National Institute for Health and Care Excellence

Final

Stroke Rehabilitation in adults (update)

Cost-utility analysis: intensity of physiotherapy rehabilitation

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Economic analysis report

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1. Introduction

There are 100,000 new strokes per year.[60] Stroke can have a significant effect on both physical function and quality of life[1, 38] for individuals and also their carers.[29] Stroke rehabilitation aims to help people regain function and improve quality of life. Many people, however, still need home adaptations and home or residential care which results in high costs that fall on both the NHS and social services and the individual (due to means testing of home and residential care).

The 2013 CG162 guideline recommended offering patients “initially at least 45 minutes of each relevant stroke rehabilitation therapy for a minimum of 5 days per week to people who have the ability to participate, and where functional goals can be achieved.” In this 2023 update, the committee reviewed additional evidence about intensity of rehabilitation and concluded that the clinical evidence supported increasing the recommended physiotherapy time to 1-2 hours, for those able to participate.

Exploring the cost-effectiveness of increased physiotherapy time was prioritised for new economic modelling as this would be a change in practice that is likely to result in a substantial resource impact to the NHS in terms of additional physiotherapy time. Some published economic studies were identified in this area based on individual clinical studies, but it was agreed that an analysis incorporating as much of the clinical evidence base as possible should be undertaken where uncertainties can be explored to help inform committee decision making.

2. Methods

2.1. Model overview

A cost-utility analysis was undertaken where lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective were considered. The analysis followed the standard assumptions of the NICE reference case for interventions with health outcomes in an NHS setting including discounting at 3.5% for costs and health effects.[41] An incremental analysis was undertaken.

2.1.1. Comparators

The existing recommendation for rehabilitation is at least 45 minutes, 5 days a week of each therapy. This analysis aims to explore whether higher intensity physiotherapy is cost effective.

The following comparators were included in the analysis:

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

The choice of intensity comparator was based on the availability of clinical evidence. The committee considered the systematic review of the clinical evidence and agreed it provided evidence that more intensive physiotherapy than is currently recommended could provide additional clinical benefit. Most of this evidence related to 1 to 2 hours of physiotherapy. Evidence was limited for other therapies. In addition, to be able to undertake cost effectiveness analysis evidence on quality of life as measured by a utility score was required. A summary of available data is included in Appendix B of this report and in Evidence Review E - Intensity of rehabilitation, which contains the full details.

The committee decided to conduct a broad and comprehensive review of the clinical evidence to understand the impact of higher intensity rehabilitation. As a result, the types of studies included are heterogenous and there was overlap with reviews of specific interventions.

This economic analysis aims to take a similarly broad approach, utilising the evidence from the clinical review to inform whether or not higher intensity physiotherapy rehabilitation may be cost effective for the NHS. This necessarily required pooling of quite different studies.

2.1.2. Population

The population of the analysis was 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.

2.2. Approach to modelling

Incremental lifetime costs and QALYs per person for more intensive physiotherapy compared to less intensive physiotherapy were calculated based on data from randomised controlled studies identified by the systematic review of the clinical evidence. Studies were included in the model if they reported:

- EQ-5D-3L quality of life data or
- measures that could be mapped to EQ-5D-3L.

2.2.1. Model structure

A systematic review of the literature was undertaken to identify existing health economic analyses of higher intensity rehabilitation for people following a stroke. This review is summarised in Evidence Review E - Intensity of rehabilitation. Existing models were considered to identify possibly relevant and appropriate model structures.

The structure used was an adaptation of the model developed as part of the 2013 CG162 guideline[40] that compared more versus less intensive therapy delivered by a multidisciplinary team. A life table approach was taken to the analysis. Life tables for England[50] were adjusted for the increased mortality in people who have had a stroke. This estimated the number of people alive after each 1-week period (each cycle) and this was used to estimate life years for people in the model. It was assumed that mortality is not impacted by the type of rehabilitation received and so life expectancy did not vary by comparator. A 1-week cycle length was used to allow physiotherapy rehabilitation costs and treatment effects to be applied by week.

Quality of life (utility) values were attributed to people who were alive in the model that depended on the rehabilitation received ('more intensive physiotherapy' or 'less intensive physiotherapy'). This resulted in differences in QALYs between patients.

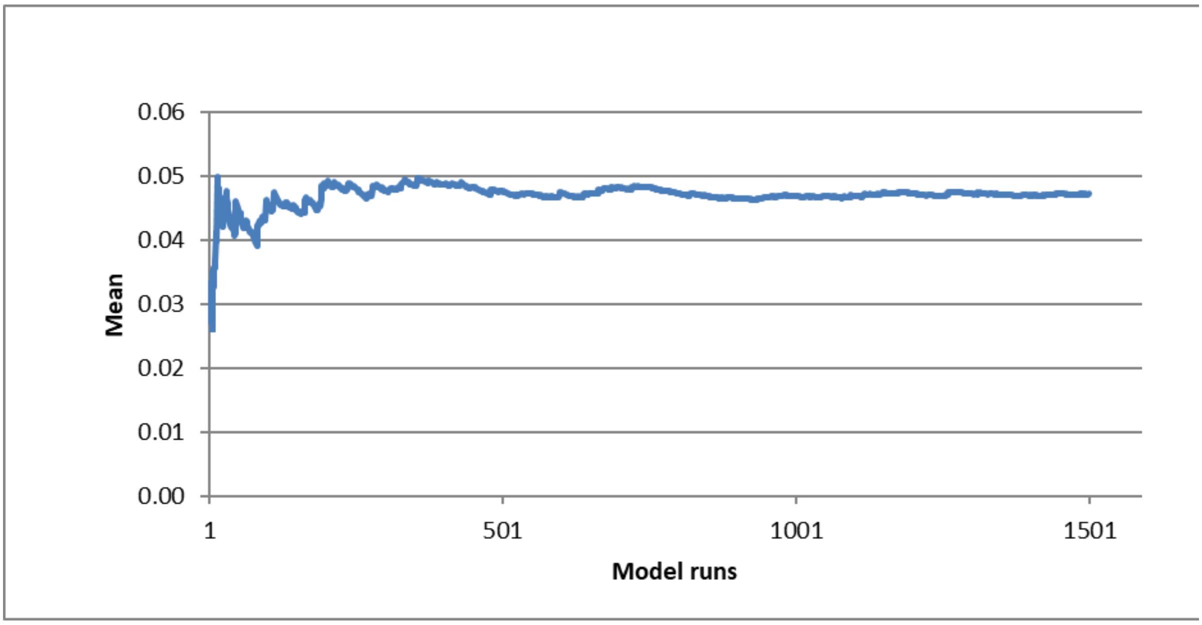
Differences in total costs between the groups were due to differences in the cost of delivering physiotherapy. Differences in care costs post-rehabilitation related to differences in outcomes were also modelled. A length of stay saving with more intensive physiotherapy was also applied in a sensitivity analysis.

2.2.2. Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 1,500 times for each analysis – and results were summarised.

When running the probabilistic analysis, multiple runs are required to account for random variation in sampling. To ensure the number of model runs were sufficient in the probabilistic analysis convergence was checked for incremental costs, incremental QALYs and incremental net monetary benefit at a threshold of £20,000 per QALY gained. This was done by plotting the number of runs against the mean outcome at that point (see example in **Figure 1**) for the base-case analysis. Convergence was assessed visually, and all had stabilised before 1500 runs.

Figure 1: Checking for convergence of incremental QALYs (lifetime analysis for Scenario 1a)



Scenario 1a: 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.
Abbreviations: QALYs=quality-adjusted life-years.

The way in which distributions are defined reflects the nature of the data, so for example cost were given a gamma distribution, which is bounded by 0, reflecting that costs cannot be less than 0. In the distributions are described in Table 1 and the specific distribution parameters are listed in Table 2 in the next section. Probability distributions in the analysis were parameterised using error estimates from data sources where possible.

Table 1: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
SMRs	Lognormal	The natural log of the mean and standard error were calculated as follows: • Mean = ln(mean cost) − $SE^2/2$ • SE = [ln(upper 95% CI) − ln(lower 95% CI)]/(1.96×2) $\sqrt{\ln \frac{SE^2 + mean^2}{mean^2}}$ This formula includes a correction to ensure the mean generated in the probabilistic analysis will be the same as the reported mean.[5]
Baseline EQ-5D % intervention time as inpatient % change in EQ-5D post-intervention	Beta	Bounded between 0 and 1. Derived from mean and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: Alpha = $mean^2 \times [(1-mean)/SE^2] - mean$ Beta = alpha×[(1−mean)/mean] Used for post-intervention EQ-5D change in order to constrain change to a reduction.
Costs Barthel Index scores	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alpha and beta values were calculated as follows:

Parameter	Type of distribution	Properties of distribution
Post-intervention EQ-5D change		• Alpha = $(mean/SE)^2$ • Beta = $SE^2/Mean$ Used for post-intervention EQ-5D change in order to constrain change to a reduction.
Difference in • Barthel Index • EQ-5D-3L • Length of stay • Care cost savings per week	Normal	Unbounded so change may be a decrease or increase. Parameterised by mean and SE.
Regression coefficients for mapping BI to EQ-5D-3L	Normal with Cholesky decomposition	Used to account for covariance between variables as well as variance. Normal distributions parameterised by mean and SE are combined with the variance-covariance matrix.

Abbreviations: 95% CI = 95% confidence interval; LOS= length of stay; SE = standard error; SMR = standardised mortality ratio.

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold and discount rate,
- general population mortality (based on national data so uncertainty is minimal),
- general population EQ-5D-3L by age and sex,
- cohort start age and proportion female,
- number of days with rehab, additional minutes per day with high intensity physiotherapy, high intensity rehabilitation duration.

In addition, various one-way and scenario sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed, and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change. Details of the one-way and scenario sensitivity analyses undertaken can be found in methods section 2.5 Sensitivity analyses.

2.3. Model inputs

2.3.1. Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the guideline committee.

There were four base case (primary) scenarios:

- 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),
    - a) intervention costs only
    - b) with post-rehabilitation care cost savings
- Scenario 2 (3-month weekly reduction applied before the difference was maintained, meaning higher intensity leads to permanent health gains).
    - a) intervention costs only
    - b) with post-rehabilitation care cost savings

A summary of the model inputs used in the base-case analyses is provided in **Table 2** below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 2: Overview of parameters and parameter distributions used in the model base-case analysis

Input	Data	Source	Probability distribution
Comparators	1. >45mins - 1hr physiotherapy, 5 days per week 2. 1-2hrs physiotherapy, 5 days per week	Clinical review of 3.1 intensity review	n/a
Population	People who have had a stroke and require physiotherapy, and able to tolerate higher intensity of therapy	Committee consensus	n/a
Cost perspective	UK NHS & personal social services	NICE reference case[44]	n/a
Time horizon	Lifetime	NICE reference case[44]	n/a
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case[44]	n/a
Cycle length	1 week	Committee consensus	n/a
Cohort settings			
Age	Female: 75 years Male: 71 years	National stroke audit data[59]	Fixed
% female	48%		
Mortality			
General population mortality	Age and sex dependent	National lifetables 2017-2019[50]	Fixed
Stroke standardised mortality ratio	Female: 2.85 (95% CI: 2.66 to 3.05) Male: 2.58 (95% CI: 2.43 to 2.75)	Brønnum-Hansen 2001[7]	Lognormal •Log mean (female/male): 1.05/0.95 •Log scale SE (female/male): 0.035/0.032
Health-related quality of life (utilities)			
General population utilities (used for age-adjustment of stroke-related utilities)	Age and sex dependent	NICE Decision Support Unit[26]	Fixed
Baseline utility	0.293	Pooled studies from systematic review for guideline update (EQ-5D-3L – direct or mapped from 5L or BI)	•BI studies: gamma (then mapped to EQ-5D-3L) •EQ-5D-5L studies: Beta (first mapped to 3L) See Appendix C for details
Change from baseline with lower intensity physiotherapy	0.120		Normal (probabilistic change from baseline values were pooled). See Appendix C for details
Difference in change from baseline with higher intensity physiotherapy	0.050		

Input	Data	Source	Probability distribution
Change per week in mean difference post-intervention	-0.0015	Rodgers 2019[57]	Gamma (applied to absolute number) •SE: 0.001 •Alpha: 1.417 •Beta: 0.001
Higher intensity physiotherapy resource use			
Days of therapy per week	5	As specified for intervention	Fixed
Additional minutes per day with higher intensity	45 minutes	Weighted average from clinical studies used to inform treatment effect	Fixed
Duration of intensity rehabilitation intervention	6 weeks		Fixed
% of inpatient rehabilitation	42%	Inpatient SSNAP 2021[59] as % of total	Beta •SE: 0.001 •Alpha: 81009.6 •Beta: 113413.5
Average number of staff required	Inpatient: 2 Post-discharge: 1.3	Committee expert opinion	Fixed
% Rehabilitation assistant	Inpatient: 25% Post-discharge: 25%	Committee expert opinion	Fixed
Barthel index			
Mean difference in BI (0-100) change from baseline at end of intervention with Higher versus lower intensity	4.856	Pooled studies from systematic review for guideline update	Normal (probabilistic change from baseline values were pooled) See Appendix C for details
Unit costs			
Physiotherapist (hospital/community)	£67/73	PSSRU 2021[32]	Gamma •SE (£67/£73): 13.40/14.60 •Alpha (£67/£73): 25.00 •Beta (£67/£73): 2.68/2.92
Rehab assistant (hospital/community)	£43/44	PSSRU 2021[32]	Gamma •SE (£43/£44): 8.60/8.80 •Alpha (£43/£44): 25.00 •Beta (£43/£44): 1.72/1.76
Care cost savings per week, per BI (0-100) point change	£46.79	O'Conner 2011[49]	Normal for total weekly cost savings and BI change •Weekly savings (mean (SE)): £1,591 (462.58) •BI point change (mean (SE)): 34 (9.89)
% care costs paid by NHS/PSS	50%	Assumption	Fixed

Abbreviations: BI = Barthel Index; NHS and PSS = National Health Service and personal social services; PSSRU = Personal Social Services Research Unit; SE= standard error; SMR = standardized mortality ratio; SSNAP Sentinel Stroke National Audit Programme.

2.3.2. Initial cohort settings

The population entering the model was assigned a start age of 75 years for women and 71 years for men, and 48% women, based on real world data from the national stroke audit in people that received physiotherapy. The data used is shown in **Table 3**. This was from an extract from SSNAP from April 2016 to March 2021 (SSNAP 2023 – reference forthcoming).

Data was only available by age band and so mean ages were estimated assuming the mean age for each age band was the mid-point of the band, and 37 and 82 for the top and bottom groups respectively.

Table 3: Age and sex distribution of patients in the SSNAP dataset who received physiotherapy rehabilitation[(a)] in England, April 2016 - March 2021

	Female		Male	
Age group	**N**	**%**	**N**	**%**
<40	2271	1.42%	2735	1.58%
40-44	1580	0.99%	2550	1.47%
45-49	2897	1.81%	5102	2.94%
50-54	4515	2.83%	8875	5.12%
55-59	5877	3.68%	12462	7.19%
60-64	7971	4.99%	15602	9.00%
65-69	11205	7.02%	18692	10.78%
70-74	17508	10.97%	24323	14.03%
75-79	23188	14.52%	26098	15.05%
>80	82641	51.76%	56966	32.85%
Estimated mean age[(b)]	**75**		**71**	
% female/male	**48%**		**52%**	

(a) *Receipt of physiotherapy is defined as >0 minutes of physiotherapy rehabilitation assessment + treatment recorded in the dataset.*
(b) *The mean age was estimated using the age group distribution and assuming the mean age for each age band was the mid-point of the band, and 37 and 82 for the top and bottom groups respectively.*

The mean age in the clinical studies used to inform treatment effects in this analysis ranged from 50 to 75 years with an average of 62 years. The proportion female ranged from 22% to 50% with an average of 42%. Real-world data was used for the initial cohort settings so that estimated QALY gains reflected expected real-world benefits in analyses where treatment benefits were extrapolated to a lifetime perspective (how treatment effects are applied in the model is described in Section 2.3.4.2). A sensitivity analysis was done using the average age and proportion female from the clinical trials used to inform treatment effects (see Section 2.5 Sensitivity analyses).

2.3.3. Life expectancy

Sex- and age-specific mortality was incorporated into the model using life tables for England adjusted to reflect the increased mortality rates in people who have had a stroke. It was assumed that mortality does not differ between more intensive and less intensive rehabilitation.

2017-2019 lifetables were used.[50] Note that later data were not used as mortality was much higher during the COVID-19 pandemic. Standardised mortality ratios (SMRs) for all-cause mortality after stroke compared with age/sex-adjusted rates for the general population reported by Bronnum-Hansen et al. 2001[7] were used. These were from a large Danish study of people who had a stroke 1982-1991 (n=4162) with up to 15 years follow-up. For females this was 2.85 (CI: 2.66, 3.05) over the course of the study and for males 2.58 (CI: 2.43, 2.75). This data was used in the modelling for CG162 and has also been used in a recently published cost-effectiveness analysis relating to stroke rehabilitation.[35] More contemporary UK data was not identified. Sensitivity analysis was done with lower SMRs to reflect that outcomes after stroke may have improved over time (see Section 2.5 Sensitivity analyses).

The SMRs were included in the probabilistic analysis using a lognormal distribution which was parameterised using the confidence intervals. General population mortality was not varied probabilistically.

2.3.4. Health-related quality of life (utilities)

The aim of more intensive physiotherapy after stroke is to improve functional outcomes and independence so ultimately quality of life. In economic evaluation, a particular measure of health-related quality of life is required known as a utility to calculate QALYs. The NICE reference case specifies that EQ-5D-3L is the preferred measure of utility in adults.

Relative treatment effects of more intensive compared to less intensive physiotherapy rehabilitation were based on the systematic review of the clinical evidence undertaken for this guideline update. For full details see Evidence Review E - Intensity of rehabilitation A introduction and quantitative.

Limited EQ-5D data was reported in the included clinical studies and so clinical outcomes were mapped to EQ-5D to maximise the data that could be incorporated into the cost effectiveness analysis.

The analysis is therefore based on studies from the clinical review that reported EQ-5D utility data, or a clinical outcome that could be mapped to EQ-5D. Methods are described in detail in the following sections.

2.3.4.1. Mapping data to EQ-5D-3L

2.3.4.1.1. Mapping from EQ-5D-5L

Of the studies that reported EQ-5D the data available was for the 5L version. This was mapped to EQ-5D-3L using the mapping function developed by the NICE Decision Support Unit using the 'EEPRU dataset'.[27] This is the mapping algorithm recommended for use in NICE analyses.

The Excel function for mapping study means was used.[48] Gender is a dichotomous input in this and so EQ-5D values were calculated for men and women separately (applying the overall study mean EQ-5D and age as gender specific values were not available) and calculating an overall study estimate as a weighted average of these estimates using the gender split in the study.

Uncertainty in the underlying EQ-5D-5L data was captured in the probabilistic analysis. Total EQ-5D-5L scores are needed for mapping at each time point. The EQ-5D-5L total score and confidence interval at baseline and each follow-up point were mapped to EQ-5D-3L (note that no change from baseline analyses were available). The standard deviation of the mapped EQ-5D-3L was calculated from the mapped confidence interval. The EQ-5D-3L change from baseline and SD at each time point were calculated; change from baseline SDs were estimated assuming a correlation coefficient of 0.5 as recommended in the NICE Guidelines Technical Support Unit (TSU) Guideline Methodology Document 2.[16] Baseline EQ-5D-3L was incorporated in the probabilistic analysis using a beta distribution as this is bounded by 0 and 1 and so reflects the likely range of a utility value (although it is acknowledged that it is possible to get negative utility) and the change from baseline at each time point using a normal distribution. Data was not available to capture uncertainty in the mapping equation.

2.3.4.1.2. Mapping other clinical outcomes

To determine how best to use the available clinical data to estimate QALYs we investigated what outcomes in the clinical review could be mapped to EQ-5D. A quality-of-life search was undertaken looking for studies in a stroke population (for search strategy see Appendix A

We additionally reviewed a published mapping database (Dakin 2020[15]) for outcomes used in the intensity clinical review.

Table 4 summarises the 6 studies identified that mapped outcome measures reported in the intensity clinical review to EQ-5D. The clinical outcomes were Barthel index (BI), modified Rankin scale (mRS), Hospital Anxiety and Depression Scale (HADS) and the functional independence measure (FIM). All of the studies mapped to EQ-5D-3L and used the UK population tariff. In the clinical review, BI was reported in 18 studies, mRS in 4 studies, HADS in 1 study and FIM in 10 studies.

Table 4: EQ-5D[(a)] mapping studies of outcomes in intensity clinical review

Author, year	Outcome	N[(b)]	Population	Mapping models investigated
Brazier, 2014[6]	HADS	286	Depression, anxiety, and phobias	OLS, Tobit, response mapping
Kaambwa 2013[2]	BI	793	Older people	OLS, CLAD and response mapping
Peiris, 2020[53]	FIM	677	Rehabilitation inpatients (e.g. stroke)	OLS; adjusted limited dependent variable mixture models
Rivero-Arias, 2010[56]	mRS	2425	Stroke and TIA	OLS, response mapping
van Exel, 2004[63]	BI	710	Stroke	OLS, response mapping
Whynes, 2013[65]	BI, mRS	1462	Stroke	OLS, response mapping

Abbreviations: BI = Barthel Index; CLAD = censored least absolute deviations; EQ-5D = EuroQol 5-dimension; FIM = Functional Independence Measure; HADS = Hospital Anxiety and Depression Scale; mRS = Modified Rankin Scale; OLS = Ordinary least squares; TIA = transient ischemic attack.
(a) All studies mapped outcomes to EQ-5D-3L using UK tariff.
(b) Responses used in analysis

Of the three studies identified that mapped BI only van Excel, 2004 could be used. The models reported in sufficient detail to use for mapping in Kaambwa, 2013 required BI subscores (not just the total score) and so could not be used. Whynes, 2013 mapping models required mRS and BI scores. The mRS mapping required discrete mRS categories to be used and so was not appropriate to use with mean study scores and so could not be used. The committee decided that mapping from HADS should not be used as this is not the primary goal of rehabilitation. The FIM mapping could not be used because it required the four subscale scores, or all the item scores whereas only total scores were available. Therefore, only BI was mapped to EQ-5D-3L for use in the analysis.

2.3.4.1.3. Mapping Barthel Index (BI) to EQ-5D-3L

The Barthel Index consists of 10 items that measure a person's daily functioning particularly activities of daily living and mobility. The total score ranges from 0 (totally dependent) to 20 (completely independent). Sometimes the score is expressed on a scale of 0 to 100 by multiplying by 5. It was the top ranked outcome measure for activities of daily living (ADL) by the committee.

The committee highlighted the BI's focus on functional mobility and a person's degree of independence and that it may not reflect all aspects of health for someone who has had a stroke (such as cognitive or speech and language abilities). However, it was ultimately deemed appropriate to use for mapping to EQ-5D particularly for interventions that focussed on physical rehabilitation such as physiotherapy as it would allow more evidence to be incorporated into the analysis, albeit evidence that is second best to direct EQ-5D data. This decision was consistent with previous stroke-related economic models which have estimated QALYs using EQ-5D valued mapped from BI scores.[30]

Van Exel 2004[63] was used to map BI to EQ-5D-3L. The van Exel, 2004 mapping equation (using combined 2-month and 6-month data):

- EQ-5D-3L = -0.25 + 0.05 BI score
- 95% Confidence intervals: intercept -0.33 to -0.19; slope 0.047 to 0.053

The NICE Decision Support Unit (DSU) report on mapping studies states that the clinical and demographic characteristics of people in the estimation sample should be as similar as possible to the characteristics of the 'target' sample to which the mapping algorithm is applied.[43] The van Exel analysis was based on a real-world stroke population from the Netherlands (n=598, mean age 73.5y, 54% female). This is similar to the UK stroke population which in the 2020/21 Sentinel Stoke National Audit was 47% female with a median age of 76 years.[59] It is slightly older than the average of the studies included in the intensity review which was mean age 64 years and 42% female. The mean age in the studies mapped for this analysis ranged from 52 to 76 years.

BI and EQ-5D data used in van Exel 2004 were assessed through patient interviews 2 and 6 months after stroke. The analysis employed ordinary least-squares (OLS) regression techniques to derive mapping algorithms using the 2-month data, the 6-month data and the combined 2- and 6-month data. The coefficients were the same in all analyses with similar CIs and similar R^2 values (0.54, 0.59 and 0.57). The model based on the combined data with the most data points was used for mapping here.

The authors reported that observed and predicted mean values by BI category did not differ significantly except for the independent category but that intraclass correlation was moderate to low because the predicted values are more clustered around the mean. Adjusted R^2, AIC and BIC statistics were not reported. Validation using an external cohort or by splitting the sample cohort was not undertaken. However, Kaambwa 2013[2] applied van Exel in an external cohort (1,189 UK intermediate care patients) and reported correlation 0.461, Root mean square error 0.327 and mean absolute error 0.242.[2]

Van Exel uses the 0 to 20 BI scale. Where RCTs reported on a scale of 0-100 this was therefore divided by five to convert to the 0-20 scale used in the algorithm.

Uncertainty in the underlying BI data was captured in the probabilistic analysis. Total BI scores are needed for mapping at each time point. BI was made probabilistic by varying the baseline BI using a gamma distribution and the change from baseline at each time point using a normal distribution. At each follow-up point, the probabilistic baseline value and change from baseline value were summed and then mapped. This ensured where change from baseline analyses had been undertaken for the study and so SD reflected covariance, these were utilised and that uncertainty in the mapping equation can also be incorporated into the analysis. Where change from baseline analysis had not been undertaken within the studies, SD were estimated assuming covariance of 0.5 as recommended in the NICE Guidelines Technical Support Unit (TSU) Guideline Methodology Document 2.[16] Uncertainty in the mapping equation was also incorporated using Cholesky decomposition and the variance-covariance matrix for the mapping equation. Covariance was not reported in the published paper and so was calculated from data provided by van Exel and formulae from Neter et al. 1983.[46] The resulting variance-covariance matrix is shown in **Table 5**.

Table 5: van Exel BI to EQ-5D mapping equation variance-covariance matrix

	Intercept/constant	BI (slope)
Intercept/constant	0.0012755	
BI (slope)	-0.0000368	0.0000023

BI = Barthel index

2.3.4.1.4. Clinical studies with utility data

12 studies out of the 32 included in the clinical review for the >1 to 2 hours physiotherapy category had data that could be used to inform QALY estimation for economic evaluation (that is EQ-5D or BI). These are shown in **Table 6**. The 7 studies comparing >1 to 2 hours physiotherapy 5 days a week to >45 minutes to 1 hour, 5 days a week were used in the base case analysis. A sensitivity analysis was done using all 12 studies (see section 2.5).

The study details and outcome available to map to EQ-5D-3L for each study are summarised in **Table 7**.

Table 6: Breakdown of >1 to 2 hours physiotherapy studies with data for EQ-5D estimation by days of therapy and lower intensity comparator

Intensity	Studies	Sum of N
>1 to 2 hours	**12**	**2031**
<5 days		
Vs >45 mins to 1 hour, <5 days	1	109
Cooke 2010		109
5 days		
Vs </= 45 mins, <5 days	1	59
Yoo 2013		59
Vs </= 45 mins, 5 days	1	70
Glasgow Augmented Physiotherapy Study 2004		70
Vs >45 mins to 1 hour, 5 days	8	1731
Cabanas-Valdes 2016		80
Han 2013		21
Jiang 2020		45
Klassen 2020		75
Lee 2012		40
Rodgers 2019		770
Tollar 2021		680
Kim 2016		20
6 days		
Vs >45 mins to 1 hour, 5 days	1	62
Askim 2010		62

Table 7: Details of clinical studies included in base-case analysis

Study	• N • Mean age • % female	Setting	Intervention (weeks)	Last follow-up (weeks)	EQ-5D/BI	Area of focus	Time since stroke[(a)]	Stroke severity	Intervention intensity detail	Control arm detail	CEA?
Cabanas-Valdes 2016[9]	• N=80 • 75 yrs • 50%	Inpatient rehabilitation (Spain)	5	5	BI	Functional independency; Core stability	Subacute 23.25 (±16.7) days	Moderate (or NIHSS 5-14)	Core stability exercises and usual care	Conventional therapy programme (1 hour)	No
Han 2013[24]	• N=21 • 50 yrs • 22%	Inpatient rehabilitation (China)	6	6	BI	Upper limb	Subacute (>5 weeks[(b)])	Not stated/ unclear	Arm training 2 hours per day	Arm training 1 hour per day	No
Jiang 2020[31]	• N=45 • NR • 36%	Inpatient rehabilitation (China)	2	4	BI	Upper limb	Subacute (mean: 20 days)	Moderate (or NIHSS 5-14)	Robot-assisted arm therapy (30 minutes twice a day); Spring arm robot used with a virtual reality game interface that matches the motor skills required to complete the exercise (in addition to usual care).	Conventional rehabilitation 30 minutes twice a day	No
Kim 2016[33]	• N=20 • 66 yrs • 41%	Inpatient rehabilitation (South Korea)	4	4	Modified BI[(c)]	Lower limb	Subacute (30 days)	Not stated/ unclear	90-minutes of circuit training classes	Conventional individual physiotherapy for 30 minutes twice a day.	No
Klassen 2020[34]	• N=75 • 57 yrs • 40%	Inpatient rehabilitation (USA)	4	52	EQ-5D-5L	Mixed	Subacute (27 days (SD 10)	Moderate (or NIHSS 5-14)	Different doses of physical therapy (Dose of 104 minutes was incorporated into the model)	Usual care (48 minutes) included physical therapy was inpatient physical therapy that progressed upper and lower limb functional exercises as tolerated.	No

Study	• N • Mean age • % female	Setting	Intervention (weeks)	Last follow-up (weeks)	EQ-5D/BI	Area of focus	Time since stroke[(a)]	Stroke severity	Intervention intensity detail	Control arm detail	CEA?
Lee 2012[37]	• N=40 • 54 yrs • 38%	Unclear setting (South Korea)	4	4	Modified BI[(c)]	Lower limb	Chronic (mean 7.15 months)	Not stated/ unclear	Balance control trainer (additional 20 minutes a day)	Usual care (1 hour per day)	No
Rodgers 2019[57]	• N=770 • 61 yrs • 39%	NHS (mostly outpatient) stroke rehab units (UK)	12	24	EQ-5D-5L (BI also collected)	Upper limb	Chronic stroke (43% were 3-12 months)	Moderate (or NIHSS 5-14)	Robot-assisted training or enhanced upper limb therapy (45 minutes, 3 times per week in addition to usual care)	Usual care only (45 minutes)	Fernandez-Garcia, 2021[20] (CUA)
Tollar 2021[61]	• N=680 • 67 yrs • 45%	Outpatient clinics (Hungary)	5	5	BI	Functional independency	Subacute 2.9 weeks (0.75 SD)	Not stated/ unclear	5 times a week twice daily Exergame sessions (2 hours)	Exergame sessions (1 hour)	No

Abbreviations: BI = Barthel index; CEA = cost-effectiveness analysis; CUA = cost-utility analysis (QALYs as outcome measure); EQ-5D-5L – Euroqol 5 dimensions – 5 level version; SD = standard deviation

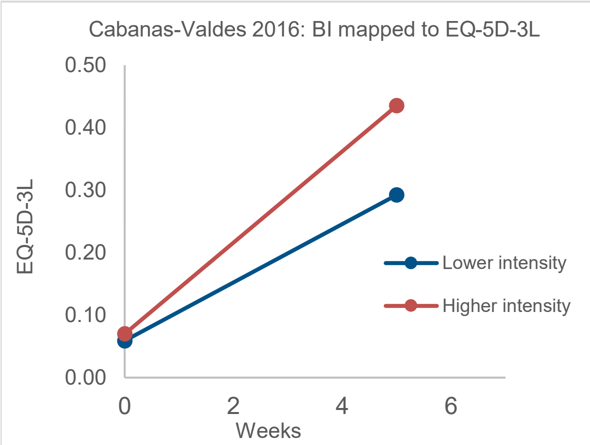
(a) Subacute stroke = 7 days – 6 months; Chronic stroke >6 months

- *All stroke patients admitted to the Affiliated Hospital of Qingdao University Medical College between November 2009 and October 2010 were considered for inclusion in the study. Days to randomisation were 38.30-41.40.*
- *BI test items (i.e., eating and grooming) were revised to reflect the Korean culture and lifestyle.*

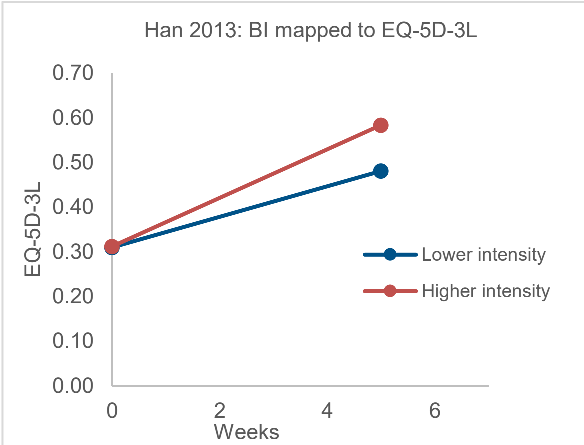
2.3.4.1.5. Data mapped to EQ-5D-3L by study

Outcomes from all available time points reported in the study were mapped to EQ-5D-3L and are shown in **Figure 2**. How this data is used in the analysis is described in Section 2.3.4.2.

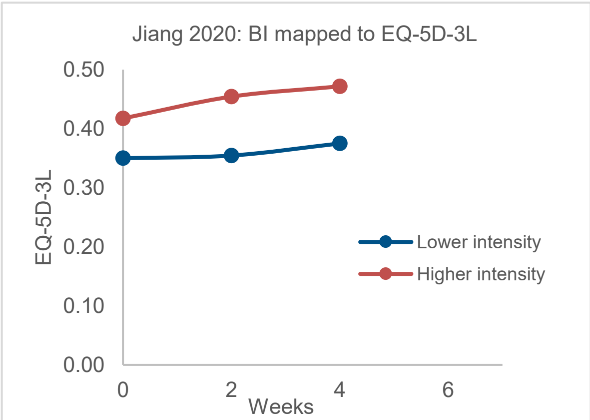
Figure 2: Data mapped to EQ-5D-3L by study



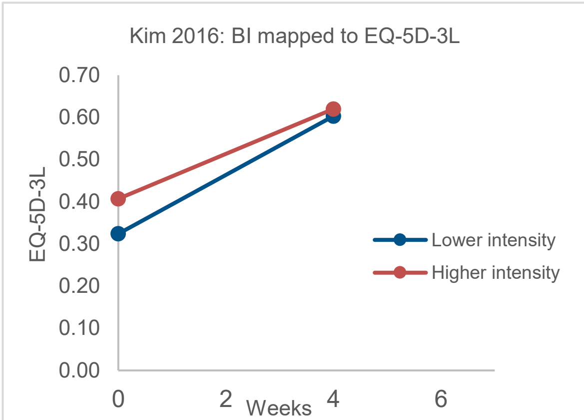
Study intervention duration: 5 weeks



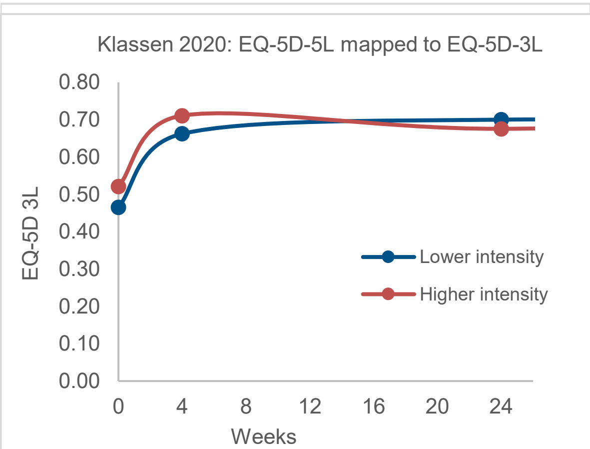
Study intervention duration: 6 weeks



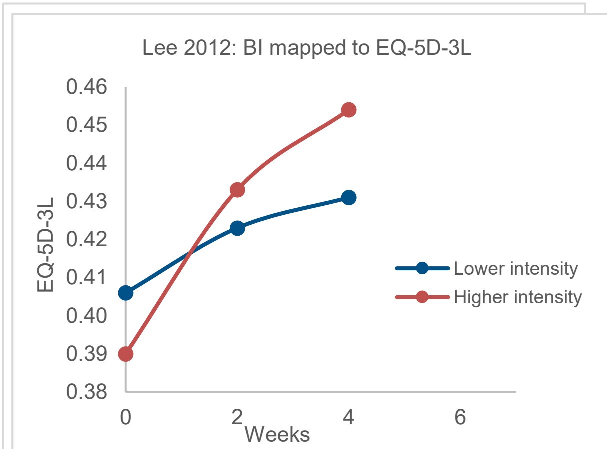
Study intervention duration: 2 weeks
Study intervention duration: 4 weeks



Study intervention duration: 4 weeks
Study intervention duration: 4 weeks



Study intervention duration: 12 weeks



Study intervention duration: 5 weeks

2.3.4.2. Treatment effect higher vs lower intensity physiotherapy

All studies reported outcomes around the time the intervention ended. A few also reported at a time point during the intervention or after the end of the intervention. As seen in the CG162 model, the assumption made about long-term effects after rehabilitation has a significant impact on cost-effectiveness estimates. Although data was limited, the difference between groups appeared to potentially reduce after the end of the intervention and so treatment effect at the end of the intervention was pooled and data after the end of the intervention were used to inform what happens in the model longer term. The available data and how it was used in the model are described in detail below.

2.3.4.2.1. Initial intervention effects

All studies measured effects around the end of the study intervention. The mean difference in change from baseline for higher versus lower intensity treatment at the end of the intervention was pooled using inverse variance meta-analysis to estimate the treatment effect (Appendix C). In line with methods used in the clinical review, a random effect meta-analysis was used as there was unexplained heterogeneity in the fixed effects meta-analysis. The resulted in a pooled mean difference in EQ-5D-3L of 0.050. Data showing the results from the clinical studies are shown in **Table 8** and **Figure 3**. The variation in results is due to the clinical review including any study that compared more physiotherapy time with less, which meant that the studies incorporated in this analysis varied in terms of setting, stroke population, the interventions used and the delivery, frequency and duration of the intervention (see section 4.2 for details). In probabilistic analysis this pooled mean difference is recalculated each time using the mean differences from the probabilistic inputs and the inverse variance weightings calculated below.

Intervention duration varied in the studies between 2 and 12 weeks but no clear trend was seen related to duration in the available data and so all durations were pooled together and applied at the weighted average intervention duration in the studies which was 6 weeks. The weighted average was calculated using the weights calculated for the treatment effect for consistency. A linear increase from 0 mean difference at baseline to the mean difference at end of intervention was applied.

A weighted average age, baseline EQ-5D-3L and change from baseline in the lower intensity group was also calculated (Appendix C Baseline EQ-5D-3L and change from baseline for lower intensity physiotherapy (CFBL-L) are applied in the model so total QALYs are estimated for each group but do not affect incremental QALY calculations (and so cost-effectiveness) because mortality does not vary between comparators in the model. Mean age is used when applying utility age adjustments over time in the model (see Section 2.3.4.3).

Table 8: End of intervention pooled EQ-5D-3L treatment effect (Base case analysis)

	Mean difference in CFBL (H – L)	Mean difference inverse variance weight[(a)]	Intervention duration (weeks)	Mean age	BL	CFBL-L
Cabanas-Valdes 2016	0.132	12.2%	5	76	0.065	0.233
Han 2013	-0.08	4.1%	6	53	0.320	0.335
Jiang 2020	0.032	14.5%	2	64	0.384	0.004
Kim 2016	-0.066	4.0%	4	66	0.366	0.279
Klassen 2020	-0.007	6.6%	4	57	0.484	0.197
Lee 2012	0.039	10.8%	4	54	0.398	0.025
Rodgers 2019	0.029	23.2%	12	61	0.219	0.036
Tollar 2021	0.101	24.6%	5	67	0.311	0.171

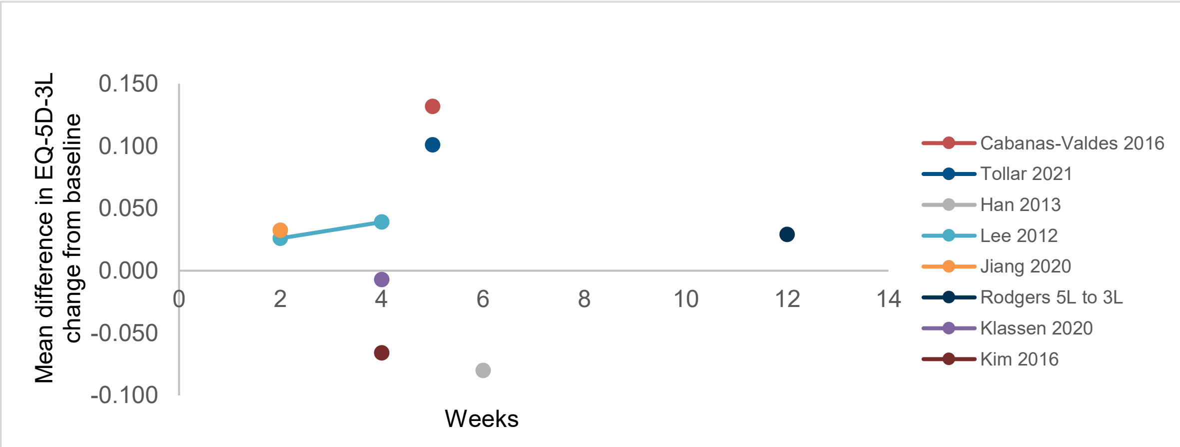
	Mean difference in CFBL (H – L)	Mean difference inverse variance weight[(a)]	Intervention duration (weeks)	Mean age	BL	CFBL-L
Pooled[(b)]	**0.050**	**100%**	**6**	**63**	**0.29**	**0.12**

Abbreviations: BL = base line EQ-5D-3L; CFBL = change from baseline; EQ-5D-3L = EuroQol 5-dimension – 3 level version; H = higher intensity; L = lower intensity.

(a) Weights calculated from inverse variance (random effects assumption) of EQ-5D-3L mean difference in CFBL with higher intensity compared to lower intensity physiotherapy.

(b) Pooling is based on a weighted average using weights calculated for treatment effect based on inverse variance.

Figure 3: Mean difference in change from baseline EQ-5D-3L with higher intensity versus lower intensity physiotherapy at end of intervention, by study



Note: All data points are at the end of study intervention except for Lee that additionally reported data at a point before end of the intervention.

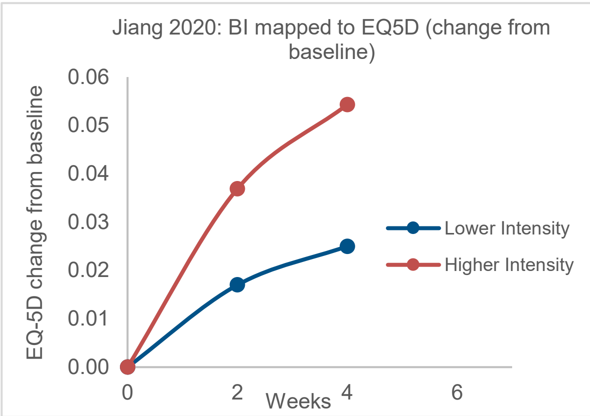
2.3.4.2.2. Longer term intervention effects

Three of the studies used to inform the model reported follow-up longer than the intervention duration: Jiang 2020, Klassen 2020, and Rodgers 2019. EQ-5D-3L change from baseline data from these studies is shown in **Figure 4** and mean difference in change from baseline is shown in **Figure 5**.

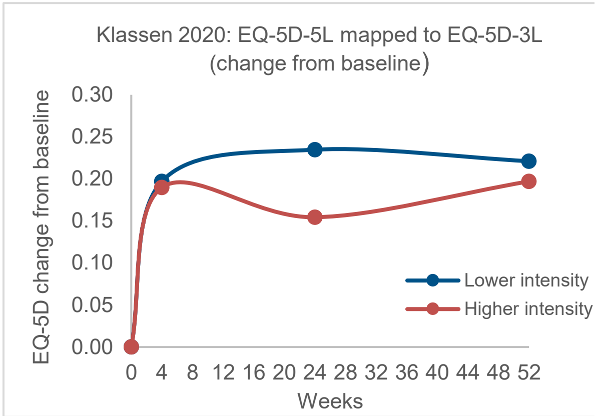
In Jiang 2020 and Rodgers 2019, EQ-5D-3L continues to increase in both the higher and lower intensity groups after the end of the study intervention but the mean difference between groups reduces over time.

Klassen 2020 did not find a benefit with higher intensity over lower intensity physiotherapy at the end of the intervention, therefore it could not be used to inform the waning of the treatment effect post-intervention.

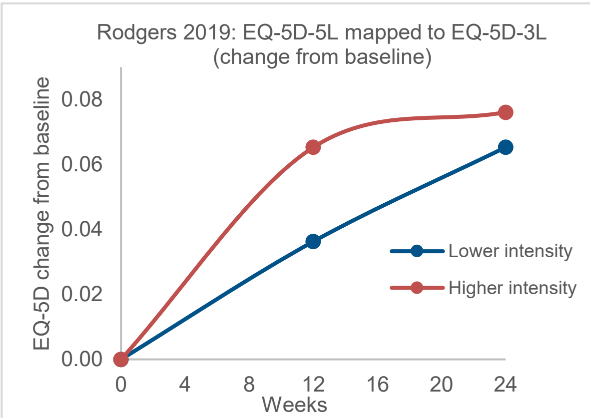
Figure 4: Change from baseline EQ-5D-3L in studies with follow-up after the end of the study intervention



Intervention duration: 2 weeks

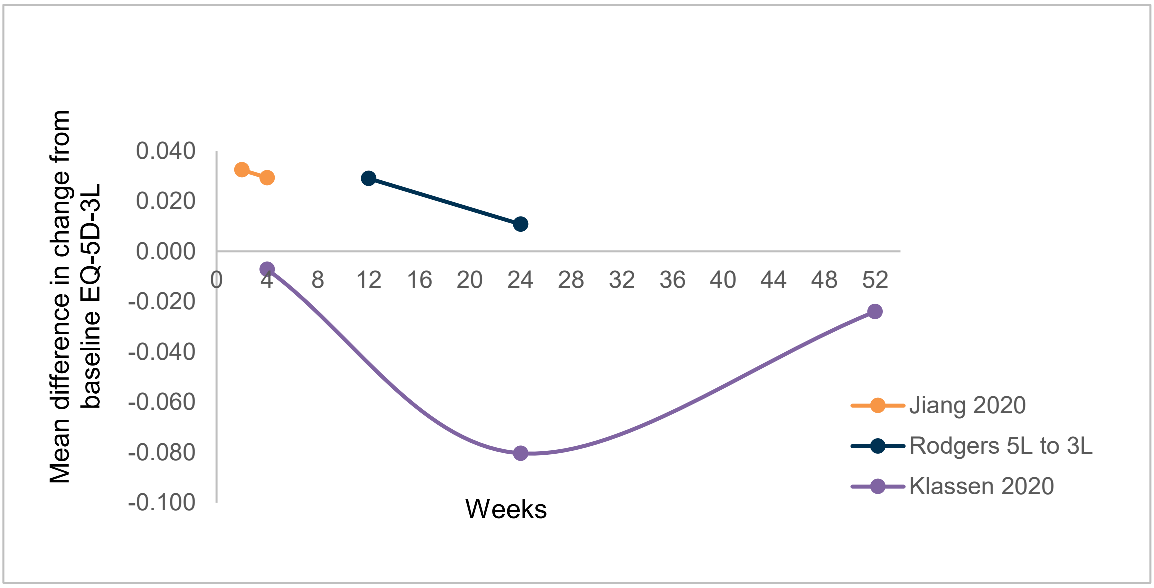


Intervention duration: 4 weeks



Intervention duration: 12 weeks

Figure 5: Mean difference in EQ-5D-3L with higher intensity versus lower intensity after end of study intervention, by study

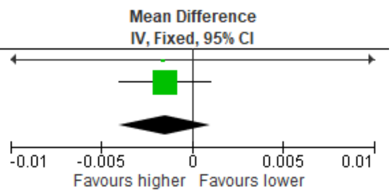


Because not all studies had follow-up beyond the intervention, and studies that did had different timepoints, it was not considered appropriate to simply use the absolute EQ-5D values. Instead, we examined how EQ-5D changed over time in the studies with data available by calculating a change per week. Initially mean change per week and associated SD (assuming linear change and a correlation co-efficient of 0.5) were obtained from each study. However, when meta-analysed inclusion of Jiang made no difference to the overall estimated mean difference (**Figure 6**) and so the Rodgers data alone was used to inform change per week in the model.

Figure 6: Change per week in mean difference in EQ-5D-3L after end of study intervention

	Higher			Lower				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Jianga	0.0087	0.0708	23	0.0103	0.0639	22	0.4%	-0.0016 [-0.0410, 0.0378]
Rodgersa	0.0009	0.0164	516	0.0024	0.0171	254	99.6%	-0.0015 [-0.0040, 0.0010]
Total (95% CI)			**539**			**276**	**100.0%**	**-0.0015 [-0.0040, 0.0010]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 1.16 (P = 0.24)



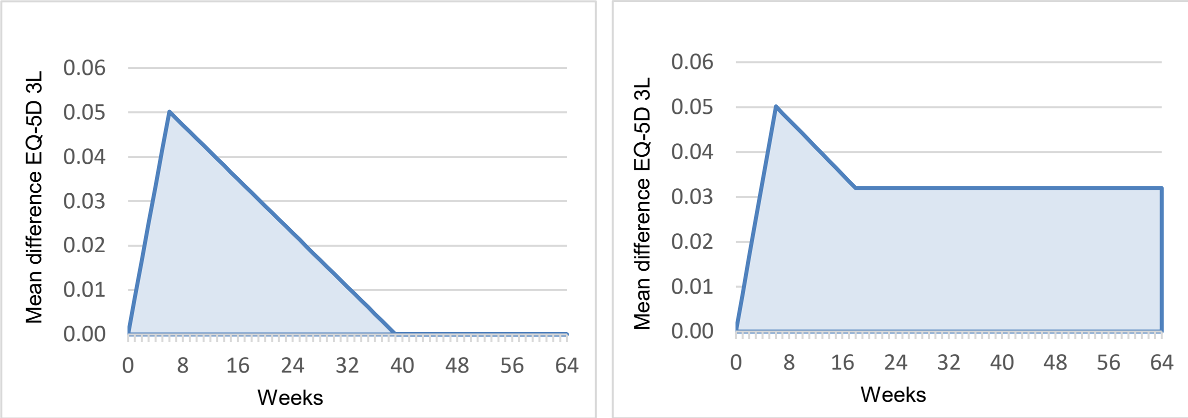
Abbreviations: CI = confidence interval; SD = standard deviation.

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 in the model as this was the follow-up period in the Rodgers study. Beyond this, an extrapolation assumption was applied:

1. 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.
2. 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.

Figure 7 below shows these two assumptions illustratively. In both scenarios the initial treatment effect is applied at 6 weeks and then the change per week from Rodgers is applied for 12 additional weeks however after that the two scenarios differ.

Figure 7: Mean difference in utility over time with higher vs lower intensity



Scenario 1: change per week applied until there is no difference between the higher and lower intensity groups. Area under the curve = QALY gain.

Scenario 2: the difference in EQ-5D between higher and lower intensity that remains 12 weeks post rehabilitation is maintained for the remaining lifetime (full lifetime not shown). Area under the curve = QALY gain.

The committee discussed whether they considered it was more likely that more intense rehabilitation led to permanent health gains for people that have had a stroke or just sped up recovery to choose a base case analysis but agreed that they were not able to do this and so requested both scenarios to be presented as separate base case analyses.

The post-rehab change per week was incorporated into the probabilistic analysis using a gamma distribution. This constrains the change in EQ-5D conservatively, so that in every model simulation the between-arm treatment effect is always reduced after the end of rehabilitation or at the extreme maintained.

2.3.4.3. Age adjustment of utilities

In the model utilities were age-adjusted to account for quality-of-life decreasing with age.

Age-specific general population EQ-5D-3L utilities were taken from an analysis of direct observations of EQ-5D-3L from the Health Survey for England 2014 as recommended in the 2022 report from the NICE Decision Support Unit.[48] These were then applied multiplicatively to age-standardise the treatment-specific utilities, such that people over the study baseline age of 63 had a lower baseline utility (**Table 9**). This was applied after the treatment effect, so that the QALYs gained from rehab will gradually reduce over the time horizon.

Age-specific utilities were not varied probabilistically.

Table 9: Utility age multipliers

	EQ-5D-3L		Multiplier used	
age	Females	Males	Females	Males
50	0.859	0.879	1.058	1.045
51	0.856	0.877	1.054	1.042
52	0.853	0.874	1.050	1.039
53	0.850	0.871	1.046	1.036
54	0.846	0.868	1.042	1.032
55	0.843	0.866	1.038	1.029
56	0.839	0.863	1.033	1.026
57	0.836	0.860	1.029	1.022
58	0.832	0.857	1.024	1.019
59	0.828	0.854	1.020	1.015
60	0.824	0.851	1.015	1.011
61	0.821	0.848	1.010	1.008
62	0.817	0.844	1.005	1.004
63	0.812	0.841	1.000	1.000
64	0.808	0.838	0.995	0.996
65	0.804	0.835	0.990	0.992
66	0.800	0.831	0.984	0.988
67	0.795	0.828	0.979	0.984
68	0.791	0.824	0.973	0.980
69	0.786	0.821	0.967	0.976
70	0.781	0.817	0.962	0.972
71	0.776	0.814	0.956	0.967
72	0.771	0.810	0.950	0.963
73	0.766	0.806	0.943	0.959
74	0.761	0.803	0.937	0.954
75	0.756	0.799	0.931	0.950
76	0.751	0.795	0.924	0.945
77	0.745	0.791	0.917	0.941
78	0.740	0.787	0.911	0.936
79	0.734	0.784	0.904	0.931
80	0.728	0.780	0.897	0.927
81	0.723	0.776	0.890	0.922
82	0.717	0.772	0.882	0.917
83	0.711	0.767	0.875	0.912
84	0.705	0.763	0.867	0.907
85	0.698	0.759	0.860	0.903
86	0.692	0.755	0.852	0.898
87	0.686	0.751	0.844	0.893
88	0.679	0.747	0.836	0.888
89	0.672	0.742	0.828	0.883
90	0.666	0.738	0.819	0.877
91	0.659	0.734	0.811	0.872

92	0.652	0.729	0.802	0.867
93	0.645	0.725	0.794	0.862
94	0.638	0.721	0.785	0.857
95	0.630	0.716	0.776	0.852
96	0.623	0.712	0.767	0.847
97	0.616	0.708	0.758	0.841
98	0.608	0.703	0.749	0.836
99	0.601	0.699	0.740	0.831
100	0.593	0.695	0.730	0.826
101	0.586	0.690	0.721	0.821

2.3.4.4. Carer quality of life

The NICE reference case perspective on outcomes states that evaluations should consider all health effects for patients, and, when relevant, carers. Carer health-related quality of life (HRQoL) was identified as an important outcome for this topic and was included in the clinical review protocol, however no evidence was identified. One physio RCT (n=59) that assessed 30 minutes of caregiver-mediated exercise (overseen by a physiotherapist) for 5 days a week to compared to usual care found no clinical important difference in carer quality of life <6 months.[64]

We then referred to the Decision Support Unit (DSU) for possible approaches to infer the impact of higher intensity on carer quality of life. The DSU conducted systematic reviews of economic evaluations that incorporated carer HRQoL in technology assessments (TAs)[54] as well as the general literature.[58] The results from both reviews concluded that a relationship did exist between HRQoL of carers (with most studies using carer-EQ-5D scores) and interventions that improved outcomes. However, there was a lack of stroke-based studies; only one[21] was identified in either review, which reported results that did not meet the criteria for the NICE reference case (cost per 1-unit improvement in the General Health Questionnaire-12 (GHQ-12)). Despite this, the reviews did conclude that including carer HRQoL consistently increased incremental QALYs, meaning that study conclusions of cost-effectiveness may be slightly conservative if full QALY gain is not captured.

Therefore, the quality-of-life search was also used to investigate whether there were any studies that explored carer quality of life in relation to stroke survivors to support incorporating this into the analysis, as measure by either:

- EQ-5D or other utility measures (e.g., 36-Item Short Form Survey (SF-36))
- Clinical outcomes reflecting the disability severity of the stroke survivor (BI, mRS)

The evidence identified was mixed: studies that assessed the relationship between carer HRQol and clinical outcomes for stroke survivors found either no relationship between disability level (BI and mRS) and carergivers (Chen 2010[12], Carod-Artal 2009[10]), while those that did find a relationship were not appropriate to use in a sensitivity analysis as they used quality of life measures other than EQ-5D-3L (Persson, 2015[55], Ogunlana, 2014[51]). Several studies reported carer quality of life decrements based on caregiver burden which could not be incorporated into the analysis. Due to the lack of data suggesting a quantitative relationship with utility and uncertainty towards the magnitude of effect, it was decided that carer quality-of-life could not be incorporated in the model.

2.3.5. Resource use and costs

As mortality does not differ between comparators it was not necessary to incorporate stroke-related costs that will not vary between people that receive higher and lower intensity physiotherapy rehabilitation. Therefore, only differences in costs between groups were included.

2.3.5.1. Additional intervention costs

Additional intervention costs will relate to the delivery of more physiotherapy time. The existing recommendation for rehabilitation is at least 45 minutes, 5 days a week. This analysis is looking at a higher intensity of 1-2 hrs 5 days a week. The additional physiotherapy time per day was based on the weighted average additional time from the clinical studies used to inform the treatment effect (see **Table 10**). This was an additional 45 minutes per day. Rehabilitation duration was based on the weighted average intervention duration from the clinical studies that informed treatment effect. This was 6 weeks (see **Table 8**). Note that this is also used as the time point when treatment effect from the trials is applied.

Table 10: Additional minutes per day with more intensive physiotherapy, by study

Input	N	Additional minutes per day 5 days a week[(a)]	Delivery
Cabanas-Valdes 2016	79	15	Not specified
Han 2013	20	60	Not specified
Jiang 2020	45	30	Not specified
Kim 2016	20	30	Group therapy[(c)]
Klassen 2020	73	56	Not specified
Lee 2012	40	20	Not specified
Rodgers 2019	675	36[(b)]	Individual therapy
Tollar 2021	641	60	Group therapy. 2 physiotherapists for 6-8 people
Weighted average		**45**	

(a) *Based on actual study mean if reported and planned time if not.*
(b) *Usual care was defined as 5 sessions per week with 3 additional sessions given in the more intensive group – additional time is therefore the total additional time divided by 5 (in line with approach taken in the clinical review)*
(c) *The control group received individual physiotherapy while the more intensive group received circuit training classes where at least two people were under the supervision of one physiotherapist who attended all classes.*

While the clinical trials included in the review were in a particular setting, in reality the rehabilitation pathway spans settings and varies by individual patient and by area. Rehabilitation will start during the acute inpatient stay for stroke. People may then either stay in hospital or be discharged via Early Supported Discharge and receive rehabilitation at home via the early supported discharge team, however the rehabilitation they receive should be the same. Following this people may be discharged from rehabilitation or transferred to a community rehabilitation team. The costs reflect average resource use for the overall population across that pathway that might receive more intensive physiotherapy. In addition to the intensity inputs described above, a number of assumptions were required to estimate costs. The following was assumed for costing purposes:

- Of the total rehabilitation duration, the proportion of time spent as an inpatient was estimated using overall rehabilitation duration in the model (6 weeks) and assuming 2.5 weeks would be as an inpatient (based on the mean inpatient stay from national audit data)[59]
- The average number of staff required to deliver more intensive physiotherapy would be 2 in hospital and 1.33 post-discharge (assuming two thirds of people have 1:1 therapy and 1/3 require 2 people), based on committee expert opinion.

- Staffing would be 75% physiotherapist time and 25% rehabilitation assistant time, based on committee expert opinion (this was also assumed in the 2013 CG162 model)[40]
- A physiotherapist would typically be band 6 and a rehabilitation assistant band 3.
- No additional time would be required for documentation, planning and meetings related to the additional rehabilitation (as the number of patients will not increase) based on committee expert opinion.

Staff unit costs of £67/73 per hour of patient-related time for a hospital/community physiotherapist respectively and £43/£44 for a hospital/community rehabilitation assistant were applied in the analysis.

Physiotherapist unit costs are applied from standard national sources[32] that account for the following:

- Average salary for band
- Salary oncosts e.g., pension
- Overheads attribution (management, admin and estates staff; non-staff overheads)
- Capital cost attribution for a physiotherapist
- Average actual working hours (taking account of holiday etc)
- Qualification costs (as reported but with productivity and individual costs excluded in line with an NHS/PSS perspective).
- Time spent not directly related to patients was also included. This was last reported in the 2015 report and was validated with the committee:[14]
  - 73% direct patient activity (time spent with patients or on patient-related tasks) and
  - 27% non-direct activities/other as (includes training, supervision and general non-patient related admin)

Rehabilitation assistant costs are not specifically reported and so have been calculated using the same methods based on an average band 3 salary for another staff group and not including qualification costs (on the basis that a specific degree qualification is not required).

Based on the above data inputs, the average additional cost per week of more intensive physiotherapy was £382.14.

In the probabilistic analysis, the proportion of time spent as an inpatient was parametrised as a beta distribution (so it varied between 0 and 1) using the reported interquartile range for the mean inpatient stay. Unit costs were parametrised as a gamma distribution (so that they were always above zero) assuming a standard error that is 20% of the mean in the absence of uncertainty information. Average staff per session, additional minutes per day and the rehabilitation duration were not varied probabilistically.

2.3.5.2. Hospital length of stay savings

Length of stay savings were not incorporated into the base-case analysis.

The committee highlighted that higher intensity physiotherapy could lead to people meeting functional goals that allow them to be discharged from hospital sooner. Length of stay was not an outcome in the clinical review and so studies in an inpatient setting were checked for this outcome. None of the studies used to inform treatment effect in the model reported length of stay as an outcome.

Three studies in the in the clinical review reported length of stay data.[18, 23, 28] This is shown in **Table 11** and **Figure 8**.

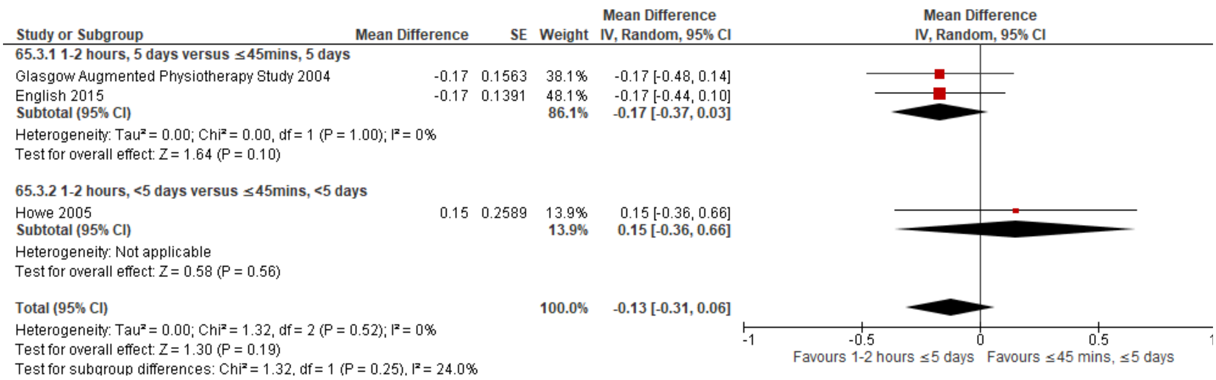
The control group in each trial had different lengths of stay (English 2015[18] (55 days); Glasgow 2004[23] (54 days) and Howe 2005[28] (23.1 days)) and all are longer than the average reported in SSNAP (17.5 days). The committee highlighted that implementation of early supported discharge has meant that length of stay in has reduced and they were concerned whether additional length of stay savings would be achievable. Recommendations for early supported discharge have also been updated in the 2023 guideline, which could lead to changes in the future regarding the length of stay for stroke survivor and thus creating additional uncertainty towards potential length of stay savings. The committee therefore agreed that length of stay savings would not be included in the base-case analysis, although a sensitivity analysis was done including them (see 2.5.7).

Table 11: Length of stay

Study	N	Category in clinical review	Mean Length of stay in hospital		Mean difference
			Lower intensity	Higher intensity	
English 2015[18]	172[(a)]	1-2 hours, 5 days a week versus ≤45 minutes, 5 days a week	55 (SD 49.0) days	46 (SD 38.0) days	• -9.2 days, p=0.23 • 17% lower
Glasgow Augmented Physiotherapy Study 2004[23]	70		54 days (range 8-180)	45 days (range 4-123)	• -9 days, p=0.29 • 17% lower
Howe 2005[28]	35	1-2 hours, <5 days a week versus ≤45 minutes, <5 days a week	23.1 (SD 17.5) days	26.5 (SD 15.7) days	• 3.4 days[(b)] • 15% higher

a) *Initial sample size was 283 but only 172 participants had completed the 4-week assessment for the relevant comparisons.*
b) *Mean difference in length of hospital stay was not statistically significant between groups.*

Figure 8: Length of stay (% reduction)



Abbreviations: CI = confidence interval; SD = standard deviation.

2.3.5.3. Other resource use

The committee also highlighted that there may be downstream cost savings with higher intensity from reducing disability / increasing independence for example from reducing residential or home care requirements and home adaptations.

Three studies assessing more intensive physiotherapy were included as economic evidence in the review, all of which reported limited information on resource use other than direct intervention costs. Chan 2015[11] only incorporated rehabilitation costs into the analysis and assumed that there were no downstream cost differences between groups. Furthermore, the analysis was based on a clinical study included in the sensitivity analysis as both trial arms were less intensive compared to the model comparison (1-2 hours, <5 days per week versus >45 minutes to 1 hour, <5 days per week).

Dohl 2020[17] was a cost-consequence analysis that also had limited applicability as it was based on a clinical study set in Norway[3] with trial arms that do not align with the model (>45 minutes to 1 hour, 7 days per week versus ≤45 minutes, <5 days per week). However, the analysis did collect patient level resource use (GP services, physiotherapy services (private and public), primary care services (home health care and rehab/nursing homes) and hospital care) in the 18-month follow-up period of the trial. The results found no differences between the groups for total costs, or for EQ-5D-5L or Barthel Index scores. Regression results also did not find a strong association between BI score and use of health care services (-0.003 (95% CI: -0.02-0.02; p>0.05), however this is not surprising given that both groups reported high BI scores (96 out of 100) at baseline. Statistical analysis of differences between resource use categories or costs were also not presented.

Fernandez-Garcia 2021[20] was the only study that included the same comparison used in the model (1-2 hours of robot-assisted arm training or enhanced upper limb therapy (EULT), 5 days per week versus >45 minutes to 1 hour of usual care, 5 days per week) as it is based on a clinical study that is used to inform the treatment effect in the base-case analysis.[57] This study was a UK within-trial analysis that collected patient level resource use at baseline and 6 months post-randomisation and found no statistically significant difference in total costs between EULT and usual care (mean difference: £665 (95% CI −£444 to £1,774; p=0.239)). However, when intervention costs were removed, the average cost per participant was higher in the usual care group for all areas of resource use (primary care, social care and medication costs) except for secondary care and other NHS and social services. Resource use estimates were not taken from this study however, as the mean difference in the Barthel Index scores between the higher intensity and usual care groups was smaller (2-point improvement in BI score) than the model estimate (4.86-point improvement in BI score), which suggests that the study population does not sufficiently reflect the overall evidence base.

Given the limitations of the economic evidence results, a targeted literature search was conducted to identify evidence of long-term care cost reductions related to clinical outcomes that could be used in the model. Studies that assessed acute care or hospital costs only were excluded.

A 2017 systematic review[66] was identified that investigated the relationship between costs of stroke and functional outcome, as measured by 90-day mRS scores. Inclusion criteria were studies that focused on reported cost data for an acute stroke population (indirect and/or direct costs i.e., hospital stay, medications, carer costs and loss of workplace earnings) with mRS scores as the health outcome. The analysis found that costs consistently increased with greater severity (increasing modified Rankin Scale score), however it was noted that existing data were limited and only 4 of the 13 included studies reported costs by mRS categories. The inclusion of only acute stroke populations limits the applicability of the results for this model. One UK study identified from the systematic review was Luengo-Fernandez 2013,[39] which reported that annual post-acute (6 months post-stroke) total costs increased as disability severity increased, with mean total costs of £2,135 for patients reporting mRS scores lower than 3, £4,165 for mRS scores of 3 or 4 and £6,324 for those with an mRS of 5. However, the study population was patients with atrial fibrillation with an average age of 80 years, suggesting that there may be additional comorbidities in this population, and the follow-up period was between 2002–2007, which may not be representative of the intensity model cohort or for current standards of care and as such, was not incorporated into the analysis.

Considering that BI mapping was used to estimate QALYs in the analysis, and committee consensus that a person’s level of independence is likely to translate to different care needs (and therefore costs), four studies identified in the targeted literature search that analysed cost differences associated with BI score were explored. Dohl 2020 was one of these studies and was subsequently not incorporated for reasons previously stated in this section, while the second study (Fattore, 2012[19]) did support the association between BI and healthcare costs but could not be used in the model as healthcare costs were reported based on BI categories (mild (BI score: 75-95), moderate (BI score: 46-74) and severe dependence (BI score: 0-45)), opposed BI scores alone.

The remaining two studies identified (O'Connor 2011[49] and Ganesh 2020[22]) were then presented to the committee to decide which should be used to capture downstream cost savings.

Ganesh 2020 investigated the correlation between late improvement (measured by ≥1mRS grades, ≥1 RMI points, and/or ≥2 BI points between 3 and 12 months) and 5-year mortality, institutionalization, and health and social care costs in a population-based cohort of 1-year ischemic stroke survivors in the UK (Oxford Vascular Study 2002-2014). The study used real-world data and conducted high-quality statistical analysis to explore the relationship between improvements in outcomes and costs, specifically focusing on late improvers. The study used data on health and social care resource use from the date of the first stroke in the study period until 5 years post-stroke. The costs included health care costs, institutionalized care (nursing home) costs, and hospital-based rehabilitation, including length of stay. The authors found that for every 1-point improvement in BI (in the late improvers), there was a saving of £2,795 (£4,753 to £837) in 5-year costs (converted to 2021 UK pounds from 2016 US dollars ($)[52]). This results in a cost per week per BI point difference of £10.75, which if applied to the pooled BI difference in the study of around 5, gives a saving of £57 per week (~£3,000 per year if the difference were maintained). Unfortunately, the study did not capture home care costs, which were considered to be a key source of cost impact by the committee.

O'Connor 2011 was a UK cost analysis of consecutive patients following a stroke (n=35) admitted for multidisciplinary rehabilitation to the inpatient rehabilitation unit at the National Demonstration Centre for Rehabilitation at the Leeds Teaching Hospitals NHS Trust over one year. The study found that care costs fell as dependency decreased, and the median estimated costs for care in the community were reduced from £1,900 to £1,100 per week, reporting a saving of £868 per week. The study divided the cost saving per week by the change in BI score to get a cost savings per BI point change, which could then be applied to the pooled difference in BI score in the studies used in the model. This results in a cost of £47 per week per BI point difference, which applied to the pooled BI difference in the model of around 5, gives a saving of £248 per week (~£13,000 per year if the difference were maintained). However, the study is small and not specifically designed to evaluate the cost per change in BI and has not formally quantified this relationship. The costs were also inflated from 1999 prices and were based on London rather than national unit costs.

The Ganesh 2020 and O'Connor 2011 studies provide valuable information on the relationship between late improvement in BI and costs. While the Ganesh 2020 study is a larger study with high-quality statistical analysis, it does not capture home care costs. The O'Connor 2011 study is smaller, and the cost savings are theoretical, but it provides cost savings per BI point difference that are more in line with those that the committee felt are likely to be affected by improvement achieved by more intensive rehabilitation and was therefore used in the base-case analysis.

Turner Stokes 1998[62] provided details about the care assessment tool used in O'Connor (Northwick Park Dependency Scale (NPDS) and Care Needs Assessment (NPCNA) tool), stating that it measures care needs, not care provision, and does not distinguish whether care is provided by family members or outside agencies. The cost savings therefore reflect a situation where all care needs are met and funded by the NHS and PSS. The committee felt that accounting for all care needs was important. However, for the base-case analysis to be in-line with the NICE reference case, costs not incurred by the NHS or PSS should be removed. Information about what this proportion should be was not provided so it was assumed to be 50%. A sensitivity analysis was done with all costs included and different percentages attributable to NHS/PSS costs. Although the paper deriving care needs and costs is potentially out of date, the committee noted that the tool is currently used within the NHS and so the resource use estimates are still considered relevant. Costs have been inflated using 2021 health care specific indices.[32]

In two of the base case analyses post-rehab care savings were included and in the other two base case analyses they were not included. The model assumes that the difference in BI between the groups changes proportionally to the changes in EQ-5D that were modelled for QALY estimation. This meant that in the scenarios where differences in EQ-5D disappearing completely over time were modelled, the downstream cost savings will also disappear over the same period, but in the scenario where EQ-5D differences are assumed to persist long term, differences in downstream costs will also persist.

2.3.5.4. Informal care costs

The committee highlighted that a high proportion of care after stroke is provided by informal carers and if dependence is reduced by high intensity rehabilitation this is likely to also reduce the burden on carers.

NICE does not typically factor in the cost of informal or unpaid care into cost-effectiveness evaluations of health interventions. However, the committee's view was that informal care plays a crucial role in stroke rehabilitation. While a rapid review of the literature did provide evidence suggesting that informal caregiving for stroke survivors is one of the largest cost components for stroke[8, 36], sufficient data was not identified that could allow quantification of changes in these costs with more intensive rehabilitation in the analysis.

2.4. Computations

The model was constructed in Microsoft Excel 2010 and was evaluated by cohort simulation. Time dependency was built in by cross referencing the cohorts age as a respective risk factor for mortality. Utility was also time dependent and was conditional on the age of the population.

Patients start in cycle 0 in an alive health state. Patients moved to the dead health state at the end of each cycle as defined by the mortality rate. The transition probability of dying was determined by applying a standardised mortality ratio (SMR) to age-dependant general population mortality rates from England life tables (ONS life tables for England 2017-19).

The QoL difference between higher and lower intensity physiotherapy (taking into account baseline differences) was the treatment effect. This was based on studies in the clinical review where reported outcomes had been mapped to EQ-5D-3L. The mapped EQ-5D change scores (i.e., change from baseline in the higher intensity and lower intensity groups from each study), were then meta-analysed using the inverse variance approach, alongside the average age and intervention duration. Treatment effect was extrapolated beyond the pooled trial data using two scenarios, due to uncertainty of the treatment effect as most studies included in the analysis didn’t report follow-up beyond 6 weeks: the first assumed a weekly reduction in the EQ-5D mean difference between higher and lower intensity until no difference was seen between the groups i.e., higher intensity speeds up health gains when recovering from stroke. The second applied a weekly reduction to the mean difference for the first 3 months post-intervention before assuming the difference was maintained for the remaining lifetime i.e., higher intensity results in permanent health gains for stroke survivors.

A 1-week cycle length was used to allow physiotherapy rehabilitation costs and treatment effects to be applied by week. Costs were calculated based on average resource use from the trials and were pooled using a weighted average based on the number of participants analysed in the study. Both base-case scenarios were modelled to generate results that incorporated either intervention costs alone or with the assumption that higher intensity physiotherapy produces ongoing care cost savings a on weekly basis stemming from a per-point reduction in BI scores.

Mortality rates were converted into transition probabilities for the respective cycle length (1 week) before inputting into the Markov model. The annual probability of death was converted into a rate, before being converted into a probability appropriate for the cycle length. The above conversions were done using the following formulae:

$Selected\ rate\ (r) = \frac{-\ln(1-P)}{t}$	Where *P*=probability of event over time *t* *t*=time over which probability occurs (1 year)
$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where *r*=selected rate *t*=cycle length (1 week)

Life years for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time spent (i.e., 1 week or 0.02 years) in the alive state of the model was weighted by a utility value that was dependent on the cycle, the long-term utility assumption being employed and the treatment group. A half-cycle correction was applied. QALYs were then discounted to reflect time preference (discount rate = r). QALYs during the first cycle were not discounted. The total discounted QALYs was the sum of the discounted QALYs per cycle.

Costs per cycle, C(t), were calculated in the same way as QALYs. In the base case, rehabilitation costs were applied to the first 6 cycles only. For scenarios that assumed ongoing care cost-savings, this was applied in cycle 7 and beyond. Costs were discounted to reflect time preference (discount rate 3.5% per year) in the same way as QALYs using the following formula:

Discounting formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

2.5. Sensitivity analyses

2.5.1. Cohort settings

2.5.1.1. Cohort age

Sensitivity analyses using a cohort start age of 50, 60, 70, 80 and 90 years was done to explore the impact of cohort age in the analysis.

2.5.1.2. Based on clinical studies used to inform treatment effects

A sensitivity analysis was done where the population entering the model was assigned a start age of 63 years and 41% female based on a weighted average from the clinical studies used to inform treatment effects instead of real-world data from the national stroke audit in people that received physiotherapy (start age 75 years for women and 71 years for men, and 48% women).

2.5.2. Mortality

2.5.2.1. Lower SMRs

Sensitivity analysis was done where SMRs were reduced by 25% and 50% to reflect that outcomes after stroke may have improved over time.

2.5.3. Clinical studies used to inform treatment effect

12 studies out of the 32 included in the clinical review for the >1 to 2 hours physiotherapy category had data that could be used to inform QALY estimation for economic evaluation (that is EQ-5D or BI). The 8 studies comparing >1 to 2 hours physiotherapy 5 days a week to >45 minutes to 1 hour, 5 days a week were used in the base case analysis. A sensitivity analysis was done using all 12 studies.

The additional study details and outcome available to map to EQ-5D-3L for each study are summarised in **Table 12**.

Table 12: Additional clinical studies included in sensitivity analysis

Study	• N • Mean age • % female	Setting	Intervention	Last follow-up	EQ-5D/ BI	Area of focus	Time since stroke(a)	Stroke severity	Intervention intensity detail	Control arm detail	CEA?
Askim 2010[4]	• N=62 • 77 yrs • 53%	Mixed (inpatient and post discharge settings) (Norway)	4 weeks	26 weeks	BI	Mixed: Upper limb and Lower limb, general physical function, functional independence	Subacute stroke	Not stated/ unclear	Three additional sessions each week for the first 4 weeks after discharge, followed by 1 additional session every week for the next 8 weeks, plus home exercises to be performed twice a day, 6 days a week	Physiotherapy emphasizing mobilization	No
Cooke 2010[13]	• N=109 • 63 yrs • 40%	Inpatient (UK)	6 weeks	12 weeks	EQ-5D	Lower limb	Stroke (not specified)	Not stated/ unclear	Additional therapy (two different types of additional therapy for the same time period)	Usual care (conventional therapy only - time period likely 1 hour, 4 days a week)	Chan, 2015[11] (CUA)
Glasgow Augmented Physiotherapy Study 2004[23]	• N=109 • 68 yrs • 41%	Inpatient (Scotland)	4 weeks	3 months; 6 months	BI, EQ-5D	Mixed	Subacute stroke	Not stated/ unclear	Conventional physiotherapy and additional therapy	Conventional physiotherapy	No
Yoo 2013[67]	• N=109 • 50 yrs • 41%	Unclear setting (South Korea)	6 weeks	6 weeks	BI	Upper limb	Chronic stroke	not stated/ unclear	Robot assisted therapy (90 minutes, three times a week, six weeks)	Conventional therapy (60 minutes, three times a week, six weeks)	No

Abbreviations: BI = Barthel index; CEA = cost-effectiveness analysis; CUA = cost-utility analysis (QALYs as outcome measure); EQ-5D-5L – Euroqol 5 dimensions – 5 level version; SD = standard deviation
(a)Subacute stroke = 7 days – 6 months; Chronic stroke >6 months

Mapped EQ-5D-3L data from these studies was incorporated into the pooled estimate of end of intervention treatment effect. The revised pooled data is shown in **Table 13**.

Table 13: Sensitivity analysis: End of intervention pooled EQ-5D-3L treatment effect

	Mean difference in CFBL (H – L)	Mean difference inverse variance weight[(a)]	Intervention duration (weeks)	Mean age	BL	CFBL-L
Studies included in base-case analysis						
Cabanas-Valdes 2016	0.1317	8.4%	5	76	0.131	0.251
Han 2013	-0.08	3.0%	6	53	0.384	0.236
Jiang 2020	0.032	9.9%	2	64	0.448	0.007
Kim 2016	-0.066	2.9%	4	66	0.366	0.279
Klassen 2020	-0.007	4.7%	4	57	0.476	0.278
Lee 2012	0.039	7.5%	4	54	0.400	0.042
Rodgers 2019	0.029	15.0%	12	61	0.222	0.047
Tollar 2021	0.1010	15.7%	5	67	0.363	0.166
Additional studies included in sensitivity analysis						
Askim 2010	-0.002	8.7%	4	77	0.473	0.161
Cooke 2010	0.072	4.8%	6	68	0.245	0.021
Glasgow 2004	-0.050	9.1%	4	68	0.371	0.183
Yoo 2013	0.003	10.3%	6	50	0.544	0.006
Pooled[(b)]	**0.064**		**6**	**65**	**0.34**	**0.13**

Abbreviations: BL = base line; CFBL = change from baseline; EQ-5D-3L = EuroQol 5-dimension – 3 level version; H = higher intensity; L = lower intensity.

a) Weights calculated from inverse variance (random effects assumption) of EQ-5D-3L mean difference in CFBL with higher intensity compared to lower intensity physiotherapy.

b) Pooling is based on a weighted average using weights calculated for treatment effect based on inverse variance.

Two of the additional studies did not show a gain in EQ-5D-3L at the end of the intervention (Askim and Glasgow) and so were not considered useful to inform how differences changed post-rehabilitation (as in the base case analysis). Cooke had a follow-up point at 12 weeks (6 weeks after the end of the study intervention) but there was high drop out in one of higher intensity groups and a published CUA based on this trial did not use this data for this reason and so the same approach has been taken here. Therefore, the base case model inputs are used after the end of the intervention in this sensitivity analysis.

2.5.4. Post-intervention treatment effect and extrapolation

2.5.4.1. Shorter time horizon

Due to the uncertainty towards extrapolating effects in the longer term, sensitivity analyses were done with shorter time horizons:

- An 18-week time horizon was selected to reflect the mean intervention time (6 weeks) and the 12-week post-rehabilitation follow-up period, based on Rodgers 2019.[57]
- A 2-year time horizon was selected as this was used in previous economic models and required less extrapolation of the model inputs than the base case assumptions.

2.5.4.2. Percentage change post-intervention

The analyses were rerun using a percentage change (rather than an absolute change) per week in the mean utility difference post-rehab with higher and lower intensity physiotherapy based on data from Rodgers 2019. This results in a 5% reduction per week.

2.5.5. Rehabilitation costs

2.5.5.1. Proportion of time rehabilitation assistant versus physiotherapist

A sensitivity analysis was done to increase the proportion of rehabilitation assistants delivering physiotherapy in the community to 50% compared with 25% in the base case.

2.5.5.2. Staff costs

A sensitivity analysis was done where staff unit costs were increased to account for potentially higher costs associated with 7-day rehabilitation services, as shown in **Table 14** below.

Note that it is unclear to what extent the unit costs in the base case already include overtime payments.

Table 14: Calculations for the estimated increase in salary costs for 7-day provision

	Days per year[(a)]		Pay rate	
Total	260	100%	**Band 4-9**	**Band 3**
Saturday	12	5%	130%	135%
Sunday	12	5%	160%	169%
Week	236	91%	100%	100%
Weighted salary uplift			104%	105%

a) *Assuming staff work one weekend a month with enhanced payments*

2.5.5.3. Number of staff required to deliver more intensive physiotherapy post-discharge

The average number of staff required to deliver more intensive physiotherapy post-discharge was increased from to 1.5 per patient, as 1.33 was included in the base-case analysis based on committee expert opinion.

2.5.5.4. Rehabilitation duration

A sensitivity analysis was done where the duration of rehabilitation was set to 10 weeks to account for costs and treatment effects associated with clinical studies that reported a longer treatment duration than the 6-week period applied in the base-case analysis.

2.5.6. Ongoing costs

2.5.6.1. Proportion of care costs funded by NHS/PSS

A sensitivity analysis was done with all costs included where different percentages (25% and 100%) of ongoing care costs were attributable to NHS/PSS costs. This was done because the study used to incorporate post-rehabilitation care cost savings did not distinguish NHS costs from care provided by family members or outside agencies.

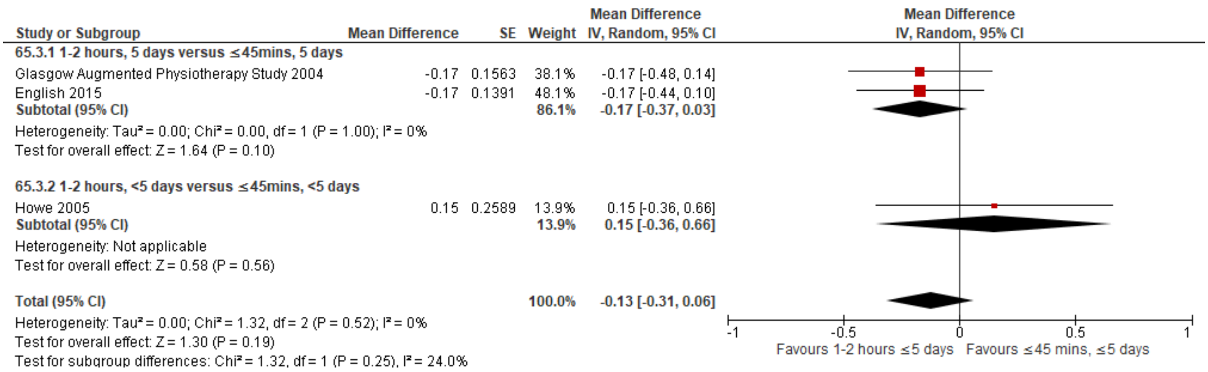
2.5.6.2. Alternative data about longer term costs

A sensitivity analysis was done where cost savings per unit reduction in BI from Ganesh 2020[22] were applied instead of O'Connor 2011.[49]

2.5.7. Length of stay reduction

A sensitivity analysis was done including a length of stay saving based on studies that had a 1-2 hours per day high intensity group. Because the studies had longer average length of inpatient stay than being used in the model, a percent reduction was applied rather than the absolute reduction from the trials (see **Figure 9**). A reduction of 17% was applied using the data from the category most close to that being considered in the model with rehabilitation 5 days a week. This reduction was then applied to the mean cost of inpatient rehabilitation, estimated using the mean number of weeks applied in the base-case analysis (based on the mean inpatient stay from national audit data)[59] and the cost per day in hospital (£266) (taken from the 2022/23 National Tariff Payment System (NTPS)[47]), which produced a total cost saving of £791 for higher intensity physiotherapy.

Figure 9: Length of stay (% reduction)



Abbreviations: CI = confidence interval; SD = standard deviation.

2.6. Model validation

The model was developed in consultation with the committee; model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the Guideline Development Team – National Guideline Centre; this included systematic checking of many of the model calculations.

2.7. Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$ Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	Cost effective if: • ICER < Threshold

2.8. Interpreting results

NICE sets out the principles that committees should consider when judging whether an intervention offers good value for money.[41, 42, 45] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

3. Results

3.1. Base case

The deterministic and probabilistic base case results are presented in Table 15 and Table 16. Probabilistic results are also presented graphically in Table 15: Base-case analysis: mean costs and QALYs per person (deterministic analysis)

Analysis	Mean cost difference (H vs L)	Mean QALY difference (H vs L)	Incremental cost per QALY gained
Scenario 1: difference diminishes at an absolute rate seen in trials until no difference			
a) Intervention costs only	£2,286	0.02	£127,266
b) With post-rehab care savings	£452	0.02	£25,180
Scenario 2: difference diminishes up to 12 weeks post-intervention, then difference is maintained for lifetime			
a) Intervention costs only	£2,286	0.21	£10,841
b) With post-rehab care savings	-£24,201	0.21	Higher dominant

Abbreviations: H = higher intensity physiotherapy; L = lower intensity physiotherapy; QALY= quality-adjusted life year.

Table 16: Base-case analysis: mean costs and QALYs per person (probabilistic analysis)

Analysis	Mean cost difference (H-L)	Mean QALY difference (H-L)	Incremental cost effectiveness ratio (ICER)	% simulations H cost-effective (£20K/QALY)
Scenario 1: difference diminishes at an absolute rate seen in trials until no difference				
a) intervention costs only	£2,279	0.05	£48,539	7%
b) with post-rehab care savings	-£3,312	0.05	Higher dominant	76%
Scenario 2: difference diminishes up to 12 weeks post-intervention, then difference is maintained for lifetime				
a) intervention costs only	£2,286	0.24	£9,676	83%
b) with post-rehab care savings	-£29,487	0.24	Higher dominant	96%

Abbreviations: H = higher intensity physiotherapy; L = lower intensity physiotherapy; QALY= quality-adjusted life year.

Figure 10. Results are presented for four base case scenarios:

- 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),
  - a) intervention costs only
  - b) with post-rehabilitation care cost savings
- Scenario 2 (3-month weekly reduction applied before the difference was maintained, meaning higher intensity leads to permanent health gains).
  - a) intervention costs only
  - b) with post-rehabilitation care cost savings

In Scenario 1a, higher intensity physiotherapy was not cost-effective compared to lower intensity, as the incremental cost effectiveness ratio (ICER) for the deterministic analysis was £127,266 per QALY gained and £48,539 in the probabilistic analysis, with an 7% probability of being cost-effective at a £20,000 NICE threshold. When post-rehabilitation care cost-savings were incorporated Scenario 1b), higher intensity physiotherapy was remained not cost-effective in the deterministic analysis (ICER of £25,180) but was dominant in the probabilistic analysis (lower costs and improved quality of life) when compared to lower intensity physiotherapy, with a 76% probability of being cost-effective.

The results showed that with Scenario 2a, higher intensity physiotherapy was cost-effective for both the deterministic (ICER of £10,841) and probabilistic analyses (ICER of £9,676), with an 83% probability of being cost-effective compared to lower intensity physiotherapy. Moreover, higher intensity physiotherapy was dominant compared to lower intensity following the inclusion of post-rehabilitation care cost-savings in both the deterministic and probabilistic analyses, with a 96% probability of being cost-effective.

Table 15: Base-case analysis: mean costs and QALYs per person (deterministic analysis)

Analysis	Mean cost difference (H vs L)	Mean QALY difference (H vs L)	Incremental cost per QALY gained
Scenario 1: difference diminishes at an absolute rate seen in trials until no difference			
a) Intervention costs only	£2,286	0.02	£127,266
b) With post-rehab care savings	£452	0.02	£25,180
Scenario 2: difference diminishes up to 12 weeks post-intervention, then difference is maintained for lifetime			
a) Intervention costs only	£2,286	0.21	£10,841
b) With post-rehab care savings	-£24,201	0.21	Higher dominant

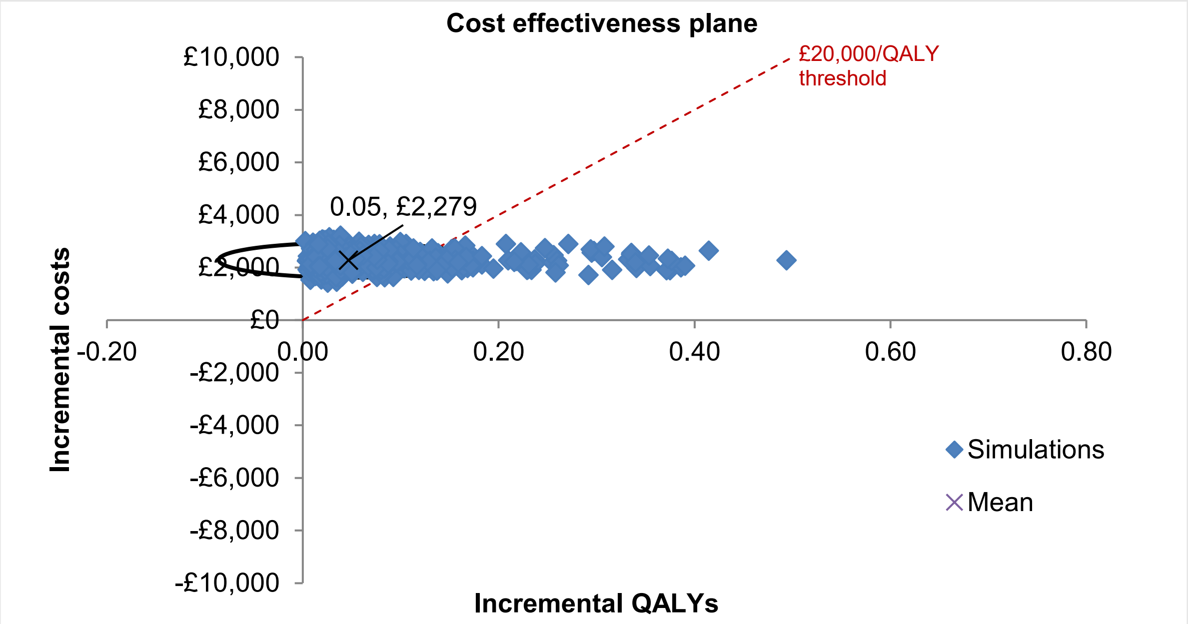
Abbreviations: H = higher intensity physiotherapy; L = lower intensity physiotherapy; QALY= quality-adjusted life year.

Table 16: Base-case analysis: mean costs and QALYs per person (probabilistic analysis)

Analysis	Mean cost difference (H-L)	Mean QALY difference (H-L)	Incremental cost effectiveness ratio (ICER)	% simulations H cost-effective (£20K/QALY)
Scenario 1: difference diminishes at an absolute rate seen in trials until no difference				
a) intervention costs only	£2,279	0.05	£48,539	7%
b) with post-rehab care savings	-£3,312	0.05	Higher dominant	76%
Scenario 2: difference diminishes up to 12 weeks post-intervention, then difference is maintained for lifetime				
a) intervention costs only	£2,286	0.24	£9,676	83%
b) with post-rehab care savings	-£29,487	0.24	Higher dominant	96%

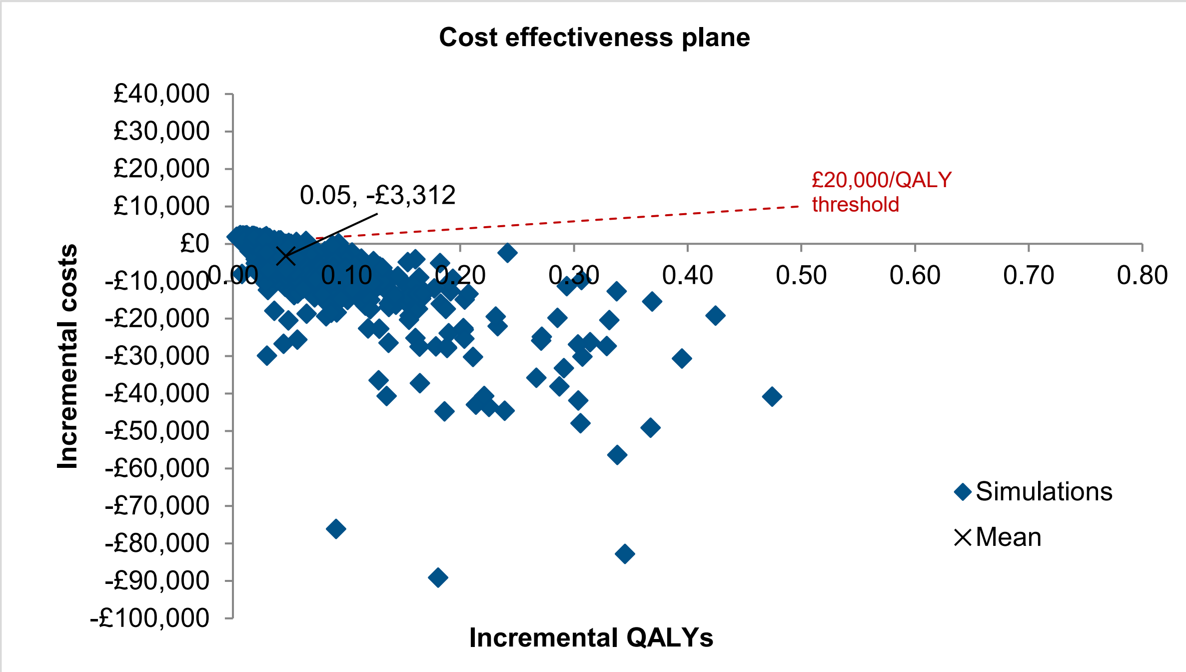
Abbreviations: H = higher intensity physiotherapy; L = lower intensity physiotherapy; QALY= quality-adjusted life year.

Figure 10: Base case results (Scenario 1a with only intervention costs applied): cost-effectiveness plane for higher intensity vs lower intensity



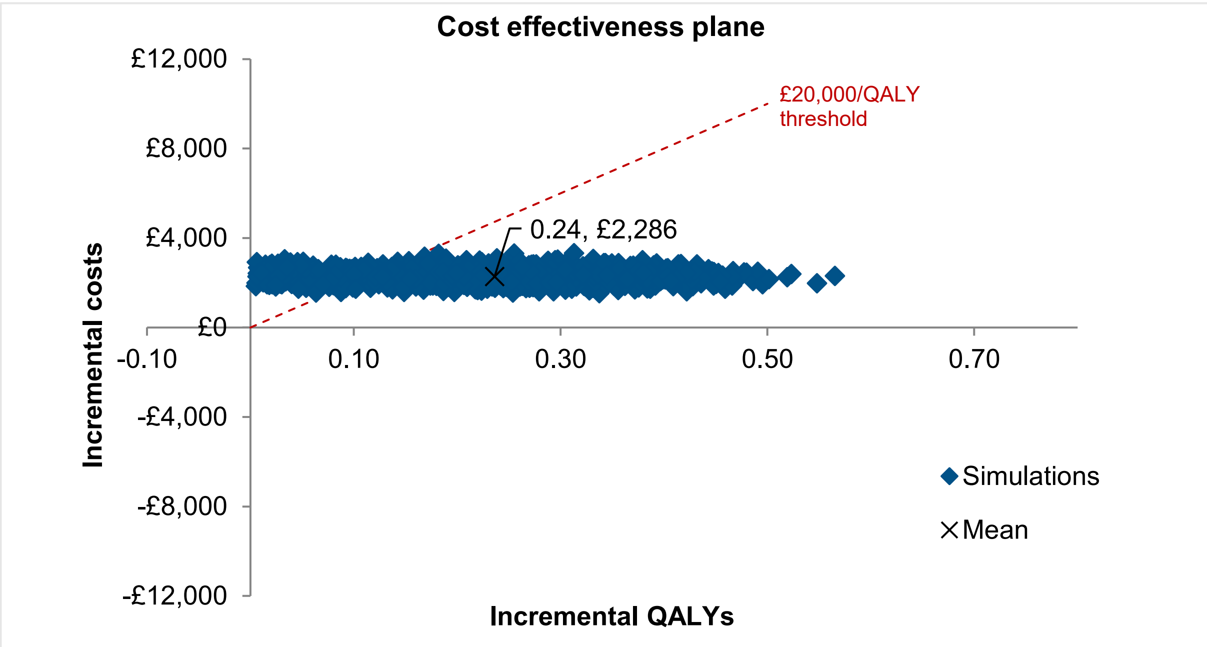
Scenario 1a: weekly reduction of EQ-5D mean difference until no difference between was seen between higher and lower intensity groups, meaning higher intensity leads to faster stroke recovery.

Figure 11: Base case results (Scenario 1b with post-rehabilitation cost savings): cost-effectiveness plane for higher intensity vs lower intensity



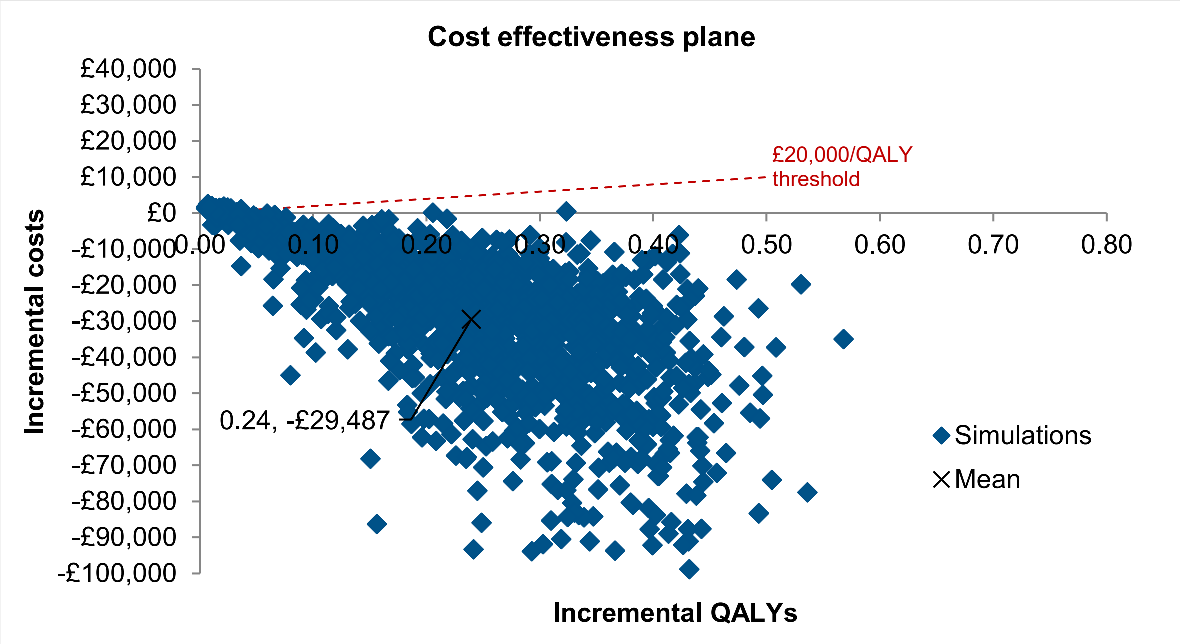
Scenario 1b: weekly reduction of EQ-5D mean difference until no difference between was seen between higher and lower intensity groups, meaning higher intensity leads to faster stroke recovery.

Figure 12: Base case results (Scenario 2a with only intervention costs applied): cost-effectiveness plane for higher intensity vs lower intensity



Scenario 2a: (3-month weekly reduction applied before the difference was maintained, meaning higher intensity leads to permanent health gains).

Figure 13: Base case results (Scenario 2b with post-rehabilitation cost savings): cost-effectiveness plane for higher intensity vs lower intensity



Scenario 2b: 3-month weekly reduction applied before the difference was maintained, meaning higher intensity leads to permanent health gains.

3.1.1. Differences between deterministic and probabilistic results

The mean costs and QALYs from the probabilistic analysis are usually considered the best estimate for use in decision making. Deterministic and probabilistic results are often very similar (as the mean of each model inputs is the point estimate). However, this is not always the case, if models are non-linear.

The deterministic analysis (using the input point estimates and not the uncertainty around them) is also calculated and it is routine to consider if these are similar, and if not why, to ensure there are no programming errors in the model.

Comparing Table 15 with Table 16, the QALY gains are larger in the probabilistic analyses than in the deterministic analyses, particularly in Scenario 1a and 1b, where the utility gain converges to zero over time. The post-rehab cost savings are also greater in the probabilistic analyses because they are explicitly correlated with the utility gain. In the case of Scenario 1B this meant that higher intensity cost more than £20,000 per QALY in the deterministic analysis but was dominant in the probabilistic analysis.

The reason that the probabilistic QALYs are larger seems to be due to:

a) When the absolute change is low the improvement in QALYs is pushed off into the future, but this is discounted (creating a non-linearity).
b) Also, when the absolute change is very low there isn't enough cycles in the model for convergence of utility to take place and therefore for some simulations there remains a significant improvement in utility over the whole lifetime.

The probabilistic results should take precedence over the deterministic ones because:

- Discounting is a fundamental part of the NICE reference case.
- It is plausible that the utilities don't converge.
- The assumption about the absolute change in the analysis is already conservative by using a gamma distribution for the absolute change. This constrains it in favour of less intensive therapy even though the confidence interval crossed zero.

Therefore, the sensitivity analyses that follow are all calculated probabilistically.

3.2. Sensitivity analyses

A number of sensitivity analyses were conducted and are described in section 2.5, with **Table 17Table 20** below presenting the results. Sensitivity analyses were applied to each of the 4 base-case scenarios and each one was conducted probabilistically.

The results for Scenario 1a (**Table 17**) remained not cost-effective for higher intensity physiotherapy across all sensitivity analyses, which was unsurprising considering that this was the most conservative option out of the base-case scenarios.

The results were also robust for Scenario 2a, as Table 17 showed that higher intensity physiotherapy remained cost-effective across most sensitivity analyses with the exception of

- an initial cohort age of 90 years (ICER of £38,472 per QALY gained),
- the 18-week time horizon (£181,443 per QALY gained) and
- 2-year time horizon (£36,382 per QALY gained).

This was expected as an older model cohort and shorter time horizons prevent the inclusion of long-term utility benefits.

For Scenario 1b (Table 18), higher intensity physiotherapy remained dominant compared to usual care for most sensitivity analyses: exceptions to this included:

- an 18-week time horizon, which resulted in higher intensity being not cost-effective (£73,059 per QALY gained),
- alternative data for post-rehabilitation care cost savings from Ganesh 2020 suggested that higher intensity had a 43% probability of being cost-effective compared to lower intensity at a £20,000 threshold (£233 per QALY gained).

The probability of higher intensity physiotherapy being cost-effective was also reduced to 48% when the proportion of post-rehabilitation care cost savings incurred by the NHS/PSS was set to 25% (however these costs would still be incurred by the individual or their families despite their exclusion from this analysis).
Table 20 presents the results for Scenario 2, where higher intensity physiotherapy remained dominant compared to lower intensity for all scenarios, apart from when an 18-week time horizon was applied (ICER of £83,543).

Table 17: Sensitivity analyses for Scenario 1a

Analysis	Mean cost difference (H vs L)	Mean QALY difference (H vs L)	Incremental cost per QALY	Probability CE @£20K
Scenario 1: difference diminishes at an absolute rate seen in trials until no difference (with intervention costs only)				
Base case	£2,279	0.05	£48,539	7%
Cohort settings				
Cohort age 63 and 41% female based on clinical studies	£2,300	0.05	£44,602	7%
Cohort initial age = 50 years	£2,296	0.07	£34,727	10%
Cohort initial age = 60 years	£2,277	0.06	£39,074	10%
Cohort initial age = 70 years	£2,292	0.05	£45,070	10%
Cohort initial age = 80 years	£2,283	0.04	£59,417	5%
Cohort initial age = 90 years	£2,229	0.03	£86,417	0%
SMRs 25%	£2,290	0.05	£45,636	9%
SMRS 75%	£2,296	0.06	£38,694	9%
Treatment effect				
Alternative clinical data: all PT studies where the intervention was >1 to 2 hours physiotherapy	£2,283	0.06	£37,588	10%
Difference diminishes at constant % instead of constant absolute change	£2,281	0.05	£42,903	6%
Time horizon				
18-week (6+12) time horizon	£2,275	0.01	£180,998	0%
2-year time horizon	£2,281	0.03	£66,484	2%
Costs				
50% RA in community	£2,164	0.05	£45,943	9%
Higher staff costs (PT 104%/ RA 105%)	£2,398	0.05	£49,408	7%
Average number of staff required: 2 inpatient / 1.5 post-charge	£2,436	0.05	£52,767	7%
Length of stay reduction applied	£1,495	0.05	£30,788	20%
Rehabilitation duration				
10 weeks	£3,801	0.05	£77,724	3%

Abbreviations: CE @£20K = cost-effective at £20,000 per QALY gained; PSS= personal social services; PT= physiotherapist; QALY= quality-adjusted life year; RA= rehabilitation assistants; SMR= standardised mortality ratio

Table 18: Sensitivity analyses for Scenario 1b

Analysis	Mean cost difference (H vs L)	Mean QALY difference (H vs L)	Incremental cost per QALY gained	Probability CE @£20K
Scenario 1a- Difference diminishes until no difference (with post-rehabilitation cost savings)				
Base case	-£3,401	0.05	Higher dominant	76%
Cohort settings				
Cohort age 63 and 41% female based on clinical studies	-£4,168	0.06	Higher dominant	84%
Cohort initial age = 50 years	-£4,841	0.07	Higher dominant	88%
Cohort initial age = 60 years	-£4,067	0.05	Higher dominant	85%
Cohort initial age = 70 years	-£3,371	0.05	Higher dominant	78%
Cohort initial age = 80 years	-£2,760	0.04	Higher dominant	70%
Cohort initial age = 90 years	-£1,340	0.03	Higher dominant	59%
SMRs 25%	-£3,645	0.05	Higher dominant	78%
SMRS 75%	-£5,941	0.06	Higher dominant	88%
Treatment effect				
Alternative clinical data: all PT studies where the intervention was >1 to 2 hours physiotherapy	-£6,500	0.06	Higher dominant	86%
Difference diminishes at constant % instead of constant absolute change	-£3,930	0.05	Higher dominant	86%
Time horizon				
18-week (6+12) time horizon	£916	0.01	£73,059	14%
2-year time horizon	-£1,757	0.03	Higher dominant	62%
Costs				
50% RA in community	-£3,135	0.05	Higher dominant	78%
Higher staff costs (PT 104%/ RA 105%)	-£3,571	0.05	Higher dominant	77%
Average number of staff required: 2 inpatient / 1.5 post-charge	-£3,150	0.05	Higher dominant	74%
Length of stay reduction applied	-£4,749	0.05	Higher dominant	89%
Care costs NHS/PSS 25%	-£613	0.05	Higher dominant	48%
Care costs NHS/PSS 100%	-£8,373	0.04	Higher dominant	93%
Alternative post-rehabilitation savings data (Ganesh)	£10	0.05	£223	43%
Rehabilitation duration				
10 weeks	-£1,795	0.05	Higher dominant	50%

Abbreviations: CE @£20K = cost-effective at £20,000 per QALY gained; PSS= personal social services; PT= physiotherapist; QALY= quality-adjusted life year; RA= rehabilitation assistants; SMR= standardised mortality ratio

Table 19: Sensitivity analyses for Scenario 2a

Analysis	Mean cost difference (H vs L)	Mean QALY difference (H vs L)	Incremental cost per QALY gained	Probability CE @£20K
Scenario 2a - Difference diminishes up to 12 weeks post-intervention, then difference maintained for lifetime (with intervention costs only)				

Base case	£2,286	0.24	£9,676	83%
Cohort settings				
Cohort age 63 and 41% female based on clinical studies	£2,302	0.388	£5,926	90%
Cohort initial age = 50 years	£2,295	0.585	£3,925	91%
Cohort initial age = 60 years	£2,273	0.426	£5,340	90%
Cohort initial age = 70 years	£2,283	0.286	£7,981	87%
Cohort initial age = 80 years	£2,282	0.145	£15,765	67%
Cohort initial age = 90 years	£2,249	0.058	£38,472	3%
SMRs 25%	£2,293	0.272	£8,426	87%
SMRS 75%	£2,287	0.516	£4,435	91%
Treatment effect				
Alternative clinical data: all PT studies where the intervention was >1 to 2 hours physiotherapy	£2,290	0.51	£4,499	91%
Difference diminishes at constant % instead of constant absolute change	£2,284	0.41	£5,638	80%
Time horizon				
18-week (6+12) time horizon	£2,291	0.01	£181,443	0%
2-year time horizon	£2,298	0.06	£36,382	4%
Costs				
50% RA in community	£2,151	0.24	£9,000	85%
Higher staff costs (PT 104%/ RA 105%)	£2,373	0.24	£9,939	83%
Average number of staff required: 2 inpatient / 1.5 post-charge	£2,425	0.23	£10,386	83%
Length of stay reduction applied	£1,502	0.24	£6,274	89%
Rehabilitation duration				
10 weeks	£3,820	0.23	£16,434	64%

Abbreviations: CE @£20K = cost-effective at £20,000 per QALY gained; PSS= personal social services; PT= physiotherapist; QALY= quality-adjusted life year; RA= rehabilitation assistants; SMR= standardised mortality ratio

Table 20: Sensitivity analyses for Scenario 2b

Analysis	Mean cost difference (H vs L)	Mean QALY difference (H vs L)	Incremental cost per QALY gained	Probability CE @£20K
Scenario 2b - Difference diminishes up to 12 weeks post-intervention, then difference is maintained for lifetime (with post-rehabilitation cost savings)				
Base case	-£29,487	0.24	Higher dominant	96%
Cohort settings				
Cohort age 63 and 41% female based on clinical studies	-£47,624	0.39	Higher dominant	98%
Cohort initial age = 50 years	-£70,338	0.58	Higher dominant	99%
Cohort initial age = 60 years	-£49,255	0.43	Higher dominant	98%
Cohort initial age = 70 years	-£35,066	0.28	Higher dominant	97%
Cohort initial age = 80 years	-£16,469	0.14	Higher dominant	95%
Cohort initial age = 90 years	-£6,091	0.06	Higher dominant	91%
SMRs 25%	-£32,463	0.27	Higher dominant	97%
SMRS 75%	-£63,991	0.51	Higher dominant	98%
Treatment effect				
Alternative clinical data: all PT studies where the intervention was >1 to 2 hours physiotherapy.	-£63,328	0.52	Higher dominant	98%
Difference diminishes at constant % instead of constant absolute change	-£45,642	0.39	Higher dominant	97%
Time horizon				
18-week (6+12) time horizon	£1,035	0.01	£83,543	13%
2-year time horizon	-£5,861	0.07	Higher dominant	91%
Costs				
50% RA in community	-£28,907	0.24	Higher dominant	97%
Higher staff costs (PT 104%/ RA 105%)	-£28,185	0.24	Higher dominant	97%
Average number of staff required: 2 inpatient / 1.5 post-charge	-£29,397	0.23	Higher dominant	96%
Length of stay reduction applied	-£29,783	0.24	Higher dominant	98%
Care costs NHS/PSS 25%	-£13,544	0.24	Higher dominant	94%
Care costs NHS/PSS 100%	-£59,838	0.23	Higher dominant	99%
Alternative post-rehabilitation savings data (Ganesh)	-£10,567	0.24	Higher dominant	94%
Rehabilitation duration				
10 weeks	-£28,516	0.23	Higher dominant	94%

Abbreviations: CE @£20K = cost-effective at £20,000 per QALY gained; PSS= personal social services; PT= physiotherapist; QALY= quality-adjusted life year; RA= rehabilitation assistants; SMR= standardised mortality ratio

4. Discussion

4.1. Summary of results

An original cost effectiveness analysis compared intensive therapy (1 to 2 hours, 5 days a week) with less intensive therapy (<45 minutes, 5 days a week) for the following scenarios:

- Scenario 1 The difference in utility disappears over time.
  - a) intervention costs only
  - b) with post-rehabilitation care cost savings
- Scenario 2 The difference in utility is maintained.
  - a) intervention costs only
  - b) with post-rehabilitation care cost savings

In each of these base case analyses, higher intensity physiotherapy was either cost-effective or dominant compared to lower intensity physiotherapy, with the exception of the most conservative scenario, 1a, (where £48,539 per QALY gained was the probabilistic result).

The results of each scenario were robust to changes in other model parameters except that:

- when there was a 2-year time horizon, both QALY gains and cost savings were reduced, and high intensity was no longer cost effective in Scenario 2a;
- when there was an 18-week time horizon, high intensity was no longer cost effective in Scenarios 1b, 2a and 2b; and
- if the cohort was aged 90, higher intensity was no longer cost effective in Scenario 2a.

4.2. Limitations and interpretation

Limited availability of evidence usable for cost-effectiveness analysis

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, respectively. Studies assessing other forms of rehabilitation (multi-disciplinary team-delivered, speech and language, occupational, and cognitive therapy) did not collect sufficient data that could be incorporated into an economic analysis.

Differences between trials informing evidence of effect

The issue of whether more intensive therapy provides better outcomes for patients a critical one for stroke rehabilitation. However, the evidence available to inform this question was limited. The committee discussed at length how best to gather clinical evidence to help inform this and agreed that the best strategy was to take an inclusive approach in order to try and maximise the evidence available to help inform this question. The review therefore included any study that compared more physiotherapy time with less irrespective of what happened during this time and irrespective of setting. This evidence has therefore been used in this cost-effectiveness analysis as our best available estimate of the treatment effect of more intensive physiotherapy rehabilitation. However, this means that the studies used vary in a number of ways:

- Setting: 4 studies[9, 24, 31, 34] assessed interventions conducted in inpatients rehabilitation settings, while 2 studies[57, 61] were based in outpatient clinics and one study did not specify the rehabilitation setting[37]
- Time since stroke and stroke severity: most studies reported that participants were in the subacute phase of stroke (7 days to 6 months), however Rodgers was based on a

chronic stroke population. People in the subacute phase may require more care which would impact the intervention costs.

- Interventions used: the clinical review included any study deemed to have more physiotherapy, even for specific intervention were provided in that time. For instance, Rodgers 2019 included robot-assisted arm training, while Tollar 2021 assessed exergame sessions that required the use of an Xbox. However, these costs were not incorporated into the analysis.
- Delivery, frequency, and duration of intervention: 4 of the 8 clinical studies included in the review did not specify whether the intervention was delivered on an individual or group-basis (see **Table 10**), which creates uncertainty as group-based interventions will incur lower staff costs. 2 studies did specify that that they were group-based while another (Rodgers, 2019) specified that it was delivered to participants individually. This study also reported that additional time for high intensity was not spread evening over week was 3 additional sessions per week over usual care.

Uncertainty about long term effects

A crucial issue for interpreting this analysis is what happens in the long term, specifically, whether more intensive rehabilitation leads to permanent differences that persist a lifetime or simply speed up recovery. The clinical study included in the model that reported the longest follow-up period available was 6 months,[57] which was 3 months after the end of the study intervention. This showed a diminishing difference between the more and less intensive groups but there remained a difference at the last follow-up. The committee discussed this issue in detail and agreed that it was simply unknown whether the treatment effect would continue to diminish or be maintained. This is a key area of uncertainty for the study conclusions as Scenarios 1 and 2 reported different results when only intervention costs were included, which was another area of uncertainty in the model.

Lack of evidence about effects on carers

Effects on carers have not been captured in this analysis. The committee highlighted that the burden on carers is high and that interventions that could improve independence of the person who has had a stoke also had the potential to reduce this burden. Evidence about this was sought in the clinical review but none was available and so this potential effect is not captured in the analysis. Evidence was also sought about the relationship between the disability of the person who has had a stroke and carer quality of life. However, evidence was mixed about whether there was a relationship, and no studies were identified that could be used to model the impact in the cost-effectiveness analysis.

Limitations in evidence about the effects on length of stay

The committee agreed that higher intensity physiotherapy was likely to lead to people meeting the functional goals required for discharge sooner. However, no evidence about length of stay was identified in the studies included in the clinical review. In the base case analysis, there was assumed to be no reduction in length of stay. The results did not seem to be sensitive to this assumption.

Additional costs of rehabilitation

The studies used to inform treatment effects in the model often did not provide details about how physiotherapy was delivered in the study and so it was unclear how many staff members were required. The committee highlighted that it was common that more than one staff member would be required to deliver physiotherapy, particularly initially. Some people would only need 1 person, some 2 and some may even need 3 or 4. In addition it may be that some physiotherapy may be delivered in a group setting, although this was considered fairly uncommon.

Limited evidence about the downstream effects on costs

The effect of post-intervention cost savings is uncertain, which is unfortunate as this is important in determining cost-effectiveness. The committee highlighted that improving functional ability has the potential to lead to substantial cost savings, for example if less nursing care is required or fewer home adjustments. Only two studies were identified as appropriate for the estimation of the effects of stroke severity on post-rehabilitation healthcare resource use. The study used in the base-case analysis (O'Connor 2011) estimated theoretical cost-savings as it measured care needs, not care provision, which necessitated an assumption to be applied for the proportion of care that would be provided for by the NHS. The results for Scenario 1b proved to be sensitive to changes to post-rehabilitation cost-savings as the probability of higher intensity physiotherapy being cost-effective was below 50% when the proportion of post-rehabilitation care cost savings incurred by the NHS/PSS was set to 25% and alternative care-cost savings data from Ganesh 2020 were applied.

The committee also highlighted savings from returning to work in terms of reduced benefit payments, however this was not incorporated into the analysis as it is not part of the NICE reference-care perspective (and if a wider societal perspective were taken it would be a transfer cost).

Duration of rehabilitation

We used a duration of rehabilitation of 6 weeks in the analysis when applying treatment effects and calculating rehabilitation costs as this was the weighted average from the trials used. Real-world data taken from SSNAP[25] shows that the actual duration of rehabilitation is longer (see **Table 21**), suggesting that the intervention costs would be higher that what was assumed for the base-case analysis, if the higher intensity was to be applied throughout rehabilitation for all patients. However, the results were not sensitive to this assumption.

Table 21: Duration of rehabilitation reported in SSNAP 2022

Rehabilitation setting	Mean LOS		Median (IQR)	
	Days	Weeks	Days	Weeks
Inpatient stay	17.5	2.5	7.1 (IQR 2.8 to 21.9)	1.0 (IQR: 0.4 to 3.1)
ESD/community team	54.9	7.8	41 (IQR 21.1 to 69)	5.9 (IQR: 3.0 to 9.9)
Inpatient + ESD/community team	72.4	10.3		

Abbreviations: ESD= early supported discharge; LOS= length of stay; IQR= interquartile range; SSNAP= The Sentinel Stroke National Audit Programme.

Comparator

The analysis looks at the cost-effectiveness of increasing the recommended amount of physiotherapy time post-stroke using studies that compared physiotherapy for five days per week for 1-2 hours versus >45 minutes to 1 hour. Although the current recommendation is for at least 45 minutes of each therapy 5 days a week (in those that can tolerate it), SSNAP data suggests that people are not always receiving this. In the inpatient setting it is reported that physiotherapy is received by the patient on 72.6% of days in hospital out of the period the patient requires physiotherapy, and the median number of minutes receive is 35 (IQR 29.6 – 45). In the community it is less, with 63% receiving physiotherapy in the required period and the median number of minutes receive is 29 (IQR 27 – 41). This suggests that the benefits of more intensive therapy could be greater than estimated by the model but so too would be the resource impact (both in terms of therapist time and potential care savings).

4.3. Generalisability to other populations or settings

This cost effectiveness analysis is taken from a UK NHS setting. The model used NHS reference costs and the cost effectiveness of higher intensity physiotherapy was assessed using NICE's £20,000 threshold. Therefore, the results of this cost effectiveness analysis may not be transferable to other countries or settings.

The model evaluated the cost effectiveness of increased intensity of *physiotherapy*. The results do not apply to other forms of therapy. For the other forms of therapy there was not enough clinical evidence to assess the effectiveness and cost effectiveness of increased intensity.

4.4. Comparisons with published studies

Two studies comparing physiotherapy interventions were included as economic evidence for this question, with neither analysis incorporating a lifetime horizon.

One study was a UK published economic evaluation[20] which assessed a 12-week intervention and found that usual care dominated both higher-intensity physiotherapy groups at 6-months follow-up (where participants received usual care plus robot-assisted arm-training or enhanced upper limb therapy (EULT)), with EULT costing £74,100 per QALY gained compared to usual care and a 19% probability being cost-effective at a £20,000 per QALY threshold. In a sensitivity analysis where the trial data on costs and outcomes was extrapolated to 12-months the ICER was £6,095 per QALY gained for EULT compared to usual care, however this result was paired with only 55% probability of being cost-effective (Robot-assisted arm training remained not cost-effective under all sensitivity analyses). This analysis was limited as it was based on a single trial and not the wider evidence base identified for this review. The trial used in this study was also incorporated into this economic analysis for the pooled treatment-effect of higher intensity physiotherapy.[57]

The second study included in the review for this topic was a Canadian cost-utility analysis[11] that assessed a 6-week intervention with an 18-week follow-up period, where participants received either additional conventional physiotherapy or functional strength training alongside conventional strength training. The base-case analysis assumed the between-group utility difference at 6 weeks would be sustained at 1 year and then gradually decline until no difference remained at 2-years post-intervention. 18-week utilities were not included in the base-case since a greater number of participants were lost to follow-up in the usual care group. The results found that both higher-intensity physiotherapy groups dominated usual care, with cost savings of £1,520 and £1,369 and QALY gains of 0.05 and 0.12 for additional conventional physiotherapy and functional strength training groups, respectively. Dominance compared to usual care remained following a sensitivity analysis that reduced the duration of effect to 1-year, while applying the 18-week follow-up results reported lower costs and lower over QALYs for higher intensity physiotherapy. A key limitation of the analysis was the inclusion of hospital bed-days saved from providing the higher intensity interventions, as this was based on expert opinion and was the main driver of cost savings. The analysis was partially applicable due to the use of 2010 Canadian resource estimates and 2013-unit costs which may not reflect the current UK NHS context. A 5% discount rate for costs and outcomes was also applied when 3.5% is the preferred rate by NICE. The trial used in this study was also incorporated into a sensitivity analysis for the pooled treatment-effect of higher intensity physiotherapy.[13]

4.5. Conclusions

Higher intensity physiotherapy (1 to 2 hours, 5 days a week) has been found to be cost effective in the post-stroke adult population when post-rehabilitation care cost savings are assumed, however this is highly dependent on assumptions made about the treatment effect over time and magnitude of post-rehabilitation care cost-savings. The heterogeneity of the studies, and the specific studies used, should be considered when interpreting this analysis.

4.6. Implications for future research

This analysis has shown that more intensive physiotherapy (1 to 2 hours, 5 days a week) is likely to be cost effective. However, if more trials are undertaken, it would be helpful if they assessed the direct impact on utility measures, so that economic evaluations are less dependent on mapping studies. In addition, trials should make efforts to minimise missing data.

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Appendices

Appendix A Search strategy

A.1 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
Current Nursing and Allied Health Literature - CINAHL (EBSCO)	1 January 2014 – 08 January 2023	Health economics studies

Database	Dates searched	Search filters and limits applied
		Exclusions (Medline records, animal studies, letters, editorials, comments, theses) Human English language
PsycINFO (OVID)	1 January 2014 – 08 January 2023	Health economics studies Exclusions (animal studies, letters, case reports) Human English language

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

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 B Clinical outcomes by study

Study	Timepoints	Mean	N	SD	SE	LCI	UCI	EQ-5D-3L mapped values Mean	LCI	UCI	SD	SE
Cabanas-Valdes 2016 BI (0-100)	Lower intensity											
	Baseline	30.9	40	15.080	2.384	26.077	35.723	0.059	0.011	0.107	0.156	0.025
	CFBL	23.3	39	16.870	2.701			0.233			0.212	
	5 weeks	54.2	39	23.320	3.734	46.671	61.789	0.292	0.217	0.368	0.241	0.039
	Higher intensity											
	Baseline	32.0	40	15.270	2.414	27.116	36.884	0.070	0.021	0.119	0.158	0.025
	CFBL	36.5	40	18.810	2.974			0.365			0.204	
	5 weeks	68.5	40	22.370	3.537	61.346	75.654	0.435	0.363	0.507	0.231	0.037
Han 2013 BI (0-100)	Lower intensity											
	Baseline	51.5	10	22.490	7.112	35.412	67.588	0.265	0.104	0.426	0.260	0.082
	CFBL	33.5	10	19.485	6.162			0.335			0.225	
	6 weeks	85	10	11.790	3.728	76.566	93.434	0.600	0.516	0.684	0.136	0.043
	Higher intensity											
	Baseline	62.5	10	22.490	7.112	46.412	78.588	0.375	0.214	0.536	0.260	0.082
	CFBL	25.5	10	19.485	6.162			0.255			0.225	
	6 weeks	88	10	11.790	3.728	79.566	96.434	0.630	0.546	0.714	0.136	0.043
Jiang 2020 BI (0-100)	Lower intensity											
	Baseline	60	22	11.340	2.418	54.972	65.028	0.350	0.300	0.400	0.120	0.026
	CFBL	0.5	22	11.652	2.484			0.004			0.124	
	2 weeks	60.45	22	11.940	2.546	55.156	65.744	0.355	0.302	0.407	0.127	0.027
	CFBL	2.5	22	11.755	2.506			0.025			0.125	
	1 month	62.5	22	12.130	2.586	57.122	67.878	0.375	0.321	0.429	0.129	0.027

	Higher intensity											
	Baseline	66.74	23	13.020	2.715	61.110	72.370	0.417	0.361	0.474	0.138	0.029
	CFBL	3.7	23	13.167	2.746			0.037			0.139	
	2 weeks	70.43	23	13.310	2.775	64.674	76.186	0.454	0.397	0.512	0.141	0.029
	CFBL	5.4	23	13.251	2.763			0.054			0.140	
	4 weeks	72.17	23	13.470	2.809	66.345	77.995	0.472	0.413	0.530	0.143	0.030
Kim 2016 BI (0-100)	Lower intensity											
	Baseline	57.4	10	22.400	7.084	41.376	73.424	0.324	0.164	0.484	0.259	0.082
	CFBL	27.9	10	14.930	4.721			0.279			0.226	
	4 weeks	85.3	10	13.700	4.332	75.500	95.100	0.603	0.505	0.701	0.158	0.050
	Higher intensity											
	Baseline	65.7	10	23.300	7.368	49.032	82.368	0.407	0.240	0.574	0.269	0.085
	CFBL	21.3	10	15.130	4.785			0.213			0.233	
	4 weeks	87.0	10	10.500	3.320	79.489	94.511	0.620	0.545	0.695	0.121	0.038
Klassen 2020 EQ-5D-5L	Lower intensity											
	Baseline	0.60	49	0.183	0.026	0.548	0.653	0.465	0.346	0.525	0.321	0.046
	CFBL1	0.15	49	0.162	0.023			0.197			0.284	
	1 month	0.75	49	0.126	0.018	0.715	0.787	0.662	0.633	0.688	0.100	0.014
	CFBL2	0.20	37	0.160	0.026			0.235			0.289	
	6 months	0.80	37	0.111	0.018	0.766	0.840	0.700	0.673	0.726	0.082	0.014
	CFBL3	0.18	37	0.167	0.027			0.221			0.283	
	12 months	0.78	37	0.143	0.023	0.737	0.832	0.686	0.651	0.720	0.108	0.018
	Higher intensity											
	Baseline	0.65	25	0.190	0.038	0.570	0.730	0.521	0.361	0.645	0.361	0.072
	CFBL1	0.17	24	0.165	0.034			0.190			0.334	
	1 month	0.82	24	0.090	0.018	0.780	0.850	0.711	0.683	0.734	0.064	0.013
	CFBL2	0.12	23	0.177	0.037			0.154			0.313	
	6 months	0.77	23	0.160	0.033	0.700	0.840	0.676	0.575	0.726	0.185	0.039
	CFBL3	0.18	21	0.165	0.036			0.197			0.333	
	12 months	0.83	21	0.080	0.017	0.800	0.870	0.718	0.698	0.754	0.066	0.014

Lee 2012 BI (0-100)	Lower intensity											
	Baseline	65.6	20	13.500	3.019	59.282	71.918	0.406	0.343	0.469	0.144	0.032
	CFBL	1.7	20	13.401	2.997			0.017			0.143	
	2 weeks	67.3	20	13.300	2.974	61.075	73.525	0.423	0.361	0.485	0.142	0.032
	CFBL	2.5	20	13.073	2.923			0.025			0.140	
	4 weeks	68.1	20	12.600	2.817	62.203	73.997	0.431	0.372	0.490	0.135	0.030
	Higher intensity											
	Baseline	64	20	17.000	3.801	56.044	71.956	0.390	0.310	0.470	0.182	0.041
	CFBL	4.3	20	17.255	3.858			0.043			0.449	
	2 weeks	68.3	20	17.500	3.913	60.110	104.928	0.433	0.351	0.799	0.511	0.114
	CFBL	6.4	20	17.521	3.918			0.064			0.187	
	4 weeks	70.4	20	18.000	4.025	61.976	78.824	0.454	0.370	0.538	0.192	0.043
Rodgers 2019 EQ-5D-5L	Lower intensity											
	Baseline	0.37	254	0.260	0.016	0.338	0.402	0.216	0.193	0.239	0.190	0.012
	CFBL	0.05	207	0.276	0.019			0.036			0.202	
	3 months	0.42	207	0.290	0.020	0.380	0.460	0.252	0.223	0.281	0.212	0.015
	CFBL	0.09	190	0.265	0.019			0.065			0.194	
	6 months	0.46	190	0.270	0.020	0.421	0.499	0.281	0.253	0.310	0.198	0.014
	Higher intensity											
	Baseline	0.38	513	0.255	0.011	0.353	0.397	0.220	0.204	0.236	0.186	0.008
	CFBL	0.09	468	0.255	0.012			0.065			0.186	
	3 months	0.47	468	0.255	0.012	0.442	0.488	0.285	0.268	0.302	0.187	0.009
	CFBL	0.10	445	0.269	0.013			0.076			0.196	
	6 months	0.48	445	0.281	0.013	0.454	0.506	0.296	0.277	0.315	0.206	0.010
Tollar 2021 BI (0-100)	Lower Intensity											
	Baseline	56	390	8.500	0.430	55.154	56.846	0.310	0.302	0.318	0.085	0.004
	CFBL	17.1	355	12.100	0.642			0.171			0.108	
	5 weeks	73.1	355	10.572	0.561	71.837	74.363	0.481	0.468	0.494	0.121	0.006
	Higher intensity											
	Baseline	56.2	290	20.980	1.232	53.775	58.625	0.312	0.288	0.336	0.211	0.012

	CFBL	27.2	286	8.920	0.527			0.272			0.183	
	5 weeks	83.4	286	8.958	0.530	82.362	84.438	0.584	0.574	0.594	0.090	0.005
Alternative clinical studies												
	Lower intensity											
	Baseline	70.8	32	16.200	2.864	64.959	76.641	0.458	0.400	0.516	0.169	0.030
	CFBL1	15.5	32	16.378	2.895			0.155			0.170	
	4 weeks	86.3	32	16.550	2.926	80.333	92.267	0.613	0.553	0.673	0.172	0.030
	CFBL2	20.2	32	16.378	2.895			0.202			0.172	
	3 months	91	32	16.550	2.926	85.033	96.967	0.660	0.6003	0.7197	0.172	0.030
	CFBL3	20.6	32	16.561	2.928			0.206			0.174	
Askim 2010	26 weeks	91.4	32	16.900	2.988	85.307	97.493	0.664	0.603	0.725	0.176	0.031
	Higher intensity											
	Baseline	72.7	30	20.000	3.651	65.232	80.168	0.477	0.402	0.552	0.209	0.038
	CFBL1	15.3	30	17.987	3.284			0.153			0.188	
	4 weeks	88.0	30	14.850	2.711	82.455	93.545	0.630	0.575	0.685	0.155	0.028
	CFBL2	19.3	30	17.987	3.284			0.193			0.155	
	3 months	92	30	14.850	2.711	86.455	97.545	0.670	0.615	0.725	0.155	0.028
	CFBL3	19.8	32	17.323	3.062			0.198			0.136	
	26 weeks	92.5	32	9.700	1.715	89.003	95.997	0.675	0.640	0.710	0.098	0.018
Cooke 2010 EQ-5D-5L	Lower intensity											
	Baseline	0.39	37	0.330	0.054	0.280	0.500	0.234	0.152	0.315	0.253	0.042
	CFBL1	0.08	32	0.320	0.057			0.059			0.246	
	6 weeks	0.47	32	0.310	0.055	0.358	0.582	0.293	0.210	0.376	0.238	0.042
	CFBL2	0.21	23	0.312	0.065			0.155			0.375	
	12 weeks	0.60	23	0.290	0.060	0.475	0.725	0.389	0.296	0.648	0.430	0.090
	Higher intensity											
	Baseline	0.39	68	0.372	0.045	0.300	0.480	0.234	0.168	0.301	0.280	0.034
	CFBL1	0.18	70	0.345	0.041			0.131			0.389	
	6 weeks	0.57	70	0.310	0.037	0.493	0.641	0.365	0.310	0.518	0.444	0.053
	CFBL2	0.21	54	0.336	0.046			0.237			0.371	
	12 weeks	0.6	54	0.280	0.038	0.523	0.677	0.472	0.333	0.557	0.421	0.057
Glasgow 2004 BI (0-20)	Lower intensity											
	Baseline	10.3	35	3.100	0.524	9.235	11.365	0.265	0.212	0.318	0.161	0.027

	CFBL1	3.8	34	3.439	0.590			0.190			0.178	
	4 weeks	14.1	34	3.700	0.635	12.809	15.391	0.455	0.390	0.520	0.192	0.033
	CFBL2	5.8	33	3.205	0.558			0.290			0.183	
	3 months	16.1	33	3.300	0.574	14.930	17.270	0.555	0.496	0.614	0.171	0.030
	CFBL3	5.9	34	4.100	0.703			0.295			0.204	
	6 months	16.2	34	4.200	0.720	14.735	17.665	0.560	0.487	0.633	0.215	0.037
	Higher intensity											
	Baseline	11.8	35	3.3	0.56	10.666	12.934	0.340	0.283	0.397	0.171	0.029
	CFBL1	2.8	33	3.4	0.58			0.140			0.174	
	4 weeks	14.6	33	3.4	0.59	13.394	15.806	0.480	0.420	0.540	0.177	0.031
	CFBL2	4.8	32	3.1	0.54			0.240			0.163	
	3 months	16.6	32	2.8	0.49	15.590	17.610	0.580	0.530	0.630	0.146	0.026
	CFBL3	5.1	31	3.7	0.66			0.255			0.162	
	6 months	16.9	31	2.7	0.48	15.910	17.890	0.595	0.545	0.645	0.143	0.025
Yoo 2013 BI (0-100)	Lower intensity											
	Baseline	75.3	11	5.0	1.51	71.94	78.66	0.503	0.469	0.537	0.057	0.017
	CFBL1	0.1	11	5.1	1.52			0.001			0.057	
	4 weeks	75.4	11	5.1	1.54	71.97	78.83	0.504	0.470	0.538	0.058	0.017
	Higher intensity											
	Baseline	77.5	11	9.6	2.89	71.05	83.95	0.525	0.461	0.589	0.109	0.033
	CFBL1	0.4	11	9.7	2.91			0.004			0.110	
	4 weeks	77.9	11	9.7	2.92	71.38	84.42	0.529	0.464	0.594	0.110	0.033

Abbreviations: BI= Barthel Index; CFBL= change from baseline; EQ-5D-3L/5L= Euroqol 5 dimensions – 3 level/5 level version; LCI/UCI= 95% confidence interval (lower/upper); SD = standard deviation; SE= standard error.

Appendix C Meta-analysis of EQ-5D-3L

	EQ-5D-3L					Weighting		Other parameters			
	BL	CFBL-L	MD	Var	1/Var	BC	All	Age	% F	Weeks	BI (0-100)
Cabanas-Valdes 2016	0.065	0.233	0.132	0.0020	456.8	12.20%	8.40%	76	50%	5	13.2
Han 2013	0.320	0.335	-0.080	0.0100	98.9	4.10%	3.00%	53	22%	6	-8.0
Jiang 2020	0.384	0.004	0.032	0.0020	646.4	14.50%	9.90%	64	36%	2	3.2
Kim 2016	0.366	0.279	-0.066	0.0105	94.9	4.00%	2.90%	66	35%	4	-6.6
Klassen 2020	0.484	0.197	-0.007	0.0056	177.3	6.60%	4.70%	57	41%	4	-0.7
Lee 2012	0.398	0.025	0.039	0.0030	367.0	10.80%	7.50%	54	38%	4	3.9
Rodgers pooled	0.219	0.036	0.029	0.0003	3931.9	23.20%	15.00%	61	39%	12	2.2
Tollar 2021	0.311	0.171	0.101	0.0001	7395.4	24.60%	15.70%	67	45%	5	10.1
Base case studies	**0.294**	**0.120**	**0.050**			**100%**		**63**	**41%**	**6**	**4.9**
Askim 2010	0.467	0.155	-0.002	0.0021	483.4	0.00%	8.70%	77	53%	4	-0.2
Cooke 2010	0.234	0.059	0.071	0.0056	178.5	0.00%	4.80%	68	40%	6	7.2
Glasgow 2004	0.303	0.190	-0.050	0.0020	539.1	0.00%	9.10%	68	41%	4	-5.0
Yoo 2013	0.514	0.001	0.003	0.0014	717.4	0.00%	10.30%	50	41%	6	0.3
All studies	**0.330**	**0.115**	**0.032**				**100%**	**64**	**42%**	**6**	**3.1**

Abbreviations: %F=percentage female at baseline; Age=mean age at baseline; BC=base case; BI=Barthel Index – difference in change from baseline; BL=baseline; CFBL-L=change from baseline in lower intensity group; MD=mean difference in change from baseline; Var= variance of the mean difference; weeks=duration of intervention in weeks