Norwegian patient registry. Most of the home care services were measured in hours per week while institutional care was measured in number of days. Unit cost of GP's and private physiotherapy services was provided by HELFO, unit cost of primary and hospital care was based on cost information from the municipality of Trondheim and St. Olav hospital, respectively.
Comments
Source of funding: Norwegian Research Council, Liaison Committee between Central Norway Regional Health Authority and Norwegian University of Science and Technology (NTNU), Joint Research Committee between St. Olavs Hospital and NTNU and by grants from the Stroke Unit Research Fund. **Limitations:** Within-trial analysis of the LAST RCT included in the clinical review and so by definition only reflects one of a number of studies identified in the clinical review relating to intensity of rehabilitation. Discounting was not applied but given only 18 months cost analysis this is not considered likely to impact results greatly. QALYs were not used as the health outcome measure. EQ-5D 5L, UK tariff, was collected and analysed in trial but numerical results not reported; authors report no difference was found. No sensitivity analyses are reported. **Other:** EQ-5D-5L performed equally well in predicting

the individual use of resources as the more traditional battery of clinical outcome measures. This suggests the HrQoL measures may be a simple and efficient way of identifying patients in need of health care after stroke, as well as targeting groups for future interventions.	
Overall applicability:[(c)] Partially applicable	**Overall quality:**[(d)] Potentially serious limitations

Abbreviations: CCA = cost-consequence analysis; DA: Deterministic analysis; PA: Probabilistic analysis: CI = confidence interval; ICER = incremental cost-effectiveness ratio; NR = not reported; RCT = randomised clinical trial, HrQoL; Health-related Quality of life.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Mean difference taken from of forest plots in guideline clinical review

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious Limitations / Very serious limitations

Study	**Fernandez-Garcia 2021** [10]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (CUA) (health outcome: QALYs) **Study design:** Within-trial analysis (RCT- RATULS[23]) In a sensitivity analysis modelling was used to extrapolate results beyond trial follow-up. **Approach to analysis:** Analysis of individual level healthcare resource use EQ-5D to estimate costs and QALYs over 6 months follow-up. Units costs applied. Adjusted	**Population:** Adults with moderate or severe upper limb functional limitation (Action Research Arm Test [ARAT] score 0–39) as a result of first-ever stroke that had occurred between 1 week and 5 years before randomisation. The median time from stroke to randomisation was 240 days (IQR 109–549 days), and participants had a mean ARAT score of 8.4 points (SD 11.8 points). A total of 409 out of 768 (53.3%) participants were receiving physiotherapy and/or occupational therapy at the time of randomisation.	**Total costs (mean per patient):** Intervention 1: £3785 (98.33% CI £2801 - £4770) Intervention 2: £5387 (98.33% CI £4777 - £5996) Intervention 3: £4451 (98.33% CI £3548 - £5354) **Incremental:** **2-1 (unadjusted as adjusted not reported):** £1601 (95% CI £706 to £2496) **3-1(adjusted):** £741 (98.33 CI –£461 to £1943)	**QALYs (mean per patient):** Intervention 1: 0.21 (98.33% CI 0.19 – 0.23) Intervention 2: 0.21 (98.33% CI 0.19 – 0.23) Intervention 3: 0.23 (98.33% CI 0.21 – 0.24) **Incremental:** **2-1 (unadjusted as adjusted not reported):** 0.00 (95% CI -0.20 to 0.20) Note that cost effectiveness based on adjusted results concluded lower QALYs. **3−1 (adjusted):** 0.010 (98.33% CI -0.005–0.025)	**ICERs** Intervention 2 was dominated by intervention 3 due to higher costs and lower QALYs. Intervention 3 versus Intervention 1): £74,100 per QALY gained CI: NR Probability cost effective (£20K threshold): intervention 1 81%; intervention 2 0%; intervention 3 19%. **Analysis of uncertainty:** Scenario 1 examined the impact of assigning a value of zero to missing total healthcare costs, resulting in the ICER between EULT and usual care increasing to £172,000.

differences between groups were calculated using regression analysis incorporating randomised group, study centre, time since stroke, baseline utility (QALY analysis only) and baseline costs (cost analysis only) as explanatory variables. **Perspective:** UK NHS and PSS **Follow-up:** 6 months **Treatment effect duration:**[(a)] 6 months **Discounting:** NA	**Patient characteristics:** N = 770 Mean age = 61 years (SD 13.5 years) Male= 60.8% **Intervention 1:** Usual care (45 minutes with a physiotherapist or occupational therapist, 5 days a week) over 12 weeks. **Intervention 2:** Robot-assisted training (45 minutes per day, 3 times per week) plus usual care over 12 weeks. **Intervention 3:** Enhanced upper limb therapy (EULT) (45 minutes with a physiotherapist, 3 times per week) plus usual care over 12 weeks.	**Currency & cost year:** 2018 UK pounds (£) **Cost components incorporated:** intervention costs, follow-up costs, primary care, therapy and community-based, services, secondary care, residential and nursing home care, social services, medication costs.		Scenario 2 examined the possibility that those participants with missing total healthcare costs may have used some services and hence incurred some costs. This decreased the ICER between EULT and usual care to £50,000 with the probability of EULT being cost-effective at a £20,000 WTP threshold increasing to 27%. Scenario 3 increased the life span of the MIT-Manus robotic gym system from 5 to 7 years. This resulted in a reduction of the mean capital costs per patient and hence, in a lower mean total cost for the robot-assisted training group (£5085) compared with the base-case analysis (£5387). Robot-assisted training remained dominated by EULT and did not change the ICER from the base case results (£74,100). A secondary per-protocol within-trial cost-effectiveness analysis removed from the data set those participants who did not receive at least 20 sessions of therapy in the robot-assisted training and the EULT programme groups was also conducted. Usual care remained the least costly option, followed by EULT and robot-assisted training. The ICER between usual care and EULT was £68,000 and the probability of usual care being cost-effective at a £20,000 WTP threshold increased to 92%.

				Extrapolation of trial data on costs and effects to 12 months: The ICER for the comparison between EULT and usual care was £6,095, however there was only a 55% probability of EULT being considered cost-effective compared with usual care at the £20,000 WTP value. Robot-assisted training had no probability of being cost-effective at this WTP value.
Data sources				
Health outcomes: Within-trial analysis of RATULS trial[23] included in the clinical review. EQ-5D collected at baseline and at 3- and 6-months post-randomisation was used to calculate QALYs using the area under the curve method. **Quality-of-life weights:** Within-RCT analysis: EQ-5D-5L mapped to EQ-5D-3L, UK population valuation tariff. **Cost sources:** Resource use from within RCT at baseline and 6 months post-randomisation. UK national unit costs applied.				
Comments				
Source of funding: National Institute for Health Research Health Technology Assessment Programme. **Limitations:** Within-trial analysis based on RATULS RCT and so only reflects this study and not the wider evidence base identified in the clinical review. **Other:**				
Overall applicability:[(b)] Directly applicable **Overall quality:**[(c)] Minor limitations				

Abbreviations: ARAT = Action Research Arm Test (scale 0-39, higher values are better); SD = standard deviation; NR = not reported; QALY=quality-adjusted life year; EULT = Enhanced upper limb therapy; IQR = Interquartile range.

a) *For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.*
b) *Directly applicable / Partially applicable / Not applicable*
c) *Minor limitations / Potentially serious Limitations / Very serious limitations*

Study	**Humphreys 2014[12] (UK)**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost effectiveness analysis (health outcome: SADQH21)	**Population:** Adults post-stroke with aphasia, living in the community identified as having low mood on either	**Change in total costs over 3 months (mean per patient) plus intervention costs:** Intervention 1: -£11.59	6-month SADQH21 score, change from baseline: Intervention 1: 0.7 Intervention 2: -6.0	ICER (Intervention 2 versus Intervention 1): £263 per point reduction on the SADQH21 (as reported in paper)

Study design: Within-trial analysis of CALM RCT (Thomas 2013)[27]. **Approach to analysis:** Cost analysis was a short-term, within-trial analysis that assessed the costs of behavioural therapy for stroke patients with aphasia and the subsequent impact on resource utilisation compared to those receiving usual care at three and six months from baseline. Note that further analysis was undertaken to extrapolate costs to 24 months but are not reported here as methods are unclear. **Perspective:** UK NHS **Follow-up:** 6 months **Treatment effect duration:**[(a)] 6 months **Discounting:** NA	the Visual Analog Mood Scale sad item (>50) or Stroke Aphasic Depression Questionnaire Hospital version 21 (SADQH21) (>6) **Patient characteristics:** Start age: 67 years Male: 63% **Intervention 1:** Usual care **Intervention 2:** Behavioural therapy (up to 20 treatment sessions over three months, with sessions lasting approximately one hour delivered by an assistant psychologist).	Intervention 2: £1,821.52 Incremental (2-1): £1,833.1 (95% CI £1,474.5 to £2,191.7) **Currency & cost year:** 2011 UK pounds **Cost components incorporated:** Intervention costs (behavioural therapy delivered by assistant psychologist with supervision from a clinical psychologist) and visits to or from occupational therapist, physiotherapist, GP, mental health nurse, practice nurse and home help contacts. Antidepressant medication costs were not included.	Incremental (2-1): -7.3 (95% CI 2.45 to 11.61) As reported in economic analysis paper. Clinical review for guideline reports mean difference of 3.1.	**Analysis of uncertainty** 1000 nonparametric bootstrap replications were generated from the sets of multiply imputed data, and mean cost and effect were plotted in a cost effectiveness plane.
Data sources				
Health outcomes: Within-trial analysis of the primary outcome was the Stroke Aphasic Depression Questionnaire 21-item hospital version (SADQH-21), taken from RCT data reported in Thomas, 2013[27] (CALM trial, n=105). **Cost sources:** Within-trial analysis of resource use measured using a self-reported questionnaire with simplified response categories (never, sometimes, often) to facilitate completion by participants with aphasia collected 2011. Standard national unit costs applied. See Table 6 below for details.				
Comments				

Source of funding: The Stroke Association, UK **Limitations:** Within-trial analysis of Thomas 2013 RCT and so only reflects this study and not the wider evidence base identified in the clinical review. Analysis of cost compare resource use collected at 6 months to that at 3 months; unclear if this is appropriate and justification not discussed. Health outcomes may not be fully captured by only considering impact on SADQH21. Limited sensitivity analysis. **Other:** None.
Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Potentially serious limitations

Abbreviations: ICER= incremental cost-effectiveness ratio; SADQH21 = Stroke Aphasic Depression Questionnaire Hospital version 21 (scale 0-30, lower values are better).

a) *For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.*
b) *See table 6 for cost breakdown of differences at baseline and 3-months*
c) *Directly applicable / Partially applicable / Not applicable*
d) *Minor limitations / Potentially serious Limitations / Very serious limitations*

Table 6: Differences over 3 months (including Intervention costs) from Humphreys 2014[12]

	Usual care			Cognitive behavioural therapy				
	N	**Mean**	**St.dev**	**N**	**Mean**	**St.dev**	**Difference**	**P-value**
Mean per patient costs for baseline								
GP cost baseline	50	£90.72	£49.88	41	£76.21	£55.35	14.5 (−7.4 to 36.4)	0.192
SLT cost baseline	50	£121.92	£142.76	41	£149.85	£154.12	−27.9 (−89.8 to 34.0)	0.373
OT cost baseline	50	£79.70	£174.09	41	£118.09	£202.66	−38.4 (−116.9 to 40.1)	0.334
PT cost baseline	50	£231.06	£360.61	41	£260.72	£357.09	−29.7 (−179.9 to 120.6)	0.696
MHN cost baseline	50	£23.56	£71.40	41	£21.87	£82.54	1.7 (−30.4 to 33.8)	0.917
Nurse cost baseline	50	£62.22	£81.06	41	£81.35	£85.81	−19.1 (−53.9 to 15.7)	0.278
Home help cost baseline	50	£307.20	£600.93	41	£524.49	£717.15	−217.3 (−491.8 to 57.2)	0.119
Total cost baseline	50	£916.38	£898.86	41	£1,232.59	£1,009.89	−316.2 (−714.1 to 81.7)	0.118

	Usual care			Cognitive behavioural therapy				
	N	**Mean**	**St.dev**	**N**	**Mean**	**St.dev**	**Difference**	**P-value**
Mean per patient 3 months								
GP cost 3 months	50	£92.74	£51.28	41	£89.74	£55.80	2.9 (−19.3 to 25.3)	0.790
SLT cost 3 months	50	£88.74	£131.41	41	£125.80	£153.81	−37.1 (−96.5 to 22.4)	0.218
OT cost 3 months	50	£85.27	£175.95	41	£82.60	£158.93	2.7 (−67.9 to 73.2)	0.940
PT cost 3 months	50	£168.98	£321.50	41	£206.57	£330.55	−37.6 (−173.9 to 98.7)	0.585
MHN cost 3 months	50	£14.14	£56.52	41	£38.00	£108.35	−23.9 (−58.9 to 11.2)	0.180
Nurse cost 3 months	50	£86.29	£86.26	41	£82.35	£82.56	3.9 (−31.5 to 39.4)	0.825
Home help cost 3 months	50	£368.64	£644.24	41	£468.29	£684.30	−99.7 (−377.0 to 177.7)	0.477
Total cost 3 months	50	£904.80	£901.04	41	£1,093.34	£865.04	−188.5 (−559.1 to 181.9)	0.315
Overall costs (Baseline + 3 months)	50	£1,821.18	£1,613.17	41	£2,325.93	£1,700.48	−504.7 (−1196.7 to 187.1)	0.151
Difference in costs over 3 months	50	–£11.59	£798.31	41	–£139.24	£802.93	127.6 (−207.4 to 462.7)	0.451
Difference in costs over 3 months + intervention costs	50	–£11.59	£798.31	41	£1,821.51	£923.21	−1833.1 (−2191.7 to −1474.5)	**0.000**

Abbreviations: GP = General practitioner; SLT=speech and language therapy; OT = occupational therapy; PT = physiotherapy; MHN = mental health nurse.

Study	Nagayama 2021[15]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Comparative-cost analysis (no health outcomes) **Study design:** Within-trial analysis of a natural experiment study (same study) with no modelled extrapolation. **Approach to analysis:** Natural experimental design provided initial insights into the association between rehabilitation intensity and medical costs during the year after discharge from a convalescent rehabilitation unit. Low-intensity was defined as hospitalisation to a convalescent rehabilitation unit before March 2011, to reflect a new policy which incentivised health care practitioners to provide more intensive rehabilitation (>120 minutes daily) for inpatients. Unit costs applied. **Perspective:** Japanese healthcare system	**Population:** Adults who were hospitalised with acute stroke in a convalescent rehabilitation unit for more than 1 month, who returned home post-discharge. **Patient characteristics:** N=405 Mean age: 52 years Male: 69% **Intervention 1:** Low-Intensity rehabilitation (n=36). Mean (SD) therapy time was 89.7 (39.7) minutes per day. Mean (SD) length of hospital stay was 93.5 (39.9) days. **Intervention 2:** High-intensity rehabilitation (n=369). Mean (SD) therapy time was 135.3 (30.9) minutes per day. Mean (SD) length of hospital stay was 96.3 (47.4) days.	**Total costs (mean (SD) per patient)[(b)]:** Intervention 1: £5,521 (£8,882) Intervention 2: £6,333 (£9,148) Incremental (2−1): £812 (95% CI: -£3,736 - £2,345 p=0.653) **Currency & cost year:** 2020 Japanese Yen (¥) converted to UK pounds (£)[(c)] **Cost components incorporated:** Medical costs including length total rehabilitation time, clinic visits and length of hospital stay.	NA	**ICER (Intervention 2 versus Intervention 1):** NA Probability Intervention 2 cost effective (£20K/30K threshold): NR/NR **Analysis of uncertainty:** NA

Follow-up: 1-year post-discharge from hospital **Treatment effect duration:**[(a)] NA **Discounting:** NA				
Data sources				
Health outcomes: NA. Natural experiment study was excluded from the clinical review as outcomes reported were not included in the review protocol. **Quality-of-life weights:** None. **Cost sources:** References for unit costs were not reported, however healthcare resource use data on individuals diagnosed with a cerebrovascular disorder were retrospectively extracted data from a Japanese insurance claims database (JMDC Inc, Tokyo, Japan) from January 2005 to December 2017. The database contains information on administrative claims data for clinic visits and hospital admissions.				
Comments				
Source of funding: JSPS KAKENHI (Grant number: JP18K17324, JP20H03914) from the Japan Society for the Promotion of Science. **Limitations:** QALYs (and cost per QALY gained) were not presented. Japanese healthcare perspective and 2005-2017 resource use estimates may not reflect current UK context. Within-trial analysis based on a retrospective natural experiment study not the wider evidence based identified in the clinical review. References for unit costs were not reported which limits interpretation of results for UK context. No probabilistic sensitivity analyses were performed. **Other:** Readmissions were not included as an outcome in the clinical review, however, this study reported that no significant difference was reported for the 1-year readmission ratio (hazard ratio: 1.09, 95% CI: 0.55-2.18: p=804)				
Overall applicability:[(d)] Partially applicable **Overall quality:**[(e)] Potentially serious limitations				

Abbreviations: 95% CI= 95% confidence interval; ICER= incremental cost-effectiveness ratio; NA= not applicable; NR= not reported; QALYs= quality-adjusted life years; RCT= randomised controlled trial.

a) *For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.*
b) *No significant differences in the medical costs reported between groups during the year after discharge (p=0.653)*
c) *Converted using 2020 purchasing power parities[20]}. 2020 unit costs were assumed based on costs reported in Japanese Yen that were converted to US dollars ($) using average currency conversion rates in March 2020.*
d) *Directly applicable / Partially applicable / Not applicable*
e) *Minor limitations / Potentially serious limitations / Very serious limitations*

Study	**National Institute for Health and Care Excellence, P.159, 2013[16]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**

Economic analysis: Cost-utility analysis (CUA) (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Simple life table-based model with utility values attributed that depended on the type of rehabilitation received ('more intensive' or 'less intensive). Based on data from the stroke subgroup of the Ryan 2006 RCT [24] including difference in utility ay 12 weeks. **Perspective:** UK NHS and PSS **Time horizon/Follow-up:** lifetime **Treatment effect duration:**[(a)] different treatment effect duration scenarios were modelled including a lifetime effect and effect disappearing over time (over 3 months, 1 year and 5 years).	**Population:** Adults and young people (16+) who have had a stroke and need rehabilitation. **Cohort settings:** Start age: 77 years Male: 39% **Intervention 1:** Less intensive multidisciplinary rehabilitation (three or less face-to-face contacts per week, for 12 weeks maximum) **Intervention 2:** More intensive multidisciplinary rehabilitation (six or more face-to-face contacts per week, for 12 weeks maximum)	**Total costs (mean per patient):** Scenario 1: utility difference maintained over lifetime: Intervention 1: NR Intervention 2: NR Incremental (2−1): £226 (95% CI: NR; p=NR) Scenario 2: utility difference disappears over time: • Over 3 months: Intervention 1: NR Intervention 2: NR Incremental (2−1): £228 (95% CI: NR; p=NR) • Over 1 year: Intervention 1: NR Intervention 2: NR Incremental (2−1): £228 (95% CI: NR; p=NR) • Over 5 years: Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.29 (95% CI: NR; p=NR) **Currency & cost year:** 2010 UK pounds (£)	**QALYs (mean per patient):** Scenario 1: Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.70 (95% CI: NR; p=NR) Scenario 2: • Over 3 months: Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.03 (95% CI: NR; p=NR) • Over 1 year: Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.08 (95% CI: NR; p=NR) • Over 5 years: Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.29 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Scenario 1: £324 per QALY gained (pa) 95% CI: NR Probability Intervention 2 is cost effective (£20K threshold): 99% Scenario 2: • Over 3 months: £6,722 per QALY gained (pa) 95% CI: NR Probability Intervention 2 is cost effective (£20K threshold): 95% • Over 1 year: £2,751 per QALY gained (pa) 95% CI: NR Probability Intervention 2 is cost effective (£20K threshold): 99% • Over 5 years: £776 per QALY gained (pa) 95% CI: NR Probability Intervention 2 is cost effective (£20K threshold): 100% **Analysis of uncertainty:** Sensitivity analysis on the length of rehabilitation sessions (30-60 minutes) did not impact the conclusions (e.g. the ICERs for scenario 1 were £216 and £455 for a 30-minute and 60-minute session, respectively).

Discounting: Costs: 3.5% Outcomes: 3.5%		**Cost components incorporated:** Rehabilitation costs, which consisted of total number/length of rehabilitation sessions and cost per hour home visit for both a rehabilitation professional and rehabilitation assistant.		Sensitivity analysis on the initial cohort age (where the model was ran using 40,50,60,70,80 and 90-year olds as the initial age) also did not change the conclusions of the analysis. Threshold analyses: • Costs: Assuming a scenario where the utility difference observed at the end of rehabilitation had disappeared over 3 months, more intensive rehabilitation would no longer be cost effective if the difference in rehabilitation cost was more than £685. When assuming that the utility difference observed at the end of rehabilitation was maintained indefinitely, more intensive rehabilitation remained cost effective until the difference in rehabilitation costs exceeded £13,433. • QALYs: threshold analysis where the difference in the number of rehabilitation sessions between the groups (difference of 6.5 to 60) was varied showed that the lifetime QALY gain required for more intensive rehabilitation to be cost effective ranged from 0.01-0.11 when the difference in number of rehabilitation sessions was varied between 6.5 and 60. It was also calculated that with a difference of 60 rehabilitation sessions with more intensive

				compared to less intensive rehabilitation, a utility gain of 0.14 would need to be maintained for 9 months in order for more intensive rehabilitation to be cost effective. • Changing the discount rate from 3.5% to 1.5% did not impact the conclusions of the analysis (ICER of £310 for scenario 1). Making the costs probabilistic did also not change any results.

Data sources
Health outcomes: The cost-effectiveness model was developed using outcomes from the RCT by Ryan (2006)[24] therefore, the initial cohort settings were based on the mean baseline characteristics from this study (N=89). Mortality was incorporated into the model using lifetables for England and Wales [19] adjusted to reflect the increased mortality rates in people who have had a stroke. Standardized mortality ratios (SMR) for all-cause mortality after stroke compared with age/sex adjusted rates for the general population reported by Bronnum-Hansen et al. (2001) [5] were used. **Quality-of-life weights:** Utility values were taken from Ryan (2006)[24] who reported EQ-5D scores for people undergoing more intensive (n=34) and less intensive (n=32) rehabilitation, using the UK tariff. Given that EQ-5D scores were only collected for a 12-week follow-up period, a series of different assumptions regarding were developed to see what happens to the difference in utility between groups observed at 12 weeks over time. Scenario 1 assumed that the difference remains the same over the remaining lifetime of the patient, while scenario 2 assumed the difference disappears over time (either over three months, one year or five years). **Cost sources:** The cost of the less and more intensive rehabilitation programmes was calculated based on the resource use from the Ryan study supplemented by assumptions where required and relevant UK unit costs. In the base-case analysis it was assumed that there was no difference in costs post-rehabilitation as data was not identified on which to base a difference. The cost per hour of home visiting takes account of the proportion of time spent on travel and non-contact time. Information was provided by AW Ryan (email January 2011) regarding the duration of rehabilitation sessions in the study (between 30 and 60 minutes) and the professionals who delivered the work (physiotherapist, occupational therapist, speech and language therapist, and rehabilitation assistant). Data was not available about the average length of sessions from the study. It was therefore assumed that typically the length of a session would be 45 minutes (midpoint of the range) and that the length of sessions did not vary between groups. Information was not available about the proportions of sessions carried out by different professionals, and so it was assumed that 75% were carried out by rehabilitation professionals and 25% by rehabilitation assistants.
Comments
Source of funding: National Institute of Health and Care Excellence (NICE)**. Limitations:** Economic model is based on a single study that compares two intensities of rehabilitation that are well below the current standard of care. The Ryan study has been excluded from the clinical review due to lack of information about the delivery of the rehabilitation that meant it couldn't be fitted into the stratifications of the protocol. Base case analysis assumed no difference in post-rehabilitation costs; however, greater functional ability could plausibly result in lower dependency and potentially lower social care costs. This would further favour more intensive rehabilitation. Several different assumptions were made to reflect different scenarios regarding the utility affect

over time due to limited time frame in which quality of life was collected (12 weeks). **Other:** Cost-utility analysis was developed as part of the previous review of this guideline (GC162).[16]	
Overall applicability:[(b)] Partially applicable	**Overall quality:**[(c)] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; QALYs= quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

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

Study	**National Institute for Health and Care Excellence[(a)] 2023 (UK)**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (CUA) (health outcome: QALYs). **Study design:** Probabilistic decision analytic model based on 8 RCTs from the clinical review. **Approach to analysis:** Lifetable analysis, where mean survival is the same for both comparators. Utility (EQ-5D-3L) increases in each arm linearly over the 6-week course of the rehabilitation. Due to a lack of evidence towards the duration of effect and long-term cost	**Population:** Adults who have had a stroke and require physiotherapy as part of their rehabilitation and who can tolerate more than 45 minutes of therapy in a day. **Cohort settings:** Start age: 75 years for females and 71 years for males. Male: 52% **Intervention 1:** Less intensive physiotherapy: >45 mins – 1 hour physiotherapy, 5 days a week	**Total costs (mean per patient):** Scenario 1a (intervention costs only): Intervention 1: £0 Intervention 2: £2,279 Incremental (2−1): £2,279 (95% CI: £1,783 to £2,851); p=NR) Scenario 1b (post-rehab care savings): Intervention 1: £0 Intervention 2: -£3,312 Incremental (2−1): Saves £3,312 (95% CI: -£25,011 to £1,725; p=NR) Scenario 2a (intervention costs only):	**QALYs (mean per patient):** Scenario 1: Intervention 1: 3.01 Intervention 2: 3.05 Incremental (2−1): 0.05 (95% CI: 0.01 to 0.22; p=NR) Scenario 2: Intervention 1: 2.83 Intervention 2: 3.06 Incremental (2−1): 0.24 (95% CI: 0.02 to 0.44; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Scenario 1a (intervention costs only): £48,539 per QALY gained (pa) 95% CI: NR Probability Intervention 2 is cost effective (£20K threshold): 7% Scenario 1b (post-rehab care savings): Higher dominant (lower costs and higher QALYs) 95% CI: NR Probability Intervention 2 is cost effective (£20K threshold): 76% Scenario 2a (intervention costs only): £9,676 per QALY gained (pa) 95% CI: NR Probability Intervention 2 is cost effective (£20K threshold): 83%

savings, 4 alternative base case scenarios were applied. **Perspective:** UK NHS and PSS **Time horizon/Follow-up:** lifetime **Treatment effect duration:**[(b)] Scenario 1: weekly reduction of EQ-5D mean difference until no difference between was seen between higher and lower intensity groups, meaning higher intensity leads to faster stroke recovery. Scenario 2: 3-month weekly reduction applied before the difference was maintained, meaning higher intensity leads to permanent health gains. **Discounting:** Costs: 3.5% Outcomes: 3.5%	**Intervention 2:** More intensive physiotherapy: 1 to 2 hours of physiotherapy, 5 days a week	Intervention 1: £0 Intervention 2: |£2,286 Incremental (2−1): £2,286 (95% CI: £1,786 to £2,862); p=NR) Scenario 2b (post-rehab care savings): Intervention 1: £0 Intervention 2: -£29,487 Incremental (2−1): Saves £29,487 (95% CI: -£86,993 to £1,036; p=NR) **Currency & cost year:** 2021 UK pounds (£) **Cost components incorporated:** Scenarios 1a to 2b all included staff time for physiotherapy and rehabiliation assistant (hospital and community-based), while post-rehabilitation ongoing care cost-savings were applied to scenarios 1b and 2b.		Scenario 2b (post-rehab care savings): Higher dominant 95% CI: NR Probability Intervention 2 is cost effective (£20K threshold): 96% **Sensitivity analyses where results changed significantly:** Scenario 1a: Higher intensity physiotherapy was not cost effective in any sensitivity analysis. Scenario 1b: • an 18-week time horizon, (£73,059 per QALY gained), • alternative data for post-rehabilitation care cost savings - higher intensity had a 43% probability of being <£20,000 per QALY gained but mean of £233 per QALY gained. Scenario 2a: •the 18-week time horizon (£181,443 per QALY gained), •2-year time horizon (£36,382 per QALY gained), •an initial cohort age of 90 years (£38,472 per QALY gained). Scenario 2b: •an 18-week time horizon, (£88,543 per QALY gained).
Data sources				

Health outcomes: The cost-effectiveness model was developed using outcomes reported in 8 RCTs included as part of the clinical review for this guideline question. Outcomes were either Barthel Index or EQ-5D-5L and were mapped to EQ-5D-3L using algorithms reported in a published mapping database (Dakin 2020{, #4444}), therefore, the initial cohort settings were based on the mean baseline characteristics from these studies. Mortality was incorporated into the model using lifetables for England and Wales{, #4430} adjusted to reflect the increased mortality rates in people who have had a stroke. Standardized mortality ratios (SMR) for all-cause mortality after stroke compared with age/sex adjusted rates for the general population reported by Bronnum-Hansen et al. (2001)[5] were used. **Quality-of-life weights:** EQ-5D-3L (UK tariff). The change per week in the mean difference in EQ-5D was applied in the model for at least 12 weeks after the end of rehabilitation, based on an included RCT (Rodgers 2019[23]) as this was the only appropriate study that reported a follow-up period longer than the intervention duration. Beyond this, an extrapolation assumption was applied as either Scenario 1, where the change per week in mean difference in EQ-5D continued to be applied until there was no difference between higher and lower intensity. This assumption equates to higher intensity speeding up rehabilitation but not resulting in lasting differences between the groups; or as Scenario 2, where the difference in EQ-5D between higher and lower intensity that remains after 12 weeks is maintained for the remaining lifetime. This assumption results in lasting differences between those that receive higher intensity and lower intensity physiotherapy. **Cost sources:** National unit costs applied for staff time. Post-rehabilitation care cost-savings were taken from O'Connor 2011.{, #4646}
Comments
Source of funding: National Institute of Health and Care Excellence (NICE)**. Limitations:** Only 12 of 32 studies included in the clinical review reported the same intensity of physiotherapy that could be used in the cost effectiveness analysis, with only 8 studies reporting the same for levels of higher and lower intensity. Evidence of treatment effect was informed using trials that were heterogeneous in nature. Lack of evidence created uncertainty towards duration of treatment effect, carer-specific treatment effects and downstream cost-savings. **Other:** Cost-utility analysis was developed using an updated version of the previous economic model conducted for this guideline review (GC162).[16]
Overall applicability:[(c)] Directly applicable **Overall quality:**[(d)] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; EQ-5D-3(5)L= Euroqol 5 dimensions with three (five) levels (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; QALYs= quality-adjusted life years
(a) An original economic model was developed for this guideline update. For details, see Evidence review E – Intensity of rehabilitation F model write-up.
(b) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.
(c) Directly applicable / Partially applicable / Not applicable
(d) Minor limitations / Potentially serious Limitations / Very serious limitations

Study	**Oyanagi 2021[21]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**

Economic analysis: Cost-effectiveness analysis (health outcome: mRS) **Study design:** Within-trial analysis of a retrospective study (same paper) with no modelled extrapolation. **Approach to analysis:** Analysis of individual level healthcare resource use to estimate costs associated with high versus normal frequencies of inpatient rehabilitation. Multivariate regression analyses were then used to examine the effects of high-frequency rehabilitation on discharge outcomes alongside selected confounding factors (e.g., age, gender, previous history of stroke). **Perspective:** Japanese healthcare system. **Follow-up:** End of hospitalisation	**Population:** Adults (≥18 years old) diagnosed with stroke in the acute phase (72 hours – 7 days) receiving inpatient rehabilitation. **Patient characteristics:** N=1,759 Mean age: 72 years Male: 60% **Intervention 1:** Normal-frequency intervention (n=654). Mean (SD) rehabilitation time was 43.6 (12.6) minutes per day delivered over a length hospital stay of 20.9 (16.0) days. **Intervention 2:** High-frequency intervention (n=1105). Mean (SD) rehabilitation time was 66.3 (16.4) minutes per day delivered over a length hospital stay of 24.1 (14.2) days.	**Total costs (median per patient):** Intervention 1: £1,286 (IQR: £810 - £2,095; p=NR) Intervention 2: £1,369 (IQR: £867 - £2,362; p=NR) Incremental (2−1): £83 (95% CI: NR; p=0.06) **Currency & cost year:** 2020 Japanese Yen (¥) converted to UK pounds (£)[(b)] **Cost components incorporated:** Medical costs during hospitalisation (drugs, injections, treatment, inspection, and imaging).	**mRS score of 0-2 at discharge[(c)]:** Intervention 1: 53% Intervention 2: 40% Incremental (2−1): -13% (95% CI: NR; p<0.001) **mRS ≤2 at discharge with respect to high-frequency rehabilitation (adjusted odds ratio):** 1.89 (95% CI: 1.25 - 2.85; p=0.002)	**ICER (Intervention 2 versus Intervention 1):** NA £638 per case of mRS>2 averted. No significant differences were observed between the two groups for total medical expenses during hospitalisation, despite the higher-frequency rehabilitation group having a higher disease severity (median NIHSS score at admission was 5 (IQR: 3-13), compared to 4 (IQR: 2-12) for normal-intensity rehabilitation (p<0.001). Probability Intervention 2 cost effective (£20K/30K threshold): NA **Analysis of uncertainty:** NR

(maximum observed was 25 days). **Treatment effect duration:**[(a)] NA **Discounting:** NA				
Data sources				
Health outcomes: Within-trial analysis of a retrospective study (same paper), where the primary outcome measures were defined as the changes in physical and neurological function from admission to discharge as assessed by the modified Ranking scale (mRS) and NIHSS scores. **Quality-of-life weights:** NA **Cost sources:** Cost year and references were not stated. Medical costs during hospitalisation were extracted from subjects' electronic medical records between January 2013 and December 2016.				
Comments				
Source of funding: Department of Physical Therapy, Niigata University of Health and Welfare and Kobe City Medical Centre General Hospital, Kobe, Japan. **Limitations:** QALYs (and cost per QALY gained) were not presented. Japanese healthcare perspective and 2013-2016 resource use estimates may not reflect UK NHS context. Within-trial analysis based on a retrospective study not the wider evidence based identified in the clinical review. Follow-up data was only collected until discharge from hospital which may not sufficiently assess the full costs and benefits. Median (not mean) outcomes reported. Intervention costs associated with increased frequency of rehabilitation were not incorporated into costs differences between groups. References for unit costs (including costs year) were not reported which limits interpretation of results for UK context. No probabilistic sensitivity analyses were performed. **Other:** Observational study was not included in the clinical review as sufficient randomised evidence was identified.				
Overall applicability:[(d)] Partially applicable **Overall quality:**[(e)] Potentially serious limitations				

Abbreviations: 95% CI= 95% confidence interval; ICER= incremental cost-effectiveness ratio; IQR= interquartile range; mRS= modified Rankin scale (scale 0-6, lower values are better); NA= not applicable; NIHSS= National Institute of Health Stroke Scale (scale 0-42, lower values are better); NR= not reported; QALYs= quality-adjusted life years.

a) *For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.*
b) *Converted using 2020 purchasing power parities[20]}. References for unit costs were not reported but 2020 was assumed based on year prior to the date study was submitted (11/01/2021).*
c) *Differences between preadmission mRS scores were not statistically significant between the groups (p<0.007). NIHSS discharge scores were not reported as NIHSS scores at admission were significantly higher in the high-frequency intervention group than in the normal frequency group (p< 0.001).*
d) *Directly applicable / Partially applicable / Not applicable*
e) *Minor limitations / Potentially serious limitations / Very serious limitations*

Study	Pila 2022[22]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**

Economic analysis: Comparative cost analysis (No health outcomes) **Study design:** Within-trial analysis of a retrospective study (same paper) with no modelled extrapolation. **Approach to analysis:** Cost analysis of higher versus lower doses of a combined program of Robot-assisted training (RT) and occupational therapy (OT), completed during the subacute phase (3 weeks to 5 months post-stroke) Units costs applied. **Perspective:** French healthcare system. **Follow-up:** Up to 17 weeks **Treatment effect duration:**[(a)] NA **Discounting:** NA	**Population:** Adults diagnosed with stroke in the subacute phase (3 weeks to 5 months) pre- and post-rehabilitation program Fugl-Meyer Assessment (FMA) scale ratings. **Cohort settings:** Mean age (SD): 62 (13) Male: 67% **Intervention 1:** Lower dose group (n=22) received a mean (SD) number of 29 (3) sessions of OT and 26 (2) sessions of RT, lasting 30 minutes each over a 17-week period. **Intervention 2:** Higher dose group (n=14) received a mean (SD) number of 31 (2) sessions of both OT and RT, with both sessions lasting 35 minutes each over a 17-week period.	**Total costs (mean per patient):** Intervention 1: £1,083 Intervention 2: £1,879 Incremental (2−1): £796 (95% CI: NR; p=6.10E^{-25}) **Currency & cost year:** 2019 Euros (converted to UK pounds (£)[(b)] **Cost components incorporated:** Hourly staff cost of an occupational therapist and the hourly cost of Robot-assisted therapy (including daily working hours, effective working days per year and operating costs for the Robot).	NA FMA scores did not differ significantly between groups (p=0.28)[(c)].	**ICER (Intervention 2 versus Intervention 1):** NR The total cost of the combined program was higher for the higher dose group (p = 6.10E^{-25}). Probability Intervention 2 cost effective (£20K/30K threshold): NR/NR **Analysis of uncertainty:** None.
Data sources				
Health outcomes: Within-trial analysis of a retrospective study (n=36 – same paper), where the FMA scale was used to rate motor impairment. The higher dose group followed the usual rehabilitation program of the "Les Trois Soleils" rehabilitation Center (Boissise-Le-Roi, France) while the lower dose group was composed of patients who participated in an RCT (reference not reported but Reference Number was stated as: ID RCB 2011-A00632-39). **Quality-of-life weights:** None. **Cost sources:** References for unit costs were not reported. Intervention costs were estimated for each of the groups				

using patients hospitalised in a neurorehabilitation unit between 2009 and 2019. The annual cost of the robotic device was calculated from the purchase value of the robot (£89,791), the operating costs (£22,448) and the amortization period (7 years). Calculation of the hourly cost of RT (£10) was based on use of the robot for 7 hours per day, 5 days per week, for 52 weeks of the year. The hourly cost of OT (£34) was calculated in the same manner, based on the average annual gross salary of junior and senior therapists (£55,598). The cost of each OT and RT session were estimated using the scheduled durations of both sessions plus the level of supervision required, which was the same for both groups for RT (one therapist for two patients, involving the cost of two robots)), while OT supervision was higher in the higher-dose group (one OT per patient for the first 30 min and two patients for the last 30 min), compared to the lower-dose group (constant level of supervision: one therapist per patient). Finally, the average numbers of RT-sessions and OT-sessions were used to calculate the cost of the combined program for each group.
Comments
Source of funding: A.D.I.R.R (Association for Development and Innovation in Rehabilitation Robotics) **Limitations:** QALYs (and cost per QALY) were not calculated. French healthcare perspective including 2009-2019 resource use estimates may not reflect current UK NHS context. Baseline outcomes and intervention effects for the higher dose group were based on single non-randomised retrospective study excluded from clinical review. Estimates of resource use were based on data from the study population and not a systematic review. Follow-up period was vaguely reported and may not sufficiently assess the full costs and benefits. Only intervention-related healthcare costs and resource use were incorporated into the analysis; no downstream resource use included. References for unit costs (including cost year) were not reported. No probabilistic sensitivity analyses were performed. **Other:** Pila et al. (2021)[22] was excluded from the clinical review as it is non-randomised study when sufficient randomised evidence was identified.
Overall applicability:[(d)] Partially applicable **Overall quality:**[(e)] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; FMA= Fugl-Meyer Assessment (scale 0-66, higher scores are better); ICER= incremental cost-effectiveness ratio; NA= not applicable; NR= not reported; QALYs= quality-adjusted life years; RCT= randomised controlled trial; RT=robotic therapy.

a) *For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.*
b) *Converted using 2019 purchasing power parities[20]}. References for unit costs were not reported but 2019 was assumed based on year prior to the date study was submitted (03/09/2021).*
c) *Mean increase in FMA score was 16 ± 13% for the HG and 11 ± 8% for the LG with no between group difference in change (p = 0.28).*
d) *Directly applicable / Partially applicable / Not applicable*
e) *Minor limitations / Potentially serious limitations / Very serious limitations*

Appendix E – Health economic model

See separate report (Evidence review E – Intensity of rehabilitation F model write-up).

Appendix F – Excluded studies

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 7: Studies excluded from the health economic review

Reference	Reason for exclusion
Marsh 2010[14]	This study was assessed as partially applicable with very serious limitations due to a combination of reasons. 2007 resource use and 2009 costs may not reflect the current UK NHS context. The validity of the method used to estimate an EQ-5D difference using multiple mapping is unclear (Western Aphasia Battery test outcomes were converted into a different aphasia scale (developed by Wade 1985[29]) before using data by Wade to derive a correlation between the aphasia scale and the Barthel Index (BI); finally, a paper by Exel 2004[28] was used to determine the relationship between the BI and EQ-5D). The assumptions used to calculate QALYs from the 24-month clinical outcomes is unclear including how EQ-5D benefit accrued over time. The analysis compared enhanced speech and language therapy to usual care, excluding the most intensive group as this was not statistically different to the enhanced group. This comparison was not consistent with the clinical review, which reported all three trial arms. Probabilistic analysis was not undertaken. Limited sensitivity analyses were undertaken.