# Advances and challenges in stroke rehabilitation

*Cathy M Stinear, Catherine E Lang, Steven Zeiler, Winston D Byblow*

**Stroke remains a leading cause of adult disability and the demand for stroke rehabilitation services is growing. Substantial advances are yet to be made in stroke rehabilitation practice to meet this demand and improve patient outcomes relative to current care. Several large intervention trials targeting motor recovery report that participants' motor performance improved, but to a similar extent for both the intervention and control groups in most trials. These neutral results might reflect an absence of additional benefit from the tested interventions or the many challenges of designing and doing large stroke rehabilitation trials. Strategies for improving trial quality include new approaches to the selection of patients, control interventions, and endpoint measures. Although stroke rehabilitation research strives for better trials, interventions, and outcomes, rehabilitation practices continue to help patients regain independence after stroke.**

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**Department of Medicine** (Prof C M Stinear PhD), **Department of Exercise Sciences** (Prof W D Byblow PhD), **University of Auckland, Auckland, New Zealand; Physical Therapy, Occupational Therapy, and Neurology, Washington University School of Medicine, St Louis, MO, USA** (Prof C E Lang PhD); **and Department of Neurology, Johns Hopkins University, Baltimore, MD, USA** (S Zeiler MD)

Correspondence to:
Prof Cathy M Stinear PhD
Department of Medicine, University of Auckland, Auckland 1142, New Zealand
**c.stinear@auckland.ac.nz**

## Introduction

Stroke is a leading cause of mortality and disability.[1] Although stroke mortality is decreasing, the prevalence of people living with the effects of stroke has increased because of the growing and ageing population.[1] The increasing number of stroke survivors creates a greater demand for rehabilitation services. Randomised controlled trials (RCTs) are essential for improving clinical practice, so that rehabilitation services can effectively meet this demand. There is much to learn from RCTs done in the past 5 years.

The aim of this Review is to critique stroke rehabilitation trials and identify ways to further improve the quality of stroke rehabilitation research. This Review focuses on trials of motor rehabilitation after stroke because motor deficits are common[2,3] and are the target of most stroke rehabilitation trials. Trials included in this Review tested training, technological, pharmacological, and neuromodulation approaches to enhance conventional therapies.

## Motor rehabilitation after stroke

Table 1 highlights the key features and findings of the 15 trials discussed in this Review, which are grouped according to type of intervention (panel 1). Most trials recruited participants at the acute and subacute stage (panel 1, table 2), and all reported improvements in both the intervention and control groups. However, 14 of the 15 trials were neutral in that there were no statistically significant differences between groups in the primary endpoint (panel 1). The only positive trial, CARS, initiated intravenous cerebrolysin within 72 h after stroke.[13] Cerebrolysin is a porcine neuropeptide preparation that was beneficial for upper limb motor capacity (panel 2). Mean Action Research Arm Test score was higher 90 days after stroke in the treatment group than the control group. Although a subsequent similar trial[28] was unable to replicate this finding, a meta-analysis has reported beneficial effects of cerebrolysin treatment on modified Rankin Score 90 days after stroke.[29] This result indicates that cerebrolysin might have potential for improving outcomes after ischaemic stroke.

Four RCTs assessed the effects of training interventions at the acute and early subacute stages of stroke (table 1). The AMOBES trial recruited participants at the acute stage and found that additional physiotherapy intended to reduce complications of immobility had similar benefits for upper and lower limb impairment as a lower dose of physiotherapy.[6] The remaining three RCTs recruited participants at the early subacute stage and found that neuromuscular electrical stimulation,[5] functional strength training,[7] and task-oriented training[4] had similar benefits for upper limb capacity as usual care. The EXPLICIT trial found that modified constraint-induced movement therapy led to increased upper limb capacity in the first 12 weeks after stroke, but this benefit was not sustained at 26 weeks.[5] Because no primary endpoint was defined and both the treatment and control groups improved to the same extent by the trial's end, a conservative interpretation is that this trial is neutral.

Five trials examined the effects of technological interventions at the subacute and chronic stages of stroke. EVREST,[8] VIRTUES,[9] and a trial by Adie and colleagues[10] investigated the effects of virtual reality and video games on upper limb motor capacity during the subacute stage of stroke, and Cramer and colleagues[12] investigated the effects of tele-rehabilitation compared with in-clinic therapy on upper limb impairment during the subacute and chronic stages of stroke. The RATULS trial investigated the effects of robot-assisted therapy on upper limb motor capacity with participants primarily at the chronic stage.[11] All these trials illustrate the feasibility of using these technologies on a large scale, and report similar benefits to those produced by a matched dose of recreational activities[8] or conventional therapy (table 1).[9–12]

Three trials investigated the effects of pharmacological agents at the acute and early subacute stages, including the CARS trial (table 1) noted earlier.[13] Treatment with a monoclonal antibody produced no further gains in gait velocity after 90 days, over and above improvements seen in patients in the placebo group.[14] Similarly, the DARS trial tested carbidopa–levodopa treatment before motor therapy sessions and found that the percentage of participants who reported walking independence was similar in the treatment and placebo groups.[15]

Three trials investigated the effects of neuromodulation in the form of electrical pharyngeal stimulation (STEPS),[17]

| | Sites and locations | Recruitment after stroke | N, age in years, number of female participants | Baseline severity score | Intervention | Control | Primary endpoint | Main result |
|---|---|---|---|---|---|---|---|---|
| **Training interventions** | | | | | | | | |
| ICARE Winstein et al (2016)[4] | 7; USA | Early subacute, within 106 days | Total N=361; intervention N=119, 60·9 (13·7)*, 55 (46%); control N=122, 61·1 (13·1)*, 50 (41%); dose-matched control N=120, 59·9 (10·5)*, 53 (44%) | Upper extremity Fugl-Meyer*: intervention 41·7 (9·5); control 41·6 (9·5); dose-matched control 41·5 (9·2) | A structured, task-oriented training programme for the upper limb, delivered in three 60 min sessions per week for 10 weeks | Usual care for 10 weeks, or usual care delivered in three 60 min sessions per week for 10 weeks | Change in the log-transformed time score for the Wolf Motor Function Test between baseline and 12 months after stroke | Neutral; mean (95% CI) log-transformed time† to complete the Wolf Motor Function Test decreased in both groups, with no difference between groups: intervention −0·8 (−1·0 to −0·6); control −0·8 (−1·0 to −0·6); dose-matched control −0·9 (−1·0 to −0·7) |
| EXPLICIT Kwakkel et al (2016)[5] | 11; Netherlands | Early subacute, within 2 weeks | Total N=159; CIMT intervention N=29, 59·0 (14·1)*, 15 (52%); CIMT control N=29, 65·3 (11·4)*, 12 (41%); NMS intervention N=50, 58·9 (11·6)*, 14 (28%); NMS control N=51, 58·5 (11·8)*, 22 (43%) | Upper extremity Fugl-Meyer*: CIMT intervention 42·9 (14·6); CIMT control 35·6 (15·0); NMS intervention 6·6 (6·9); NMS control 7·3 (7·1) | Favourable prognosis subgroup 60 min per day of modified CIMT 5 days per week for 3 weeks; unfavourable prognosis subgroup 60 min per day of EMG-triggered neuromuscular stimulation of the finger extensors 5 days per week for 3 weeks | Usual care delivered 30 min per day, 5 days per week for 3 weeks | Time course of the Action Research Arm Test score modelled over 5, 8, 12, and 26 weeks after stroke | Neutral; mean Action Research Arm Test score increased in all groups, and to a greater extent in patients with a favourable prognosis in the intervention group up to 8 weeks after stroke. However, this outcome was not sustained, and there were no differences between intervention and control group scores* at 12 and 26 weeks after stroke: CIMT intervention 50·8 (7·4); CIMT control 45·6 (15·0); NMS intervention 15·9 (19·6); NMS control 15·8 (19·1) |
| AMOBES Yelnik et al (2017)[6] | 9; France | Acute, within 72 h | Total N=104; intervention N=52, 67 (61·0–75·5)‡, 17 (33%); control N=51, 65 (58–78)‡, 22 (43%) | Motor Fugl-Meyer‡: intervention 9·5 (2·0–28·5); control 7 (1–18) | Physiotherapy to prevent immobility complications for 45 min per day, at least 5 days per week, until ten sessions were completed within 14 days or until discharge from the acute stroke unit | Physiotherapy to prevent immobility complications for 15–20 min per day, at least 5 days per week, until ten sessions were completed within 14 days or until discharge from the acute stroke unit | Change in motor Fugl-Meyer Assessment score between baseline and 90 days later | Neutral; median motor Fugl-Meyer score‡ increased in both groups, with no difference between groups: intervention 22·0 (12–56); control 27·5 (12–40) |
| Pomeroy et al (2018)[7] | 3; England | Early subacute, within 60 days | Total N=288; intervention N=145, 71·9 (12·7)*, 49 (34%); dose-matched control N=143, 72·4 (12·3)*, 53 (37%) | Action Research Arm Test*: intervention 24·7 (18·9); dose-matched control 26·2 (17·4) | Functional strength training for up to 1·5 h per day, up to 5 days per week, for 6 weeks, in addition to usual care | Movement performance therapy for up to 1·5 h per day, up to 5 days per week, for 6 weeks, in addition to usual care | Change in Action Research Arm Test score between baseline and the end of the 6-week intervention period | Neutral; mean Action Research Arm Test score* increased in both groups, with no difference between groups: intervention 9·7 (11·7); control group 7·9 (9·2) |
| **Technological interventions** | | | | | | | | |
| EVREST Saposnik et al (2016)[8] | 14; Canada Argentina, Peru, Thailand | Early subacute, within 3 months | Total N=141; intervention N=71, 62 (13)*, 25 (35%); dose-matched control N=70, 62 (12)*, 22 (31%) | Chedoke-McMaster‡: intervention 4 (3–5); dose-matched control 5 (4–5) | Ten 60 min sessions in 2 weeks of Wii games, such as tennis, darts, and bocce ball | Ten 60 min sessions in 2 weeks of recreational activities, such as playing cards, bingo, and ball games | Time to complete six items on the Wolf Motor Function Test, grip strength, and a card flip task, at the end of the 2-week intervention | Neutral; mean time* to complete the Wolf Motor Function test decreased in both groups, with no difference between groups: intervention 64·1 s (104·0); control 39·8 s (35·5) |

(Table 1 continues on next page)

| | Sites and locations | Recruitment after stroke | N, age in years, number of female participants | Baseline severity score | Intervention | Control | Primary endpoint | Main result |
|---|---|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | | | |
| VIRTUES Brunner et al (2017)[9] | 5; Norway, Denmark, Belgium | Early subacute, within 3 months | Total N=120; intervention N=62, 62 (23–89)§, 20 (32%); dose-matched control N=58, 62 (41–87)§, 23 (40%) | Action Research Arm Test*: intervention 25·8 (18·3); dose-matched control 24·2 (18·6) | Upper limb virtual reality training for up to 60 min per day, up to 5 days per week, for 30 days, in addition to usual care | Conventional upper limb therapy for up to 60 min per day, up to 5 days per week, for 30 days, in addition to usual care | Action Research Arm Test score at the end of the 30-day intervention period | Neutral; mean Action Research Arm Test score* increased in both groups, with no difference between groups: intervention 37·7 (19·5); control 36·8 (18·8) |
| Adie et al (2017)[10] | 10; UK | Early and late subacute, within 6 months | Total N=235; intervention N=117, 66·8 (14·6)*, 51 (44%); dose-matched control N=118, 68·0 (11·9)*, 53 (45%) | Action Research Arm Test*: intervention 41·2 (15·9); dose-matched control 41·0 (16·6) | Wii training for the upper limb for up to 45 min daily, for 6 weeks, in addition to usual care | Upper limb exercises for up to 45 min daily, for 6 weeks, in addition to usual care | Action Research Arm Test score at the end of the 6-week intervention period | Neutral; mean Action Research Arm test score* increased in both groups, with no difference between groups: intervention 47·6 (14·2); control 49·0 (13·6) |
| RATULS Rodgers et al (2019)[11] | 4; UK | Early and late subacute, and chronic, within 5 years | Total N=770; intervention N=257, 59·9 (13·5)*, 101 (39%); control N=254, 62·5 (12·5)*, 101 (40%); dose-matched control N=259, 59·4 (14·3)*, 100 (39%) | Action Research Arm Test*: intervention 8·5 (11·9); control 8·1 (11·5); dose-matched control 8·7 (11·9) | Robot-assisted upper limb training for up to 45 min per day, 3 days per week, for 12 weeks, in addition to usual care | Usual care for 12 weeks, and enhanced upper limb therapy for up to 45 min per day, 3 days per week, for 12 weeks, in addition to usual care | The percentage of patients in each group whose Action Research Arm Test score increased by a prespecified number of points depending on baseline score, between baseline and the end of the intervention period | Neutral; 103 (44%) of patients in the intervention group, 85 (42%) of patients in the control group, and 118 (50%) of patients in the dose-matched control group achieved the primary endpoint, with no difference between groups |
| Cramer et al (2019)[12] | 11; USA | Early and late subacute, and chronic, within 9 months | Total N=124; intervention N=64, 62 (14)*, 14 (23%); control N=62, 60 (13)*, 20 (32%) | Upper extremity Fugl-Meyer*: intervention 42·8 (7·8); control 42·7 (8·7) | 18 supervised and 18 unsupervised 70 min therapy sessions distributed over 6–8 weeks with supervision delivered by videoconference | 18 supervised and 18 unsupervised 70 min therapy sessions distributed over 6–8 weeks with supervision delivered in person | Change in upper extremity Fugl-Meyer Assessment score between baseline and 30 days after the intervention period | Neutral; mean upper extremity Fugl-Meyer score* increased in both groups, with no difference between groups; intervention 7·9 (6·7); control group 8·4 (7·0) |
| **Pharmacological interventions** | | | | | | | | |
| CARS Muresanu et al (2016)[13] | 13; Poland, Romania, Ukraine | Acute, within 72 h | Total N=208; intervention N=104, 64·9 (9·8)*, 34 (33%); control N=104, 63·0 (10·6)*, 41 (39%) | Action Research Arm Test‡: intervention 0·0 (21·5); control 2·0 (18·0) | 30 mL of cerebrolysin and 70 mL of saline administered intravenously once per day for 21 days and standardised usual care | 100 mL of saline administered intravenously once per day for 21 days and standardised usual care | Change in Action Research Arm Test score between baseline and 90 days after stroke | Positive; mean Action Research Arm Test score* increased in both groups, with a greater increase in the intervention group: intervention 30·7 (19·9); control group 15·9 (16·8) |
| Cramer et al (2017)[14] | 30; USA, Canada, Germany, UK | Acute, within 72 h | Total N=134; intervention N=65, 68·2 (11·9)*, 31 (48%); control N=68, 67·1 (11·2)*, 29 (43%) | National Institutes of Health Stroke Scale¶: intervention 10 (3–19); control 9·5 (3–20) | Two intravenous infusions of a monoclonal antibody to myelin-associated glycoprotein (GSK249320) | Two intravenous infusions of a placebo | Change in gait velocity between baseline and 90 days after stroke | Neutral; mean gait velocity* increased in both groups, with no difference between groups: intervention 0·55 m/s (0·46); control 0·56 m/s (0·50) |
| DARS Ford et al (2019)[15] | 51; UK | Early subacute, within 42 days | Total N=593; intervention N=308, 67·5 (13·6)*, 121 (39%); control N=285, 69·6 (12·7), 108 (38%)* | Patient-reported Rivermead Mobility Index*: intervention 2·4 (2·2); control 2·5 (2·2) | 125 mg co-careldopa (levodopa 100 mg; carbidopa 25 mg) administered orally up to 60 min before usual care motor rehabilitation therapy sessions for up to 6 weeks | Placebo administered orally up to 60 min before usual care motor rehabilitation therapy sessions for up to 6 weeks | The percentage of patients in each group that reported being ability to walk at least 10 m independently 8 weeks after randomisation | Neutral; 125 patients (41%) in the intervention group and 127 patients (45%) in the control group achieved the primary endpoint, with no difference between groups |

(Table 1 continues on next page)

| | Sites and locations | Recruitment after stroke | N, age in years, number of female participants | Baseline severity score | Intervention | Control | Primary endpoint | Main result |
|---|---|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | | | |
| **Neuromodulation interventions** | | | | | | | | |
| EVEREST Levy et al (2016)[16] | 21; USA | Chronic, after 4 months | Total N=164; intervention N=94, 56·4 (11·3)*, 42 (45%); control N=58, 57·4 (10·7)*, 20 (35%) | Upper extremity Fugl-Meyer*: intervention 37·6 (6·1); control 37·6 (5·9) | Electrical epidural stimulation delivered over the ipsilesional primary motor cortex during 65 h of upper limb rehabilitation distributed over 6 weeks | 65 h of upper limb rehabilitation distributed over 6 weeks | The percentage of patients in each group that improved their upper extremity Fugl-Meyer Assessment score by at least 4·5 points, and Arm Motor Ability Test score by at least 0·21 points, measured between baseline and 4 weeks after rehabilitation | Neutral; 32% (95% CI 22–41) of patients in the intervention group and 29% (17–41) of patients in the control group achieved the primary endpoint, with no difference between groups (actual patient numbers not reported) |
| STEPS Bath et al (2016)[17] | 20; Denmark, France, Germany, Spain, UK | Early subacute, within 42 days | Total N=162; intervention N=87, 74·0 (9·9)*, 39 (45%); control N=75, 74·9 (12·6)*, 29 (39%) | Penetration Aspiration Score*: intervention 4·7 (2·1); control 4·7 (1·9) | Pharyngeal electrical stimulation delivered at 5 Hz for 10 min on 3 consecutive days and usual care | Sham pharyngeal electrical stimulation delivered for 10 min on 3 consecutive days and usual care | Penetration Aspiration Score determined with videofluoroscopy 2 weeks after the third stimulation session | Neutral; mean Penetration Aspiration Score* improved (decreased) in both groups, with no difference between groups: intervention 3·7 (2·0); control 3·6 (1·9) |
| NICHE Harvey et al (2018)[18] | 12; USA | Chronic, after 3 months | Total N=199; intervention N=132, 59·2 (13·3)*, 44 (33%); control N=67, 57·6 (12·7)*, 25 (37%) | Upper extremity Fugl-Meyer*: intervention 34·0 (12·2); control 35·0 (12·5) | 1 Hz repetitive transcranial magnetic stimulation delivered over the contralesional primary motor cortex before upper limb physical therapy in 18 sessions distributed over 6 weeks | Sham 1 Hz repetitive transcranial magnetic stimulation delivered over the contralesional primary motor cortex before upper limb physical therapy in 18 sessions distributed over 6 weeks | The percentage of patients in each group whose upper extremity Fugl-Meyer Assessment score increased by at least 5 points between baseline and 6 months after the end of the intervention period | Neutral; 76 patients (67%) in the intervention group and 39 patients (65%) in the control group achieved the primary endpoint, with no difference between groups |

Sample size is the number of participants randomised. Maximum scores: Motor Fugl-Meyer Assessment=98 (upper extremity plus lower extremity scores, without reflexes);[8] upper extremity Fugl-Meyer Assessment=66; Action Research Arm Test=57; Chedoke-McMaster=7; National Institutes of Health Stroke Scale=42; Patient-reported Rivermead Mobility Index=14; Penetration Aspiration Score=8. CIMT=Constraint-Induced Movement Therapy. NMS=Neuromuscular stimulation. EMG=Electromyography. *Mean and SD. †Mean and 95% CI. ‡Median and IQR. §Mean and range. ¶Median and range.

***Table 1:*** **Summary of multicentre randomised controlled trials assessing motor rehabilitation interventions**

electrical epidural stimulation (EVEREST),[16] and repetitive transcranial magnetic stimulation (NICHE) at the early subacute and chronic stages of stroke (table 1).[18] Stimulation was paired with physical therapy in the EVEREST and NICHE studies.[16,18] Although these trials were neutral, they illustrate the feasibility of using neuromodulation interventions in multicentre studies. EVEREST and NICHE delivered the intervention over 6 weeks at the chronic stage,[16,18] and STEPS delivered three sessions of stimulation at the early subacute stage.[17] The feasibility of longer intervention durations at the early subacute stage should be explored in future trials.

The neutral results of all but one trial could indicate that the tested interventions had similar benefits to usual care (in the case of training or technological interventions), or had no additional benefit when added to usual care (in the case of neuromodulation or pharmacological interventions). Neutral results might also reflect the challenges of designing and doing stroke rehabilitation RCTs.

## Improving stroke rehabilitation trials

The design, conduct, and reporting of stroke rehabilitation RCTs presents important challenges, and consensus is developing around the best ways to address these challenges.[30] Involving patients in co-design could increase the relevance of trials and their outcomes.[31,32] Further suggestions for improving stroke rehabilitation RCTs are described later and summarised in panel 3.

### Fidelity and concealment

Delivering rehabilitation interventions in a standardised and blinded manner is a complex and time-intensive process.[33] Training and technological interventions typically require therapists to individualise and progress the intervention. Doing so in a standardised, reproducible way

### *Panel 1*: Glossary of recovery and rehabilitation terms

**Recovery and rehabilitation**

*Recovery*
The extent to which body structure and function return to their before-stroke state.[19]

*Spontaneous biological recovery*
Recovery from impairment that occurs during the first 3 months after a stroke as a result of endogenous biological processes rather than behavioural, pharmacological, or neuromodulatory interventions.[20,21]

*Compensation*
The use of new movement (or behavioural) patterns resulting from the adaptation of remaining neural substrate. Compensations can be adaptive, which is characterised by the use of alternate movement patterns during the accomplishment of a task, or they can be substitutive, which is characterised by the use of different effectors or assistive devices to replace lost motor components.[22] Note that in any individual patient, return of motor capacity might be a combination of recovery and compensation.[23]

*Rehabilitation*
Interventions designed to help a person who has had a stroke, or other disabling condition, to regain lost body functions and activities, maximise independence in daily activities, and facilitate participation in home and community life.

*Prognostic biomarker*
A biological, anatomical, or physiological measure associated with differential disease outcomes. Prognostic biomarkers can be used to select patients most likely to have a particular outcome after stroke for trials of interventions aimed at altering this outcome.[24,25]

*Predictive biomarker*
A biological, anatomical, or physiological measure that predicts the response to a treatment. Predictive biomarkers can be used to select patients most likely to benefit from a stroke rehabilitation intervention.[24,25]

**Stages of stroke recovery**[19]

*Hyperacute*
0–24 h after stroke.

*Acute*
1–7 days after stroke.

*Early subacute*
7 days to 3 months after stroke.

*Late subacute*
3–6 months after stroke.

*Chronic*
6 months or more after stroke.

**Types of intervention**

*Training interventions*
Involve physical activity in the form of strength or task training, or both.

*Technological interventions*
Involve physical activity in the context of gaming, virtual reality, robotics, and tele-rehabilitation.

*Pharmacological interventions*
Involve combining a pharmacological agent with usual care therapies.

*Neuromodulation interventions*
Involve combining electrical or magnetic stimulation with usual care therapies.

**Rehabilitation trial terms**[26]

*Primary endpoint*
A single measure made at a single timepoint, which forms the basis of the sample size calculation and subsequent statistical analysis. The overall trial result is based on the statistical analysis of the primary endpoint.

*Positive trial*
The primary endpoint is significantly better for participants in the treatment group than participants in the control group.

*Neutral trial*
The primary endpoint is similar for participants in the treatment and control groups.

*Negative trial*
The primary endpoint is significantly worse for participants in the treatment group than participants in the control group.

is difficult. Some trials have addressed this difficulty by reporting detailed protocols for the treatment and control interventions along with therapist training programmes to ensure consistent delivery,[4,5,7,11,12] but protocols are not readily available for the other training and technological intervention trials.[6,8–10] Pharmacological interventions face the challenge of timing delivery relative to the participants' engagement in physical therapies as part of their usual care. Although this relative timing might not be important for some pharmacological agents, it might be for others. For example, less than 10% of participants in the DARS trial were eligible for per-protocol analyses because of low fidelity of treatment timing and therapy dose,[34] which might have contributed to this trial's neutral result. Using the TIDieR checklist[35] or the Rehabilitation Treatment Specification System[36] will improve the reporting of experimental and control interventions and the reproducibility of trials.

Concealment of group allocation can also be difficult. Placebo pharmacological agents can look identical to the experimental agent and sham neuromodulation interventions can be designed to maintain masking of participants, therapists, and researchers. But concealment is rarely possible with training and technological interventions because of the physical nature of these interventions. Only the reviewed trials of pharmacological agents[13–15] and

| | Intervention type | Intervention target | Intervention duration | Trial duration | Primary endpoint time | Follow-up after the primary endpoint |
|---|---|---|---|---|---|---|
| **Acute** | | | | | | |
| AMOBES; Yelnik et al (2017)[6] | Training | Upper and lower limb impairment | 2 weeks | 90 days | End of trial; 90 days after stroke | None |
| CARS; Muresanu et al (2016)[13] | Pharmacological | Upper limb capacity | 3 weeks | 90 days | End of trial; 90 days after stroke | None |
| Cramer et al (2017)[14] | Pharmacological | Lower limb capacity | 6 days | 180 days | 11 weeks after intervention; 90 days after stroke | 180 days after stroke |
| **Subacute** | | | | | | |
| ICARE; Winstein et al (2016)[4] | Training | Upper limb capacity | 10 weeks | 12 months | End of trial; up to 14 months after stroke | None |
| EXPLICIT; Kwakkel et al (2016)[5] | Training | Upper limb capacity | 3 weeks | 26 weeks | End of trial; 26 weeks after stroke | None |
| Pomeroy et al (2018)[7] | Training | Upper limb capacity | 6 weeks | 6 months | End of intervention; up to 14 weeks after stroke | 6 months after stroke |
| EVREST; Saposnik et al (2016)[8] | Technological | Upper limb capacity | 2 weeks | 4 weeks | End of intervention; up to 14 weeks after stroke | 6 weeks after randomisation |
| VIRTUES; Brunner et al (2017)[9] | Technological | Upper limb capacity | 4 weeks | 4 months | End of intervention; up to 4 months after stroke | 3 months after randomisation |
| Adie et al (2017)[10] | Technological | Upper limb capacity | 6 weeks | 6 months | End of intervention; up to 32 weeks after stroke | 6 months after randomisation |
| Cramer et al (2019)[12] | Technological | Upper limb impairment | 8 weeks | 12 weeks | End of trial; up to 12 months after stroke | None |
| DARS; Ford et al (2019)[15] | Pharmacological | Lower limb capacity | 6 weeks | 12 months | End of intervention; up to 14 weeks after stroke | 6 months and 12 months after randomisation |
| STEPS; Bath et al (2017)[17] | Neuromodulation | Swallowing impairment | 3 days | 12 weeks | 2 weeks after intervention; up to 8 weeks after stroke | 3 months after randomisation |
| **Chronic** | | | | | | |
| RATULS; Rodgers et al (2019)[11] | Technological | Upper limb capacity | 12 weeks | 6 months | End of intervention; up to 63 months after stroke | 6 months after randomisation |
| EVEREST; Levy et al (2016)[26] | Neuromodulation | Upper limb impairment | 6 weeks | 30 weeks | 4 weeks after intervention; at least 6 months after stroke | 30 weeks after randomisation |
| NICHE; Harvey et al (2018)[18] | Neuromodulation | Upper limb impairment | 6 weeks | 8 months | End of trial; up to 20 months after stroke | None |

*Table 2:* **Summary of design features of multicentre randomised controlled motor rehabilitation trials**

non-invasive neuromodulation[17,18] were able to conceal group allocation from participants. All 15 reviewed trials attempted to conceal group allocation from assessors responsible for collecting outcome data. Seven report whether concealment was successful,[4,5,7,8,10,11,18] and four report that assessors were unmasked to variable extents.[4,7,10,11] Improving and evaluating the fidelity of interventions and concealment of group allocation could improve trial quality, although these actions might require additional human resources.

## Control interventions and dose

Experimental interventions are often evaluated against so-called conventional, standard, or usual care. These descriptors represent a heterogeneous group of therapies that vary across countries, are poorly defined and described in the literature,[37] and are hard to compare across RCTs. Selection of appropriate control interventions is hampered by a scarcity of knowledge about their active ingredients.[37–39] Doses of experimental and control interventions can also be constrained by available time and resources. The dose and intensity of physical therapies can differ between the treatment and control groups, and might be delivered alongside so-called usual rehabilitation therapies during trials, further complicating the interpretation of results.

All 15 reviewed trials reported the planned dose of experimental and control interventions, and all except AMOBES,[6] EXPLICIT,[5] and Pomeroy and colleagues[7] reported the delivered doses. Encouragingly, planned intensity was matched between experimental and control groups for seven trials of technological[8–12] and training[4,7] interventions. Three training intervention trials planned higher intensities for the experimental group than for the

control group.[4–6] Most of the four training intervention trials delivered experimental and control interventions at an intensity lower than recommended by clinical guidelines (3·75–10·00 h per week).[40,41] Experimental and control interventions produced similar benefits, even when experimental interventions were delivered at a higher intensity.

Participants in most trials engage in conventional therapies as part of their usual care, in addition to the experimental or control intervention. Usual care therapies completed by participants during the trial were not measured or not reported by three trials of training interventions,[6,7,39] two trials of technological interventions,[10,11] one pharmacological trial,[13] and two neuromodulation trials.[17,18] Thus, there might be important, unknown, between-group differences in overall rehabilitation experience. The remaining seven trials report that the control group intentionally completed a similar amount of therapy to the experimental group,[8,9,12,16] intentionally completed less therapy than the experimental group,[4] or unintentionally completed more[15] or less[14] therapy than the experimental group. Unknown and unintentional differences can confound the interpretation of results and limit comparisons between trials, and are best avoided.

Reporting the dose of the delivered interventions and usual care therapies completed by participants during RCTs could improve the transparency of future trials. Deciding how best to report the dose of physical therapies is challenging given that dose has several variables (eg, repetitions, therapy intensity as repetitions per unit of time, total active therapy time, and therapy session frequency). Dose variables to control and report will vary depending on the active components of the intervention (eg, delivered doses of task-specific training *vs* cardiorespiratory exercise require different variables) and must be determined in advance.

## Stage of recovery

Most motor recovery occurs in the first 3 months after stroke.[21,42,43] This time period is therefore a critical window of opportunity for experimental interventions to shape recovery and outcomes.[44,45] The neurobiological mechanisms of recovery during the subacute stage are complex and still being elucidated. Generally, ischaemic stroke induces a cascade of effects on gene expression, cellular function, and the structure of surviving tissues, most of which promote recovery. These endogenous mechanisms are widespread and most active early after stroke,[43,46,47] and are largely responsible for recovery from motor impairment.[20,21] Usual care therapies and training interventions are thought to promote improvements in motor capacity primarily through compensation (panel 1).[20–22] Future research could seek to improve recovery by enhancing endogenous and therapy-driven processes at the early subacute stage. Although testing interventions against the backdrop of spontaneous recovery from impairment presents particular challenges, these can be at least partly addressed by selection of patients and endpoint measures.

***Panel 2*: WHO definitions[27]**

**Impairment**
Deficit in body structure or function, such as decreased strength, or loss of sensation.

**Activity**
Execution of a task or action. Activity limitations are difficulties a person has when trying to complete tasks such as dressing, bathing, or walking.

**Capacity**
Activity limitation that is captured in a structured setting with a standardised measure such as the Action Research Arm Test or walking speed over 10 m. Alternate terms include function and functional capacity.

**Performance**
Activity limitation that is captured in an unstructured setting during daily life. Performance can be self-reported on a questionnaire such as the Motor Activity Log, or directly measured using tools such as accelerometry or step counting devices.

Trials at the chronic stage make detection of intervention effects easier, but these trials pose other challenges. For example, chronic non-use of the paretic upper limb and general physical deterioration can influence baseline measures of impairment and capacity. The benefits of interventions at the chronic stage might therefore relate to reconditioning that helps patients return to their previous best, rather than specific neurological effects that help patients make a further recovery over and above their previous best. This challenge could be addressed by engaging all participants in a reconditioning programme, then randomising once baseline measures are stable.

The majority of stroke rehabilitation RCTs published over the past few decades have recruited patients at the chronic stage.[48] For 215 RCTs, including 489 groups and 12 847 participants in the Stroke Centralized Open-Access Rehabilitation database, the mean time of enrolment was 509 days after stroke (median 141 days).[48] Enrolment of patients in rehabilitation trials at the chronic stage of stroke is problematic because the majority of recovery and rehabilitation service delivery occurs during the early subacute stage. Encouragingly, only three of the 15 reviewed trials were done at the chronic stage (table 2). This finding illustrates a growing capacity for doing multicentre trials at the stages of stroke when interventions might have the greatest benefits for motor recovery and outcomes.

For more on the **Stroke Centralized Open-Access Rehabilitation database** see https://keithlohse.github.io/SCOAR_data_viz/

## Patient selection

The 15 reviewed trials selected patients using primarily clinical criteria, including upper age limits,[5,8,13,14] and minimum[4–8,11,12,14,16–18] and maximum scores[4,5,7,9–16,18] on clinical

### *Panel 3*: Suggestions for improving stroke motor rehabilitation trials

These suggestions are intended for people designing and doing trials of stroke motor rehabilitation. They also identify features to consider when evaluating the quality of planned and completed trials. The EQUATOR network provides more general advice for the design and conduct of various trial types.

**Planning**

*Recruitment*

- Enhance recruitment by embedding researchers within clinical teams to increase access to patients
- Consider including patients with ischaemic and haemorrhagic stroke, and a history of previous stroke, when appropriate
- At the subacute stage, recruit and randomly assigned all participants within 2 weeks after stroke to ensure groups are matched for initial impairment
- At the chronic stage, obtain multiple baseline assessments or use preconditioning, or both, to better detect effects specifically related to the intervention
- Select and stratify participants using prognostic biomarkers to reduce interparticipant variability in expected outcomes, or predictive biomarkers that have a plausible relationship to the intervention's known or hypothesised biological mechanisms of action

*Measures*

- Select appropriate domain-specific endpoint measures, based on the intervention's target, stage of stroke recovery, and phase of trial
- Consider obtaining primary endpoint or follow-up measures at least 6 months after stroke if testing an intervention at the subacute stage
- Select appropriate measures of dose, considering the known or hypothesised active ingredients of the treatment and control interventions
- Consider making follow-up measures after the primary endpoint

*Conduct and reporting*

- Ensure sufficient staff resources to maintain group allocation concealment
- Reduce barriers to research participation by providing aphasia-friendly information to potential participants with communication difficulties, and providing interpreter services and transportation as needed
- Develop and report detailed treatment protocols, including therapist and assessor training programmes
- Measure and report planned and delivered doses of treatment and control interventions, and any rehabilitation delivered separately from the trial
- Report rationales for inclusion and exclusion criteria

For more on the **EQUATOR network** see http://www.equator-network.org/

assessment scales. Two trials of pharmacological agents also used stroke lesion volume as a selection criterion.[13,14] Future trials might consider explicitly stating both the rationale for selection criteria, and the links between the criteria and the intervention's expected mechanisms of action.

Trials at the acute stage recruited patients within 72 h after stroke, and trials at later stages had wider recruitment time windows (table 1). For early subacute trials, the narrowest recruitment time window was within 2 weeks after stroke[5] and the widest was up to 106 days after stroke,[4] thereby including patients at the beginning, middle, and end of the spontaneous recovery process. Thus, there could be important differences between patients in the degree of improvement they have during the trial because of spontaneous biological recovery, which might not be matched between groups and cannot be untangled from the effects of the intervention. This problem is not solved by reporting no statistically significant difference between groups in mean baseline scores. Instead, the degree of improvement that is likely to result from spontaneous biological recovery processes needs to be matched between groups,[49,50] and this might be at least partly addressed by recruiting all participants within a narrow window of time after stroke, such as 2 weeks. The intervention can then be started at an appropriate time, based on its hypothesised or known mechanisms of action.

Patient selection using prognostic biomarkers (panel 1) might improve the matching of intervention and control groups, and enrich the sample, as reviewed elsewhere.[49,51] Several measures made within days after stroke are related to subsequent motor recovery and outcome, including a variety of measures obtained with electroencephalography, transcranial magnetic stimulation, structural and functional MRI techniques, and genetic assays.[49,51] However, these measures are often related to subsequent motor recovery at the group level. Prognostic biomarkers need to accurately predict motor recovery or outcome for individual patients to be useful for patient selection or stratification in trials. The functional status of the corticospinal tract evaluated with transcranial magnetic stimulation is a robust predictor of upper limb recovery[20,49,50] and outcomes[52] for individual patients, and is considered ready for use in clinical trials.[51] This prognostic biomarker is particularly important for trials that recruit patients with moderate-to-severe initial upper limb impairment, for whom baseline clinical scores are poor predictors of motor recovery.[49,52]

Future trials could also incorporate predictive biomarkers (panel 1) to select patients who are most likely to respond to the intervention's mechanism of action. For example, the EVEREST trial delivered epidural stimulation over the ipsilesional motor cortex at the chronic stage and reported a neutral result (table 1).[16] Post-hoc analyses found that patients with a functionally intact ipsilesional corticospinal tract, and less structural damage to this tract, were more likely to have improvements in upper limb performance than patients without a functional corticospinal tract and more structural damage to this tract.[53] This finding illustrates the importance of selecting patients who have the biological substrate required to benefit from the intervention. To date, no multicentre RCT using non-invasive stimulation to improve motor performance has specifically selected patients on the basis of corticospinal tract viability. Although a single protocol is unlikely to benefit all patients at the subacute or chronic stage,[54,55] stimulation protocols could be developed and prescribed on the basis of key predictive biomarkers of corticospinal tract function.

Patient stratification on the basis of corticospinal tract functional status could allow more confident interpretation of RCTs that report positive results for upper limb motor

recovery. For example, the CARS trial recruited patients with severe initial upper limb impairment within 72 h after stroke (table 1).[13] Patient characteristics and baseline clinical scores were balanced between treatment and control groups. However, patients with a functional corticospinal tract had markedly better upper limb motor recovery than those without a functional corticospinal tract, despite having similar baseline clinical scores.[49] There might have been more patients with a functional corticospinal tract, who had a greater recovery regardless of treatment, in the treatment group than the control group, and this difference might have contributed to the trial's positive result.

Future trials aimed at improving upper limb motor recovery could disambiguate the current evidence by recruiting patients within a narrow time window after stroke and by using an assay of corticospinal tract functional integrity when selecting and stratifying patients with initially severe upper limb paresis. Biomarkers need to be developed for trials aimed at improving lower limb motor recovery, language, and swallowing.

### Selecting the best primary and secondary endpoints

A further challenge to stroke rehabilitation RCTs is the selection of primary and secondary endpoints, both in terms of the measures and the time at which they are made. Trials of interventions that target the motor domain ought to select endpoint measures that are specific to motor impairment, capacity, and performance (panel 2). Exploratory early phase trials could usefully deploy measures at all three levels, and later phase trials could prioritise measures of capacity and performance that capture the intervention's effects on patients' daily activities and participation. Global measures of independence or disability, such as the modified Rankin Scale, are not sufficiently sensitive to serve as primary endpoint measures for trials of interventions that target the motor domain.

The primary endpoint measure ought to be selected considering the intervention's known or hypothesised mechanisms and timecourse of action. For example, neuromuscular electrical stimulation of paretic leg muscles reduces impairment by increasing strength but has no effect on walking capacity,[56] which needs to be reflected in the choice of primary endpoint measure. Patients can also learn to use compensatory movement strategies to overcome impairments, such as trunk movement to compensate for synergistic coupling of the shoulder and elbow during reaching with the paretic arm.[57,58] The adoption of such strategies might contribute to activity improvements but might not be detected with an impairment-based endpoint. Early phase RCTs might make primary endpoint measures immediately after intervention to detect a signal of benefit, whereas later phase RCTs might make primary endpoint measures at a later time to detect sustained beneficial effects.

Primary endpoints can be an absolute measure of outcome, such as the Action Research Arm Test score after intervention, or a measure of recovery over time, such as the change in Action Research Arm Test score between baseline and after intervention. Using change in a score as the primary endpoint measure can be challenging for trials done at the subacute stage, because scores are expected to improve during this time because of spontaneous biological recovery and usual care, irrespective of possible intervention effects. This problem can be at least partly overcome by recruiting all participants within an early and narrow timeframe and using prognostic biomarkers to match groups.

Patients were recruited in wide time-windows after stroke (table 2), intervention durations varied from 3 days to 3 months, and primary endpoint measures were made at the end of the intervention, after the intervention, or at the end of the trial. This variation hampers direct comparisons between trials. Eight of the 12 reviewed trials at the acute and subacute stages assessed primary endpoint measures before participants reached the chronic stage of recovery (6 months after stroke; table 2). In this situation, participants might continue to improve after the primary endpoint measure. For example, the intervention might accelerate recovery during the subacute stage, but the control group might catch up and have similar outcomes at 6 months after stroke. Primary endpoint or follow-up measures could usefully be obtained once the subacute stage is complete, to detect whether the intervention produces longer term benefits. The inclusion of patient-reported secondary endpoint measures, preferably selected in consultation with patient representatives, would also increase the relevance of trial results.

### Practical challenges

The practical challenges associated with stroke rehabilitation RCTs vary between countries and health-care systems in terms of structural barriers to recruitment and retention of participants in trials. Although academic medical centres serve as key clinical infrastructures for acute stroke management trials, rehabilitation is often provided by dispersed and separate organisations and systems. Participants usually must be physically present at the research site to receive the intervention, which is typically delivered 1–5 days per week for 2–8 weeks. The challenges of trial organisation and intervention fidelity increase as patients move from acute care hospitals to inpatient, outpatient, and community settings for their rehabilitation. Initial and continuing participation in rehabilitation trials is affected by factors such as geographical location, the patient's stroke severity, comorbidities, social circumstances, family preferences, and transportation and caregiver availability. Providing transportation is a practical measure that can facilitate participation.

The rate of participant recruitment into the reviewed trials was typically slow regardless of stage after stroke. Eight of the 15 trials recruited less than 0·5 participants per site per month.[5,6,8,11,12,14–17] The trial with the highest

recruitment rate enrolled two participants per site per month.[7] Preliminary work to evaluate the feasibility of planned RCTs and acceptability of the intervention could help to identify and address factors that might limit recruitment. Researchers' access to patients at the acute and early subacute stages might be limited by the location and policies of health-care organisations caring for these patients. The experimental and control interventions might compete with usual care for participants' time and energy, for which research participation is not prioritised by patients or clinical teams. Extensive inclusion and exclusion criteria can also limit the proportion of patients who are eligible for participation. Patients who are excluded because of communication difficulties, either due to aphasia or language barriers, represent an understudied subset of the stroke population.[59] Provision of aphasia-friendly trial information and interpreting services as needed would facilitate recruitment. Embedding investigators in clinical environments to enable daily access to patients,[60] and designing interventions that can be accommodated within the time constraints of routine clinical care, will also facilitate recruitment and the uptake of beneficial interventions in clinical practice.

For future rehabilitation trials, consideration could be given to inclusion of patients with both ischaemic and haemorrhagic stroke. Unlike acute stroke management or secondary prevention trials, the type of stroke appears to have little effect on motor recovery[51] or outcome.[53] If the biological target of the rehabilitation intervention is indifferent to type of stroke, including both stroke types when safe to do so could increase recruitment rates. Of the 15 trials reviewed here, ten included patients with both ischaemic and haemorrhagic stroke. The remaining five trials excluded patients with haemorrhagic stroke, and three of these were the only trials unable to recruit the required sample size.[7,15,18] Inclusion of patients with a history of previous stroke, provided no residual motor deficits are present, could also increase recruitment.[60]

## Implications for clinical practice

There is no clear evidence that interventions tested in large multicentre stroke rehabilitation trials are superior to current care. Furthermore, patients benefited from both the experimental and control interventions at both the subacute and chronic stages. This finding indicates that meaningful improvements in motor impairment and capacity are possible for most patients (table 1).

Stroke rehabilitation guidelines have increased the recommended amounts of therapy in the past 5 years,[40,41,61] but the optimal amount of therapy is currently an open question. Animal experiments indicate that higher amounts of motor training are associated with better motor recovery.[62–64] Additionally, evidence based on meta-analyses of clinical trial data shows that higher amounts of motor therapy are associated with better outcomes in humans.[65,66] However, RCTs that test different doses of the same training intervention at the subacute[67] and chronic[68] stages have not shown added benefits from 2–3 times the usual doses received in routine clinical care.[69] Whether or not very large amounts of motor training at the early subacute stage can substantially improve recovery and outcomes remains an open and important question.[70,71]

A prospective observational study of people at the chronic stage of stroke found that 90 h of physical therapy distributed over 5 days per week for 3 weeks reduced upper limb motor impairment.[72] However, this study is limited by unblinded assessments and the absence of a control group. Another study randomly assigned participants at the chronic stage to three physical therapy interventions and found that 300 h of therapy distributed over 5 days per week for 12 weeks also reduced upper limb motor impairment, with no effect of group allocation.[73] Thus, further therapy at the chronic stage can be beneficial, although the possible contributions of reversing non-use of the paretic upper limb and general physical deterioration is unknown. A dose effect does not appear to be present as both studies report improvements in mean upper extremity Fugl-Meyer Assessment score of around 9–10 points, despite a 3 times difference in therapy dose.[74,75] Overall, some rehabilitation service appears to be better than none in the context of RCTs[56] as well as in clinical practice.[69,74]

Some studies have tested new ways to increase the amount of rehabilitation delivered while minimising the need for additional resources. In addition to telerehabilitation,[12] one approach is to train family members and caregivers to deliver therapy. A meta-analysis of six trials of caregiver-mediated exercise with 333 participants was inconclusive because of the trials' general low quality.[75] Since then, family-led rehabilitation in the ATTEND trial, which randomly assigned 1250 participants within 1 month after stroke, was able to more than double the amount of inpatient rehabilitation (5 h *vs* 2 h), as well as enabling 30 additional daily minutes for 1 month following discharge from the hospital.[76] The additional rehabilitation provided by family members did not result in better outcomes, measured with the modified Rankin Score. Shifting rehabilitation to family or caregivers can effectively and safely increase the amount of therapy completed; however, the greater amounts of therapy achieved in the trials did not provide added benefit.

In summary, currently available conventional therapies can improve outcomes after stroke, as indicated by the benefits had by participants in control groups. These benefits mainly involve improved activity capacity, which in turn can reduce disability, caregiver burden, and institutionalisation, and improve participation and quality of life.[61] Novel interventions that interact with the mechanisms of spontaneous biological recovery are needed to reduce motor impairment after stroke and enable more independent activity and participation. In the meantime, making sure that people with stroke have access to rehabilitation services is the best option for improving their motor capacity and performance in daily life.

### Search strategy and selection criteria

References for this Review were identified through searches of PubMed for articles published from Jan 1, 2014, to July 5, 2019. We used combinations of the terms "stroke", "rehabilitation", and "trial", and applied no language restrictions. We also identified articles through searches of our own files. Multicentre RCTs with blinded assessment that randomly assigned at least 100 participants were considered if they tested an intervention that involved motor rehabilitation therapy or had a primary endpoint that evaluated voluntary motor function, or both. Trials with a primary endpoint measure of general disability or independence, such as the AVERT trial by the AVERT Trial Collaboration group, are outside the scope of this Review because neither the intervention nor the primary endpoint measure were specific to rehabilitation of voluntary movement. The final reference list was selected by author consensus on the basis of originality, impact, and topical relevance.

## Conclusion and future directions

The increasing number of large, multicentre RCTs at the early subacute stage is a positive development in the field of stroke rehabilitation research. To date, most trials have been neutral, in that the experimental and control interventions produce similar benefits for motor recovery and outcomes. This Review suggests ways to improve the design and conduct of future stroke rehabilitation trials (panel 3). These suggestions include widening inclusion criteria to include ischaemic and haemorrhagic stroke types when warranted, patients with history of previous stroke, and those with communication difficulties, to improve both the recruitment rate and the generalisability of results. This Review also includes suggestions for narrowing inclusion criteria by recruiting patients within a short time-window early after stroke and using biomarkers for patient selection, to reduce inter-subject variability and enrich the sample. Future trials will also benefit from improving treatment fidelity and concealment, the use of domain-specific primary endpoint measures that are carefully aligned with the intervention's mechanisms of action, and reducing barriers to research participation. Clinical practice can continue to identify and remove barriers that limit patients' access to appropriate rehabilitation services, so that as better treatments become available the capacity to deliver them will improve.

#### Contributors

CMS did the initial literature search. All authors contributed equally to writing and revising all aspects of the manuscript.

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