Review protocol for robot assisted arm training

ID	Field	Content
0.	PROSPERO registration number	CRD42021283317
1.	Review title	In people after stroke, what is the clinical and cost effectiveness of robot-assisted arm training in improving function and reducing disability?
2.	Review question	In people after stroke, what is the clinical and cost effectiveness of robot-assisted arm training in improving function and reducing disability?
3.	Objective	To determine the clinical and cost-effectiveness of robot-assisted arm training in improving function for people after a stroke.
4.	Searches	Mehrholz, J. et al. (2018). Electromechanical and robot-assisted arm training for improving activities of daily living, arm function and arm muscle strength after stroke. Cochrane Database of Systematic Reviews. 9. DOI: 10.1002/14651858.CD006876.pub5. The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • CINAHL • AMED • Epistimonikas Searches will be restricted by: • English language studies • Human studies • Date limitation: From January 2018. Other searches: • Inclusion lists of systematic reviews

		The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Adults and young people (16 or older) after a stroke
6.	Population	Inclusion: • Adults (age ≥16 years) who have had a first or recurrent stroke (including people after subarachnoid haemorrhage). Exclusion: • Children (age <16 years) • People who had a transient ischaemic attack
7.	Intervention/Exposure/Test	• Robot-assisted arm training (all types pooled together)
8.	Comparator/Confounding factors	Any other intervention (including usual care and no treatment – all comparators pooled together) Confounding factors (for non-randomised studies only): • Presence of comorbidities • Stroke severity • Time period since stroke

9.	Types of study to be included	• Systematic reviews of RCTs
		• Parallel RCTs
		• Cross over trials (only the first study period will be included)
		• Non-randomised studies (if insufficient RCT evidence is available)
		  ○ Prospective cohort studies
		  ○ Retrospective cohort studies
		  ○ Case-control studies
		
		Published NMAs and IPDs will be considered for inclusion.
		
		Non-randomised studies will only be included if all of the key confounders have been accounted for in a multivariate analysis. In the absence of multivariate analysis, studies that account for key confounders

		with univariate analysis or matched groups will be considered.
10.	Other exclusion criteria	• Non-English language studies. • Non comparative cohort studies • Before and after studies • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	People with a reduction in arm function after a stroke. This may include people in an acute (<7 days), subacute (7 days – 6 months) or chronic (>6 months) time horizon.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: At the following time periods: • Post-intervention (outcomes reported immediately after the intervention has finished). • ≥6 months (the longest time period will be used for this outcome. If the outcome is less than 6 months, then it will be included but downgraded for indirectness). • Person/participant generic health-related quality of life (continuous outcomes will be prioritised) o EQ-5D o SF-6D o SF-36 o SF-12 o Other utility measures (AQOL, HUI, 15D, QWB) • Carer generic health-related quality of life (continuous outcomes will be prioritised) o EQ-5D o SF-6D o SF-36 o SF-12 o Other utility measures (AQOL, HUI, 15D, QWB) • Activities of daily living (continuous outcomes will be prioritised) o Barthel Index o Functional Independence Measure o Other relevant scales • Arm function (continuous outcomes will be prioritised) o Fugl-Meyer assessment

		○ Other relevant scales • Arm muscle strength (continuous outcomes will be prioritised) ○ Motricity Index Score ○ Other relevant scales • Spasticity (continuous outcomes prioritised) ○ Modified Ashworth Scale ○ Tardaieu Scale ○ Patient-reported Impact of Spasticity Measure ○ Numeric Rating Scale for Spasticity ○ Modified Penn Spasm Frequency Scale • Stroke-specific Patient-Reported Outcome Measures (continuous outcomes will be prioritised) ○ Stroke-Specific Quality of Life (SS-QOL) ○ Stroke Impact Scale (SIS) ○ Stroke-specific Sickness Impact Profile (SA-SIP30) ○ Neuro-QOL ○ PROMIS-10 ○ Satisfaction with International Classification of Functioning, Disability and Health – Stroke (SATIS-Stroke) • Withdrawal for any reason (dichotomous outcome) • Adverse events (dichotomous outcomes) ○ Cardiovascular events ○ Injuries and pain ○ Other reported adverse events If not mentioned above, other validated scores will be considered and discussed with the committee to deliberate on their inclusion.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).

		10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I • Case control study: CASP case control checklist
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of

		the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • WinBUGS will be used for network meta-analysis, if possible given the data identified.
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: Severity (as stated by category or as measured by NIHSS scale): • Mild (or NIHSS 1-5) • Moderate (or NIHSS 5-14) • Severe (or NIHSS 15-24) • Very severe (or NIHSS >25) Time after stroke at the start of the trial: • Hyperacute <72 hours • Acute 72 hours – 7 days • Subacute 7 days – 6 months • Chronic >6 months Region of upper limb trained • Distal limb • Proximal limb Dose (hours per day) • <1 hour • ≥1 hour Dose (days per week) • <5 days per week • ≥5 days per week Dose (duration) • <6 weeks • ≥6 weeks Level of supervision • Supervised • Unsupervised • Mixed Type of movement delivered by robotic device • Passive movement • Active assisted movement • Mixed

18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	24/02/2021			
22.	Anticipated completion date	14/12/2022			
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☐	☐
		Piloting of the study selection process		☐	☐
		Formal screening of search results against eligibility criteria		☐	☐
		Data extraction		☐	☐
		Risk of bias (quality) assessment		☐	☐
		Data analysis		☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail StrokeRehabUpdate@nice.nhs.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre			
25.	Review team members	From the National Guideline Centre: Bernard Higgins (Guideline lead)			

		George Wood (Senior systematic reviewer) Madelaine Zucker (Systematic reviewer) Kate Lovibond (Health economics lead) Claire Sloan (Health economist) Joseph Runicles (Information specialist) Nancy Pursey (Senior project manager)
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10175
29.	Other registration details	N/A
30.	Reference/URL for published protocol	N/A
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Adults; Intervention; Movement; Robot assisted arm training; Stroke; Upper limb

33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☒	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	