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# BMJ Open

## The effect of rehabilitation interventions on physical function and immobility-related complications in severe stroke- a systematic review

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3 The effect of rehabilitation interventions on physical function and immobility-related  
4 complications in severe stroke- a systematic review  
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**ABSTRACT**

Objective: To evaluate the effectiveness of rehabilitation interventions on physical function and immobility-related complications in severe stroke.

Design: Systematic review of electronic databases (MEDLINE, EMBASE, CINAHL, AMED, PEDro, DORIS, CENTRAL) searched between January 1987 and November 2018.

Methods: The PRISMA statement guided the review. Randomised controlled trials comparing the effect of one type of rehabilitation intervention to another or usual care on physical function and immobility-related complications for patients with severe stroke were included. Studies that recruited participants with all levels of stroke severity were included only if subgroup analysis based on stroke severity was performed. Two reviewers screened search results, selected studies using pre-defined selection criteria, extracted data and assessed risk of bias for selected studies using piloted proformas. Marked heterogeneity prevented meta-analysis and a descriptive review was performed. The GRADE approach was used to assess the strength of the evidence.

Results: 28 studies (n=2,677, mean age 72.7 years, 49.3% male) were included in the review. 24 studies were rated low or very low quality due to high risk of bias and small sample sizes. There was high quality evidence that very early mobilisation and OT intervention in care homes were no more effective than usual care. There was moderate quality evidence supporting short-term benefits of wrist and finger neuromuscular electrical stimulation in improving wrist extensor and grip strength, additional upper limb training on improving upper limb function and additional lower limb on improving upper limb function, independence in activities of daily living, and gait speed and independence.

Conclusions: There is a paucity of high-quality evidence to support the use of rehabilitation interventions to improve physical function and reduce immobility-related complications after severe stroke. Future research investigating more commonly used rehabilitation interventions, particularly to reduce post-stroke complications, is required.

PROSPERO registration number: CRD42017077737

Keywords: stroke rehabilitation, physiotherapy, occupational therapy

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first systematic review to investigate rehabilitation interventions specifically to survivors of severe stroke
- The review included outcomes on immobility-related post-stroke complications, which contribute to high levels of caregiver burden
- Marked heterogeneity of included studies prevented meta-analysis
- Most included studies were rated as low or very low-quality evidence due to unclear or high risk of bias as well as recruitment of very small samples

## INTRODUCTION

Despite advances in stroke management over recent decades, stroke remains one of the most common causes of death and disability globally. |1,2| The mainstay of treating stroke is stroke rehabilitation, which aims to enable a person to achieve their optimal physical, cognitive, communicative, emotional and social level of function. |3-5| Rehabilitation of physical function comprises a large component of stroke rehabilitation programmes delivered by health-care professionals, such as physiotherapists and occupational therapists.6-8 Whilst several systematic reviews support the use of rehabilitation interventions to improve aspects of physical function, such as motor function, balance, walking speed and activities of daily living, |9-11| it is not clear from these reviews if these interventions are effective for survivors of differing levels of stroke severity, particularly severe stroke.

Severe stroke can be understood as a stroke resulting in a significant amount of brain tissue damage and multiple neurological impairments, which leads to a significant loss of function and residual disability. |12| Dependent upon how it is measured, 14 - 31% of people who sustain a stroke globally are classified as having a severe stroke, |13-18| a cohort of the stroke population that experiences worse outcomes compared to survivors of less severe stroke. |19-30| In the initial hospitalisation phase post-stroke, they are more likely to develop acute medical complications, which are negatively associated with functional recovery. |19| Three month mortality can be as high as 40%, compared to just under 5% for those patients with mild stroke. |20-22| Survivors of severe stroke spend longer in hospital, resulting in increased hospital costs, and demonstrate slower and less functional recovery, resulting in greater dependency when they are discharged from hospital. |14,15,23,25| For those discharged from hospital, survivors of severe stroke are at least eight times more likely to be discharged to a nursing home. |25,26| Longer-term care costs, which mostly support survivors of severe stroke, represent 49% of total stroke care spending globally. |27| In the first year post severe stroke, mortality can be as high as 60% |20| and survivors of severe stroke also experience very high levels of immobility-related complications, such as falls, contracture, pain, and pressure sores. |28,29| Due to this residual disability, the physical assistance provided by caregivers to look after survivors of

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3 severe stroke as well as the psychosocial and emotional impact of the stroke on caregivers  
4 result in high levels of caregiver burden. |30|  
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9 As there are a number of significant issues faced by survivors of severe stroke, rehabilitation  
10 of severe stroke should focus on addressing these poor outcomes, particularly reduced  
11 physical function and its associated complications. However, the extent to which  
12 rehabilitation can address these outcomes is not clear. A previous systematic review  
13 demonstrated positive benefits of inpatient stroke rehabilitation, such as reduced mortality  
14 and hospital length of stay, and uncertain benefit on improving functional recovery. |31|  
15 However, this review did not explore the effect of specific interventions delivered within  
16 inpatient rehabilitation on improving physical function or on reducing immobility-related  
17 complications. Most trials investigating the efficacy of rehabilitation interventions on  
18 physical function have either not recruited survivors of severe stroke or not reported results  
19 specifically for survivors of severe stroke. |9-11| Therefore, it is not known if research  
20 findings are applicable to survivors of severe stroke. It is not clear whether rehabilitation  
21 should focus more on functional restoration, which may be incomplete or not possible, or  
22 reducing immobility-related complications, which may lessen longer-term burden for  
23 caregivers of severe stroke survivors. Due to this lack of clarity, there is an urgent need to  
24 summarise evidence-based rehabilitation interventions designed to optimise physical  
25 function and reduce immobility-related complications for this cohort of the stroke  
26 population.  
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43 This systematic review aims to establish the effectiveness of rehabilitation interventions on  
44 physical function and immobility-related complications for survivors of severe stroke and  
45 identify areas for future rehabilitation research for these patients.  
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## 50 **METHODS**

51 The systematic review has been reported according to the Preferred Reporting Items for  
52 Systematic Reviews and Meta-analysis (PRISMA) statement (see supplementary file 1). |32|  
53 The protocol for the systematic review has been published previously. |33|  
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## Study design

The systematic review included randomised controlled trials (RCTs). The systematic review excluded quasi-experimental, correlational and descriptive study designs. Studies were selected according to the PICO (participant, intervention, comparator and outcome) format. The systematic review protocol provides full details of the PICO components. | 33 |

## Search strategy

### Information sources

Electronic searches of the following databases were conducted: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Allied and Complementary Medicine Database (AMED), Physiotherapy Evidence Database (PEDro), Database of Research in Stroke (DORIS) and the Cochrane Central Register of Controlled Trials (CENTRAL). An example search strategy is shown in supplementary file 2. Databases were searched from January 1987 to November 2018. The search timeframe was guided by a scoping review of the literature (demonstrating very few published RCTs before 2000) and a consideration to include studies reflecting current clinical practice. Ongoing studies were identified by searching the Stroke Trials Registry ([www.strokecenter.org/trials/](http://www.strokecenter.org/trials/)) and clinicaltrials.gov. These sources were searched from 2012 to 2018 as it was assumed that studies before these dates would have been completed and published. References from included studies were hand searched and any potentially relevant study was included for review. Forward citation checks of included studies were also performed. To avoid language or cultural bias, studies in any language or geographical location were included.

## Data management and study selection

The results from the literature search were uploaded to a reference management programme (Refworks) and duplicate references were removed. A final list of non-duplicated references was generated by one author (MM). The titles and abstracts of the search results were screened independently by two review authors (MM and JJ) and full text articles were obtained for relevant studies. Full text articles were reviewed by the same two authors (MM and JJ) independently to determine if studies met the inclusion criteria using an inclusion/exclusion checklist previously piloted. Any difference in opinion between the



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3 two authors were resolved by a third review author (CS). Two review authors (MM and JJ)  
4 independently performed data extraction for all eligible articles using a data extraction  
5 proforma previously piloted.  
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### 10 11 **Risk of bias and quality assessment**

12 Risk of bias was assessed by two review authors independently (MM and JJ) using the  
13 Cochrane Collaboration tool for assessing the risk of bias across six main domains (sequence  
14 generation, allocation concealment, blinding, incomplete outcome data selective outcome  
15 reporting, other bias) . [34] A risk of bias judgement of 'high', 'low' or 'unclear' was  
16 determined for each of these main domains. The strength of evidence was assessed using  
17 the Grading of Recommendations Assessment, Development and Evaluation (GRADE)  
18 approach. [34] The five domains considered by the GRADE approach included risk of bias,  
19 inconsistencies between studies, indirectness, imprecision and publication bias. The quality  
20 of the evidence was ranked high, medium, low or very low by two review authors  
21 independently (MM and JJ).  
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### 33 **Data analysis**

34 As stated in the systematic review protocol, it was decided that if more than five adequately  
35 powered studies demonstrate homogeneity in terms of rehabilitation interventions and  
36 outcomes, results for individual outcomes would be pooled quantitatively using meta-  
37 analysis. Due to the limited number and marked heterogeneity in rehabilitation  
38 interventions and outcomes of the selected studies, it was not appropriate to undertake a  
39 meta-analysis. Therefore, a descriptive review of results was performed. As there may be  
40 differences in recovery rates and outcomes according to the time post-stroke, studies were  
41 grouped into three timeframes post-stroke determined on the basis of when participants  
42 were recruited to the study and when the study finished. These timeframes were the acute  
43 to early subacute stage (up to 3 months post-stroke), acute to late-subacute stage (up to 6  
44 months post-stroke) and chronic stage (greater than 6 months post-stroke). These  
45 timeframes were chosen based on recommendations for the standardised measurement of  
46 sensorimotor recovery in stroke trials. [35] Study findings were presented according to  
47 these three timeframes.  
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## RESULTS

The initial literature review identified 7589 articles (Figure 1). After removing duplicates and screening titles and abstracts, 1083 full text articles were assessed for eligibility. 28 studies were included in the systematic review.<sup>[36-67]</sup> 2677 participants were recruited to these studies- mean participant age was 72.7 years and 49.3% were male. The main reasons for excluding studies were due to not recruiting participants with severe stroke, not providing results separately for participants with severe stroke or not providing sufficient information to determine if the participants had sustained a severe stroke.

The characteristics of the included studies are provided as tables in the supplementary file 2. 16 studies were completed within the acute-early subacute phase, eight studies were completed within the acute-late subacute phase and four studies were completed within the chronic phase post-stroke. 20 different interventions were evaluated across the 28 studies. The assessment of risk of bias for each study is presented in Figure 2.

### Outcomes

60 measures of physical function and immobility-related post-stroke complications were identified across the studies. The measures were classified as measures of body function (n=18), activity (n=26), participation (n=8) and post-stroke complications (n=8). These measures were grouped together as 16 different outcomes:

- Body function: cardiorespiratory function, neurological impairment, sensorimotor function
- Activity: activities of daily living (ADLs), balance and postural control, gait, general physical activity, upper limb function
- Participation: extended ADLs, perceived health status, quality of life
- Complications: caregiver burden, depression, mortality, shoulder pain/dislocation, spasticity

For each outcome, there was usually only one study investigating the effectiveness of a specific rehabilitation intervention in each time frame post-stroke. Most of these studies were rated as providing very low or low-quality evidence for these outcomes (see supplementary file 2). Outcomes which were supported by studies providing moderate or

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3 high quality of evidence are reported in this section. Forest plots are included for key  
4 outcomes, although effect sizes were not estimable for studies that did not provide raw  
5 data and were not pooled due to heterogeneity in rehabilitation outcomes.  
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## 10 Body function

### 11 *Sensorimotor Function*

12 Seventeen studies evaluated changes in sensorimotor function. Ten studies were completed  
13 in the acute to early subacute phase post-stroke, |38-40,42,43,45-49| five studies were  
14 completed in the acute to late subacute phase post-stroke |53,56,60,62,63| and two studies  
15 were completed in the chronic phase post-stroke. |64,66| The most frequently used  
16 outcome measures of sensorimotor function were the Fugl-Meyer Assessment, used in 11  
17 studies, and the MRC scale for muscle strength, used in 5 studies. Figure 3 provides a visual  
18 representation of the studies' effect sizes.  
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20 In the acute to early subacute phase post-stroke, there was moderate quality evidence from  
21 one study that a 6-week course of neuromuscular electrical stimulation (NMES) applied to  
22 the wrist and finger extensors in conjunction with usual therapy resulted in no improvement  
23 in wrist active movement compared to usual therapy. |49| Wrist strength and grip strength  
24 improved in the NMES group during the treatment period although these improvements  
25 were not evident at the 9-month follow-up.  
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## 40 Activity

### 41 *Activities of Daily Living*

42 Twenty studies explored independence and ability to perform activities of daily living (ADLs).  
43 Eleven studies were completed in the acute to early subacute phase, |36,37,41-43,45-50|  
44 seven studies were completed in acute to late subacute phase |52,54-57,60-63| and two  
45 studies were completed in the chronic phase. |65,67| Eighteen studies used the Barthel  
46 Index as the main outcome measure to assess independence in ADLs. Four studies used the  
47 Modified Rankin Scale and three studies used the Functional Independence Measure. Figure  
48 4 provides a visual representation of studies' effect sizes.  
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50 In the acute to early subacute phase, there was high quality evidence that frequent, higher  
51 dose, very early mobilisation commencing within 24 hours post-stroke did not result in more  
52 patients being less dependent in ADLs at 3 months post-stroke compared to usual care,  
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3 which traditionally started more than 24 hours post-stroke. |36| However, caution is  
4 required with interpreting this finding as the sub-group analysis of patients with severe  
5 stroke was not powered for this outcome. There was moderate quality evidence that a 6-  
6 week course of NMES applied to the wrist and finger extensors in conjunction with usual  
7 therapy resulted in no difference in ADL independence compared to usual care. |49|

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12 In the acute to late subacute phase, there was moderate quality evidence that additional LL  
13 therapy in conjunction with regular physical rehabilitation performed in the first 20 weeks  
14 post-stroke improved ADL independence whilst the intervention was being delivered when  
15 compared to regular physical rehabilitation alone. |57| However, these improvements were  
16 not seen 6 months post-stroke.

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21 In the chronic phase, there was high quality evidence that a 3-month OT intervention  
22 provided to residents in care homes resulted in no difference in ADL independence  
23 compared to usual care. |65| Similar caution is required with interpreting this finding as the  
24 sub-group analysis of patients who were severely or very severely disabled was not  
25 powered for this outcome.  
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### 31 32 *Gait*

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Nine studies investigated gait, which included gait ability and gait speed. Six studies were  
performed in the acute to early subacute phase, |38-40,43,45,48| two studies were  
performed in the acute to late subacute phase |57,60| and one study was performed in the  
chronic phase. |64| The Functional Ambulation Classification was used in eight studies,  
making it the most frequently used outcome measure of gait ability. The 10-metre walk test  
was used in five studies, making it the most frequently used outcome measure of gait  
speed. Figure 5 provides a visual representation of studies' effect sizes.

Only one study demonstrated moderate quality evidence. In the acute to late subacute  
phase, additional LL therapy in conjunction with regular physical rehabilitation performed in  
the first 20 weeks post-stroke improved gait ability and speed when compared to regular  
physical rehabilitation alone. |57| However, these improvements were not seen 6 months  
post-stroke.

### *General Physical Activity*

Eight studies examined the effects of different interventions on improving general physical activity. Six studies were performed in the acute to early subacute phase, |37,38,40,45,46,51| one study was performed in the acute to late subacute phase |60| and one study was performed in the chronic phase. |65| General physical activity was defined as a composite of multiple physical tasks completed within one assessment, such as upper or lower limb function, transfers, gait and balance. Outcome measures used to assess general physical activity included the Rivermead Mobility Index, Rivermead Mobility Assessment and Motor Assessment Scale. Only one study demonstrated high quality evidence. In the chronic phase, a 3-month OT intervention provided to residents in care homes resulted in no difference in physical activity compared to usual care. |65|

### *Upper Limb Function*

Four studies investigated changes in upper limb function, |46,49,57,66| of which two provided moderate quality evidence. |49,57| In the acute to early subacute phase, a 6-week course of NMES applied to the wrist and finger extensors in conjunction with usual therapy resulted in no difference in upper limb function compared to usual care. |49| In the acute to late subacute phase, additional UL or LL therapy in conjunction with regular physical rehabilitation performed in the first 20 weeks post-stroke improved upper limb function 6 months post-stroke when compared to regular rehabilitation. |57|

### *Participation*

#### *Extended Activities of Daily Living*

Five studies investigated the effect of different interventions on extended ADLs, |37,38,44,56,57| of which one provided moderate quality evidence. In the acute to late subacute phase, additional UL or LL therapy in conjunction with regular physical rehabilitation performed in the first 20 weeks post-stroke improved performance in extended ADLs 6 months post-stroke when compared to regular rehabilitation. |57|

#### *Quality of Life*

Three studies examined quality of life, |54,57,65| of which two were moderate or high quality. |57,65| In the acute to late subacute phase, there was moderate quality evidence

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3 that there was no benefit of additional UL or LL therapy to regular physical rehabilitation  
4 performed in the first 20 weeks post-stroke on improving quality of life 6 months post-  
5 stroke. |57| In the chronic phase, there was high quality evidence that a 3-month OT  
6 intervention provided to residents in care homes resulted in no difference in quality of life  
7 compared to usual care. |65|  
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#### 14 Complications

##### 15 *Depression*

16 Four studies explored changes in depression, |37,55,65,66| of which one was high  
17 quality. |65| In the chronic phase, a 3-month OT intervention provided to residents in care  
18 homes resulted in no difference in depression compared to usual care.  
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##### 25 *Mortality*

26 One study investigated the effect of very early mobilisation on mortality. |36| There was  
27 high quality evidence that frequent, higher dose, very early mobilisation commencing within  
28 24 hours post-stroke did not result in more patients dying at 3 months when compared to  
29 usual care, which traditionally started more than 24 hours post-stroke.  
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#### 36 Other Outcomes

37 There was low quality of evidence for cardiorespiratory function (2 studies) |39,43| and  
38 caregiver burden (1 study). |37| There was very low to low quality of evidence for  
39 neurological impairment (3 studies), |41,60,62| balance and postural control (8  
40 studies), |37,40,45,51,53,60,64,67| perceived health status (2 studies), |37,66| shoulder  
41 pain and dislocation (1 study), |66| and spasticity (6 studies). |38,43,46,52,60,66| Further  
42 details of these outcome and studies are included in the supplementary file 2.  
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## 51 **DISCUSSION**

### 52 **Main Findings**

53 Although 28 RCTs investigating 20 different rehabilitation interventions were identified in  
54 this review, there was a paucity of high-quality evidence to support the use of these  
55 interventions to improve physical function and reduce immobility-related complications  
56 after severe stroke. Most studies were rated as low or very low-quality evidence due to  
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3 unclear or high risk of bias as well as recruitment of very small samples. The majority of  
4 these studies were single centre RCTs, further reducing their generalisability to wider clinical  
5 practice. Only two large, multicentre studies were rated as high quality. [36,65] In both  
6 studies, results suggested that the treatment intervention was no more effective than usual  
7 care practice. However, patients with severe stroke or severe disability post-stroke  
8 comprised a smaller sample within these larger trials. Analyses of data from these sub-  
9 groups may not be powered to detect changes between the treatment and usual care  
10 interventions and therefore caution is required in interpreting the studies' findings.  
11 In the AVERT trial, [36] very early and frequent mobilisation commencing within 24 hours  
12 post-stroke did not result in more patients being less dependent in ADLs or dying at 3  
13 months post-stroke compared to usual care, which traditionally started more than 24 hours  
14 post-stroke. However, there was a trend in the data towards favouring usual care practice  
15 for patients with severe stroke. It could be argued that patients with severe stroke, who  
16 often present with multiple physical and cognitive impairments, may be less likely tolerate  
17 very early and intensive therapy in the first few days after stroke. This would suggest that  
18 mobilising patients less intensively after 24 hours may be more beneficial than very early  
19 and frequent mobilisation. In the OT in care home trial, [65] a 3-month, goal-orientated OT  
20 intervention for stroke survivors living in care homes did not result in improved ADL ability,  
21 quality of life or reduced depression up to 1-year post-intervention. The authors  
22 hypothesised that the lack of treatment effect may have been due to the care home  
23 residents' disability severity, which may have limited their engagement in therapy.  
24 However, a content analysis of the OT intervention by the research team revealed that the  
25 mean number of OT visits over the period was 5.1 (SD 3.0), the median session time was 30  
26 minutes (IQR 15-60 minutes) and only 15% of OT time was used to provide ADL and mobility  
27 training. Although session length and duration were dependent upon the care home  
28 resident's ability to engage, it is possible that a more frequent OT intervention that focussed  
29 more on ADL and mobility training may have resulted in different findings.

### 54 **Implications for Practice and Research**

56 In light of these findings, it may be necessary to re-evaluate the design of future trials  
57 investigating rehabilitation interventions in severe stroke. As it is not known if survivors of  
58 severe stroke respond to interventions in the same ways as survivors of milder stroke, there  
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3 may be a need for more proof of concept studies to understand the mechanisms of recovery  
4 in severe stroke more fully. The high number of small, low-quality, single-centre RCTs  
5 investigating a broad range of interventions may suggest that larger, high-quality multi-  
6 centre RCTs investigating fewer interventions are warranted. However, outcome  
7 evaluations alone are insufficient to understand why certain interventions do or do not  
8 work. It is recommended that evaluations of complex interventions, such as stroke  
9 rehabilitation, use process evaluations alongside outcome evaluations. [68] Process  
10 evaluations enable an understanding of how to implement an intervention as well as how  
11 participants respond to and interact with the intervention. Therefore, future trials should be  
12 guided by more proof of concept research and involve both outcome and process  
13 evaluations.  
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16 In this review, the most frequently investigated outcomes were functional tasks, such as  
17 ADLs and gait ability. However, Pereira et al. has suggested that individuals with severe  
18 stroke are likely to make limited functional improvement with inpatient rehabilitation in the  
19 their review of rehabilitation after severe stroke. [31] They also advocated more focus on  
20 discharge planning and reducing post-stroke complications during inpatient rehabilitation  
21 for patients with severe stroke. Whilst the extent to which patients can improve functionally  
22 after severe stroke is not clear, there is merit in further exploring the effect of rehabilitation  
23 in the prevention and management of post-stroke complications in severe stroke. Sackley et  
24 al. investigated the prevalence of immobility-related complications in the first year after  
25 severely disabling stroke and found a very high prevalence of falls, contractures, pain and  
26 pressure sores. [28] However, with the exception of spasticity, there was very little focus on  
27 the prevention or management of post-stroke complications in the studies selected for our  
28 systematic review. In addition to a lack of focus on immobility-related complications, only  
29 one study explored caregiver burden, known to be very high amongst carers looking after  
30 survivors of severe stroke. [30] Future research in the rehabilitation of severe stroke should  
31 therefore focus more on the effectiveness of rehabilitation interventions in the prevention  
32 and management of immobility-related complications in severe stroke.  
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35 This review identified several studies investigating technological interventions, such as  
36 treadmill training and robot-assistive devices, and more novel interventions, such as  
37 thermal stimulation. However, it is not clear how commonly used these interventions are in  
38 clinical practice. Additionally, there were no trials studies of interventions commonly used  
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3 with survivors of severe stroke, such as positioning, sitting balance and seating. |69| This  
4 mismatch between available research evidence, which may not reflect current practice, and  
5 clinical practice, which may have limited research evidence to support its use, may present a  
6 dilemma for therapists, who are expected to base healthcare decisions on the best available  
7 and relevant evidence. |70| Therefore, future research is required to understand what  
8 interventions are currently being used in clinical practice. Knowledge of currently used  
9 rehabilitation interventions may guide future trials investigating their efficacy in improving  
10 physical function and reducing immobility-related post-stroke complications.  
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### 20 **Strengths and Limitations**

21 In terms of strengths, this is the first systematic review to investigate rehabilitation  
22 interventions specifically to survivors of severe stroke, who tend to be underrepresented in  
23 stroke rehabilitation research, and the identification of topics for future rehabilitation  
24 research will hopefully guide much needed research for this cohort of the stroke population.  
25 As well, the outcomes of the review focussed on not just physical function but immobility-  
26 related post-stroke complications, which are known to be higher in the severe stroke  
27 population and contribute to high levels of caregiver burden. |28-30| In terms of limitations,  
28 it has been reported that the defining severe stroke is difficult due to different criteria used  
29 to classify severity. |71| The use of objective scores on validated outcome measures to  
30 classify stroke severity in our systematic review, necessary to ensure that participants had  
31 actually sustained a severe stroke, may have precluded the inclusion of studies that either  
32 used different scoring systems or outcome measures to classify stroke severity. However,  
33 these studies were discussed in detail amongst three review authors to determine suitability  
34 for inclusion and therefore it is likely that the number of relevant studies excluded from the  
35 review was minimal. Another limitation is the use of data from subgroups within larger  
36 clinical trials. As subgroup analyses may not be powered to detect changes between groups,  
37 caution is required in the interpretation of findings from these trials. In addition, raw  
38 subgroup data were not fully reported in some studies preventing estimation of effect sizes.  
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### 55 **CONCLUSION**

56 There was a paucity of high-quality evidence to support the use of rehabilitation  
57 interventions to improve physical function and reduced immobility-related complications  
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3 after severe stroke. Future research should be guided by more proof of concept studies and  
4 involve outcome and process evaluations to more fully understand the impact of different  
5 interventions on patients with severe stroke. Future research should investigate the effect  
6 of more clinically used interventions, such as positioning, sitting balance and seating. Future  
7 research should also investigate the effect of interventions on post-stroke complications  
8 known to be high after severe stroke, such as contracture, pressure sores and caregiver  
9 burden.  
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### 18 **Authors' Contributions**

19 MM is the guarantor of the review. MM, CS and CM were involved in the design of the  
20 protocol and systematic review. MM conducted scoping searches. MM and JJ piloted the  
21 inclusion/exclusion form. MM piloted the data extraction form. MM was the first reviewer  
22 and JJ was the second reviewer for the systematic review. AD provided statistical support  
23 for the systematic review. MM drafted the manuscript. All authors read and approved the  
24 final manuscript.  
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### 32 **Competing Interests**

33 None declared.  
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### 38 **Funding**

39 This project forms part of MM's PhD which is funded by The Dunhill Medical Trust [grant  
40 number RT62/0116]. The funder has had no input on the design of the protocol and will  
41 have no input on the analysis and interpretation of the results of the systematic review, or  
42 publication of the systematic review.  
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### 49 **Patient consent**

50 Not required.  
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### 54 **Patient/public involvement**

55 Patients or the public were not involved in the design, conduct, reporting or dissemination  
56 of this research.  
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### 30 **FIGURE LEGENDS**

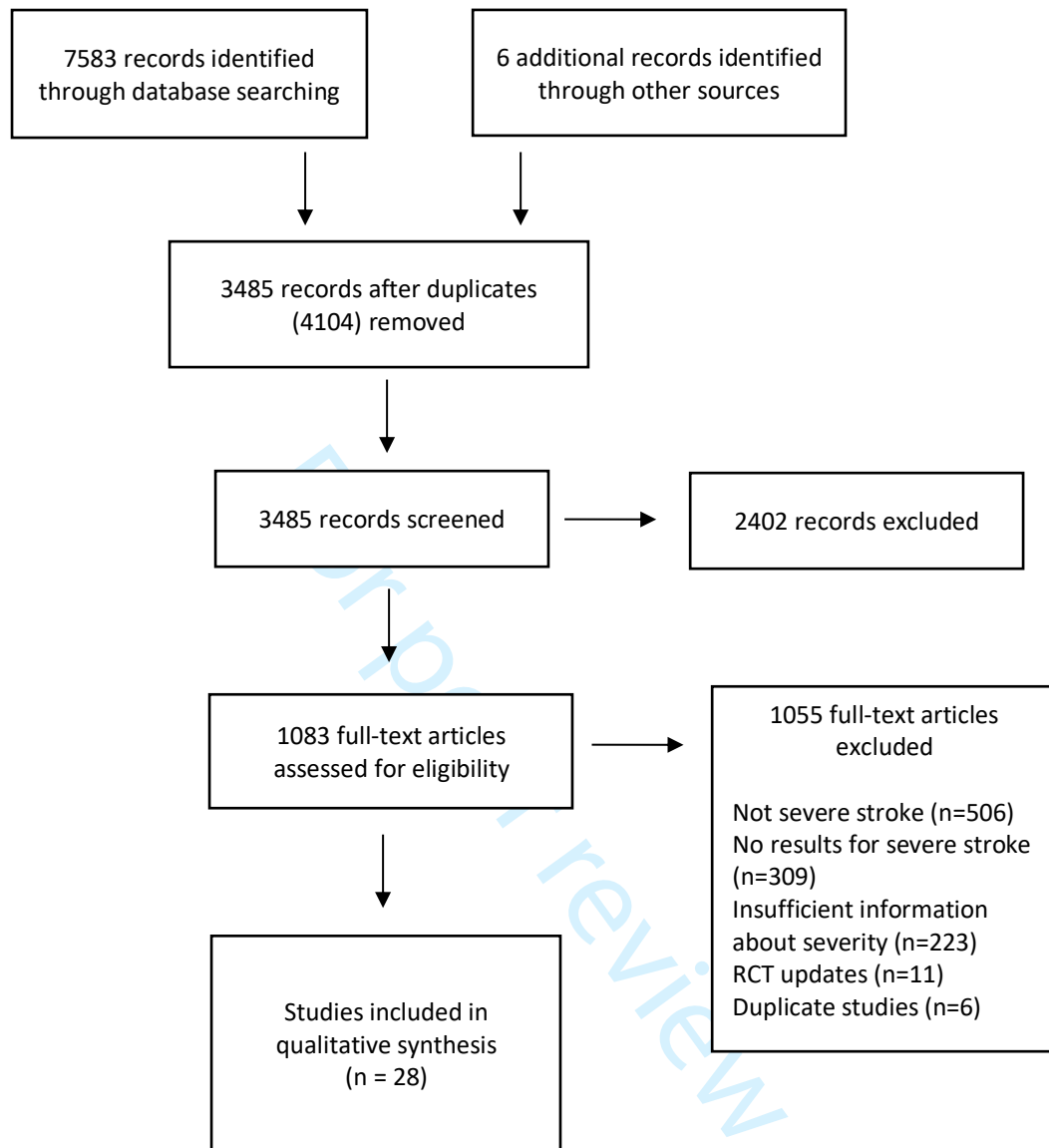
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32 Figure 1- Flow chart of studies

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34 Figure 2- Risk of bias of individual domains in the included studies

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36 Figure 3- Interventions for sensorimotor function

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38 Figure 4- Interventions for ADL ability and independence

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40 Figure 5- Interventions for gait ability and speed  
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Random sequence generation (selection bias)  
Allocation concealment (selection bias)  
Blinding of participants and personnel (performance bias)  
Blinding of outcome assessment (detection bias)  
Incomplete outcome data (attrition bias)  
Selective reporting (reporting bias)  
Other bias

AVERT Triallists' Colloboration 2015	+	+	+	+	+	+	?
Bagley et al. 2005	+	+	-	+	+	?	-
Bai et al. 2014	+	?	-	+	+	-	-
Bradley et al. 1998	+	?	-	+	?	?	+
Calabro et al. 2015	+	?	?	+	?	?	+
Chaiyawat and Kulkantrakorn 2012	+	+	-	-	+	?	-
Chang et al. 2012	+	+	?	+	+	?	+
Chen et al. 2011	+	+	?	+	+	?	+
di Lauro et al. 2003	+	+	?	+	+	?	-
Fong et al. 2013	+	+	?	+	+	?	+
Franceschini et al. 2009	+	?	?	+	-	?	?
Jongbloed et al. 1989	+	?	+	+	?	?	+
Katz-Leurer et al. 2003	+	?	?	+	?	?	+
Kwakkel et al. 1999	+	+	+	+	+	?	+
Liang et al. 2012	+	+	?	+	+	?	+
Lincoln et al. 1999	+	+	-	+	?	?	+
Min et al. 2008	?	?	-	?	?	?	+
Morone et al. 2011	+	?	?	+	+	?	+
Ochi et al. 2015	+	+	?	+	+	?	+
Rodrigues et al. 2017	+	+	?	+	?	?	+

Rosewilliam et al. 2012

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Sackley et al. 2015

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Sanchez-Sanchez et al. 2014

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Tang et al. 2014

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Volpe et al. 2008

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Yue et al. 2012

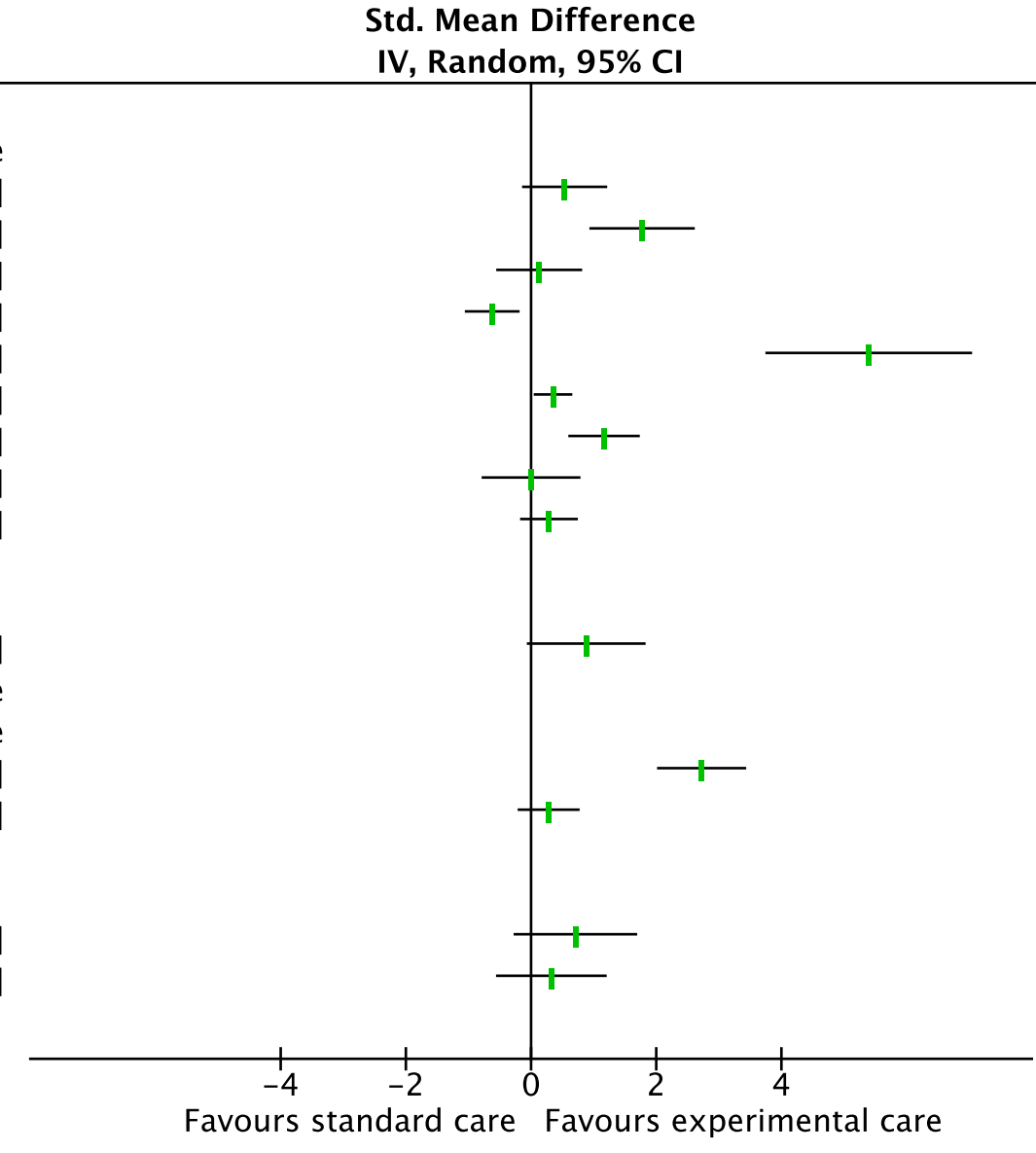
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Zhang and Li 2014

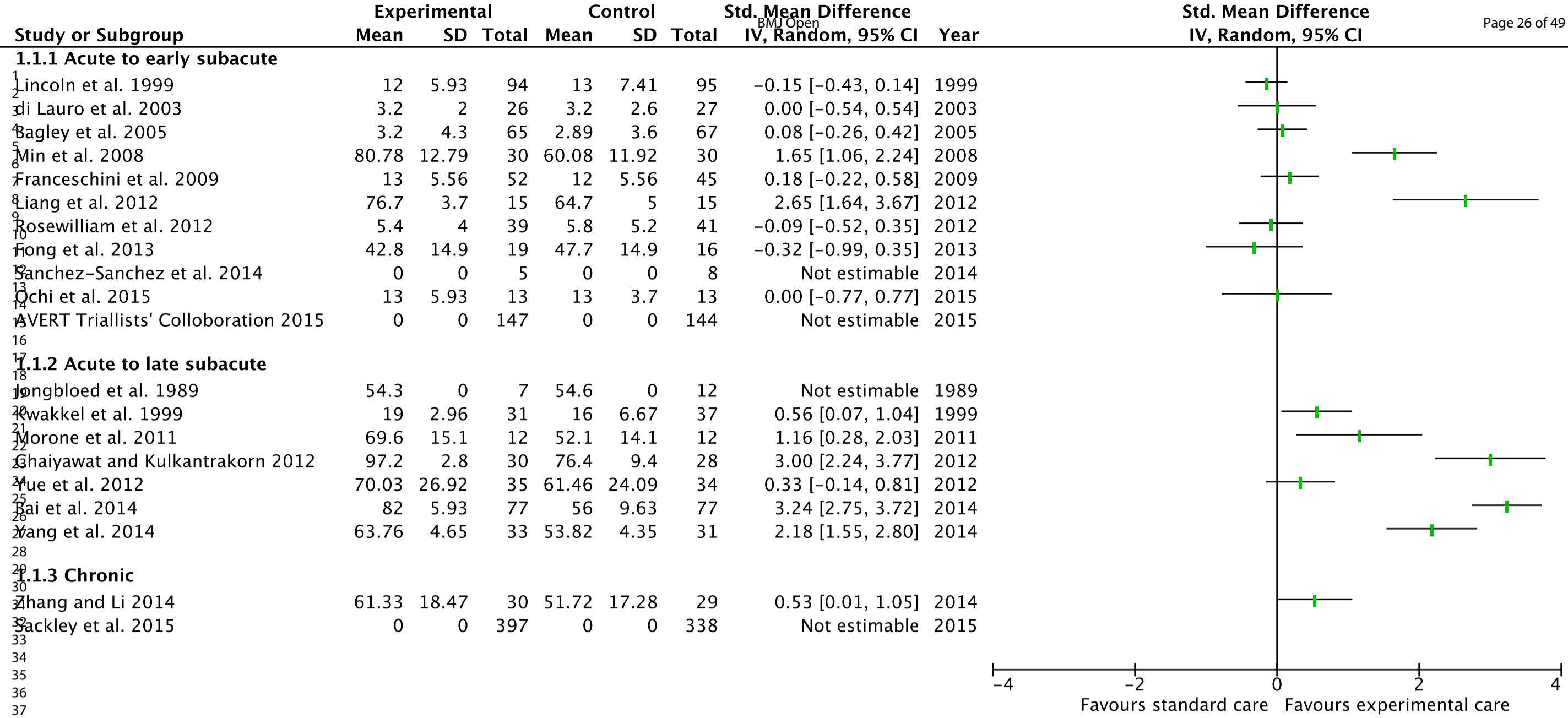
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Study or Subgroup	Experimental Mean	Experimental SD	Total	Control Mean	Control SD	Total	Std. Mean Difference IV, Random, 95% CI
<b>1.3.1 Acute to early subacute</b>							
Bradley et al. 1998	0	0	7	0	0	6	Not estimable
Chang et al. 2012	22.7	5.7	20	19.6	5.6	17	0.54 [-0.12, 1.20]
Chen et al. 2011	14	3.7	17	6	5.04	16	1.77 [0.95, 2.59]
Fong et al. 2013	12	11.3	19	10.6	9.5	16	0.13 [-0.54, 0.80]
Franceschini et al. 2009	59	30.37	52	76	22.59	42	-0.62 [-1.04, -0.20]
Liang et al. 2012	22.2	1.1	15	16.1	1.1	15	5.40 [3.77, 7.03]
Lincoln et al. 1999	11	36.3	94	0	25.19	95	0.35 [0.06, 0.64]
Min et al. 2008	75.37	10.02	30	64.21	8.83	30	1.17 [0.62, 1.72]
Ochi et al. 2015	9	8.89	13	9	7.41	13	0.00 [-0.77, 0.77]
Rosewilliam et al. 2012	10.2	16.2	39	6.3	10.3	41	0.29 [-0.15, 0.73]
<b>1.3.2 Acute to late subacute</b>							
Galabro et al. 2015	25	6	10	19	7	10	0.88 [-0.05, 1.81]
Jongbloed et al. 1989	0	0	7	0	0	12	Not estimable
Morone et al. 2011	0	0	12	0	0	12	Not estimable
Yang et al. 2014	37.55	2.09	33	28.71	4.07	31	2.72 [2.03, 3.42]
Zue et al. 2012	65.93	24.05	35	58.79	26.17	34	0.28 [-0.19, 0.76]
<b>1.3.3 Chronic</b>							
Rodrigues et al. 2017	20	1.48	10	18	3.7	8	0.71 [-0.26, 1.67]
Volpe et al. 2008	15.73	2	11	15.1	1.7	10	0.32 [-0.54, 1.19]



For peer review only



For peer review only

Study or Subgroup      Experimental      Control      Std. Mean Difference  
 Mean   SD   Total   Mean   SD   Total   IV, Random, 95% CI

Std. Mean Difference  
 IV, Random, 95% CI

1.2.1 Acute to early subacute

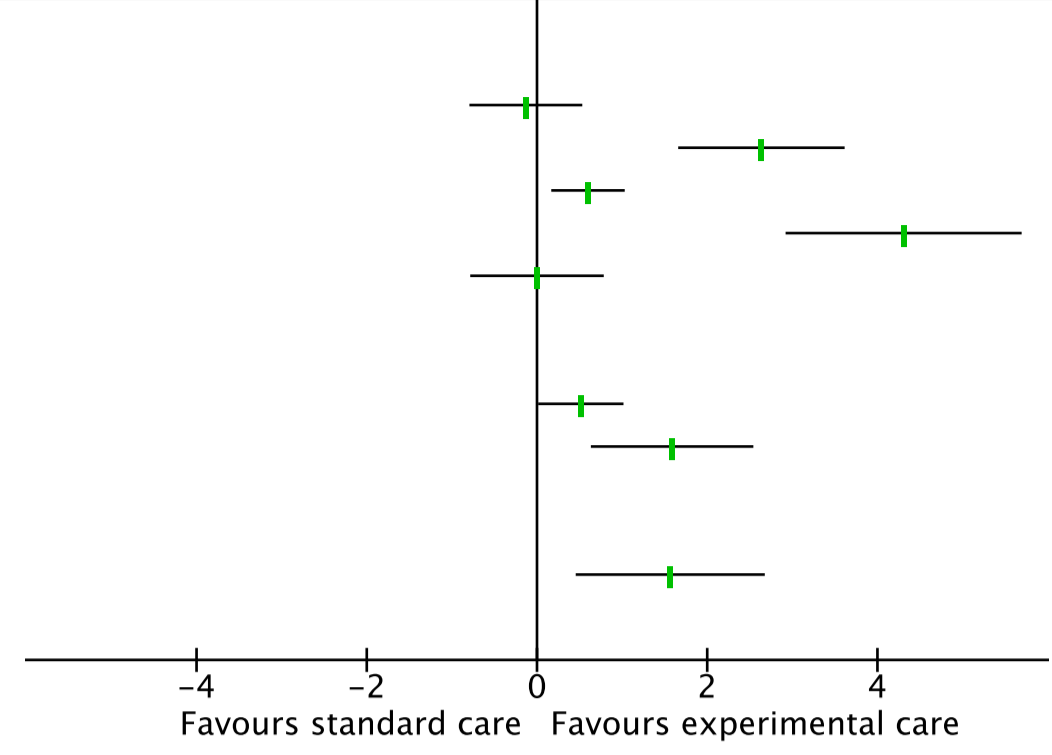
1	Bradley et al. 1998	0	0	6	0	0	4	Not estimable
2	Chang et al. 2012	1.3	0.7	20	1.4	0.8	17	-0.13 [-0.78, 0.52]
3	Chen et al. 2011	2	0.37	17	1	0.37	16	2.64 [1.67, 3.60]
4	Franceschini et al. 2009	3	1.48	52	2	1.85	42	0.60 [0.18, 1.02]
5	Liang et al. 2012	2.6	0.1	15	1.9	0.2	15	4.31 [2.94, 5.68]
6	Ochi et al. 2015	3	0.74	13	3	0.37	13	0.00 [-0.77, 0.77]

1.2.2 Acute to late subacute

7	Kwakkel et al. 1999	4	1.48	31	3	2.22	37	0.52 [0.03, 1.00]
8	Morone et al. 2011	2.6	0.9	12	1.2	0.8	12	1.59 [0.65, 2.53]

1.2.3 Chronic

9	Rodrigues et al. 2017	2.6	0.2	10	2.1	0.4	8	1.57 [0.47, 2.66]
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# PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract page
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Abstract page, 2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary file
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3, 4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3, 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	N/A



# PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary file
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary file, 6-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12, 13
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

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**Supplementary File 2**

## Supplementary Material- Medline Search Strategy

1. exp Stroke/
2. severe stroke.mp.
3. stroke severit\*.mp.
4. stroke disabilit\*.mp.
5. exp Physical Therapy Modalities/
6. exp Occupational Therapy/
7. exp Nursing Care/
8. physical rehabilitation.mp.
9. exp Stroke Rehabilitation/
10. exp Patient Positioning/
11. exp Posture/
12. exp Exercise/
13. exp Exercise Therapy/
14. passive exercise.mp.
15. exp "Range of Motion, Articular"/
16. manual technique.mp.
17. active exercise.mp.
18. Resistance Training/
19. exp Muscle Stretching Exercises/
20. exp Electric Stimulation/
21. exp Electric Stimulation Therapy/
22. exp Wheelchairs/
23. seat?.mp.
24. exp "Equipment and Supplies"/
25. exp Teaching/
26. exp Education/
27. exp Motor Skills/
28. exp Movement/
29. motor function.mp.
30. motor recovery.mp.
31. exp "Recovery of Function"/
32. exp "Activities of Daily Living"/
33. functional independence.mp.
34. physical independence.mp.
35. complicatio\*.mp.
36. exp Pain/
37. exp Contracture/
38. exp Pressure Ulcer/
39. exp Respiratory Tract Infections/
40. exp Urinary Tract Infections
41. Muscle Spasticity/
42. Venous Thrombosis/
44. exp Pulmonary Embolism/
44. exp Accidental Falls/
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- 12 56. limit 53 to ("all adult (19 plus years)" and randomized controlled trial)
- 13 57. limit 54 to ("all adult (19 plus years)" and randomized controlled trial)
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Supplementary Table 1- Studies conducted in the acute – early subacute (&lt;3 months) phase post-stroke

Study	Intervention Description	Intervention Duration	Intervention Delivered By	Stroke Severity Measure	Sample Size and Characteristics	Main Outcome Measures	Main Results	Quality of Evidence
AVERT trial collaboration group 2015 <sup>1</sup>	Very early mobilisation vs Usual care	Up to 14 days	PT and nursing staff	NIHSS	Very early mobilisation group NIHSS >16 (n=147) Usual care group NIHSS >16 (n=144)	Favourable outcome (mRS 0-2) and mortality at 3 months	No difference in favourable outcome or mortality between groups	High
Bagley et al. 2005 <sup>2</sup>	Oswestry standing frame + standard physiotherapy vs Standard physiotherapy	14 daily sessions	PTs	BI <sup>^</sup>	Oswestry group (n=71) Median BI 1 (IQR 0-3) Control group (n=69) Median BI 2 (IQR 1-3)	RMI, BI, HADS, NEADL, RMA, MAS (balance, sit to stand sections), TCT, CSI, GHQ-28	No differences between groups for all outcome measures. No differences in number of treatment sessions between groups or number of staff members required to treat each patient.	Low
Bradley et al. 1998 <sup>3</sup>	EMG biofeedback + conventional physiotherapy vs Placebo EMG + conventional physiotherapy	6 weeks	PTs	RMI	EMG group RMI ≤3 (n=7) Conventional PT group RMI ≤3 (n=6)	MBS, mAS, 10MWT, RMI, sensation, proprioception NEADL	No differences between groups for MBS, RMI, NEADL and 10MWT. No improvements in mAS, sensation and proprioception for both groups.	Very low
Chang et al. 2012 <sup>4</sup>	Robot-assisted BWS treadmill gait training + conventional physiotherapy vs Conventional physiotherapy	2 weeks	PTs	FAC LL FMA	Robot-assisted group (n=20) Mean FAC 0.5 (SD 0.5) Mean LL FMA 17.2 (SD 5.5) Conventional group (n=17) Mean FAC 0.4 (SD 0.5) Mean LL FMA 16.8 (SD 5.7)	FAC, LL MI, LL FMA, Peak VO <sub>2</sub>	Improvements in LL FMA and peak VO <sub>2</sub> in robot-assisted gait training group. No improvements in LL MI and FAC for both groups.	Low

1						Thermal stimulation group (n=17)		Thermal stimulation group demonstrated greater recovery gains compared to standard rehabilitation group in all outcomes except PASS.	
2						Median FAC 0 (IQR 0-1)	LL FMA, LL MRC, mAS, mMAS, PASS (trunk control items), BBS, FAC		Low
3	Chen et al. 2011 <sup>5</sup>	Thermal stimulation + standard rehabilitation vs Standard rehabilitation	6 weeks	Thermal stimulation- PTs	FAC LL FMA	Median LL FMA 7 (4-11.5)		No difference between groups in MAS.	
4				Standard rehabilitation- PTs and OTs		Standard rehab group (n=16)			
5						Median FAC 0 (IQR 0-1)			
6						Median LL FMA 6 (4.3-12.0)			
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12	Di Lauro et al. 2003 <sup>6</sup>	Intensive rehabilitative treatment vs Ordinary rehabilitative treatment	14 days	Therapists and nursing staff	BI^	Intensive rehab group (n=29)	BI, mNIHSS	No differences between groups in BI or mNIHSS	Very low
13						Mean BI 1.4 (SD 1.4)			
14						Ordinary rehab group (n=31)			
15						Mean BI 1.5 (SD 1.5)			
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22	Fong et al. 2013 <sup>7</sup>	Cueing wristwatch + conventional rehabilitation vs Sham wristwatch + conventional rehabilitation	3 weeks	Wristwatch- OTs	Motor FIM	Cueing wristwatch group (n=19) Mean motor FIM 25.6 (SD 8.3)	UL FMA, FTHUE, motor FIM, total number of UL movements	No differences between groups for UL FMA, FTHUE and motor FIM. More total UL movements in cueing wristwatch group but not significantly different between groups.	Low
23				Conventional rehab- OT, PT, ST		Sham wristwatch group (n=16)			
24						Mean motor FIM 28.2 (SD 10.0)			
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33	Franceschini et al. 2009 <sup>8</sup>	BWS treadmill gait training + conventional treatment vs Conventional treatment	4 weeks	PTs	BI^	Treadmill training group (n=52)	MI, TCT, mRS, BI, FAC, AS, LL proprioception, 6MWT, 10MWT, BS, WHS	No differences between groups. All patients were able to walk at discharge.	Low
34						Median BI 6 (IQR 3-9)			
35						Median FAC 0 (IQR 0-0)			
36						Conventional group (n=45)			
37						Median BI 5 (IQR 3-7)			
38						Median FAC 0 (IQR 0-0)			
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2	Katz-Leurer et	Leg cycle ergometer +		Leg cycle		Leg cycle ergometer and			
3	al. 2003 <sup>9</sup>	regular therapy	8 weeks	ergometer- PTs	SSS	regular rehabilitation	FAI	No differences in decline in FAI	Low
4		vs		Regular		groups- actual number of		between groups	
5		Regular therapy		therapy- PT, OT,		(SSS <30) not reported			
6				ST					
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11								Improvements in LL FMA, LL MRC,	
12	Liang et al.	Thermal stimulation +		Thermal		Thermal stimulation group		FAC and mMAS in thermal	
13	2012 <sup>20</sup>	standard rehabilitation	6 weeks	stimulation- PTs	BI*	(n=15)	LL FMA, LL MRC,	stimulation group post-intervention	
14		vs		Standard		Mean BI 30.3 (SD 11.1)	FAC, BBS, mMAS, BI	and at 3-month follow-up.	
15		Standard rehabilitation		rehabilitation-		Standard rehab group		Improvements in BBS and BI in	Low
16				PTs and OTs		(n=15)		thermal stimulation group only at 3-	
17						Mean BI 27.7 (SD 14.3)		month follow-up. Except for LL-FMA,	
18								all improvements disappeared at 6-	
19								month and 12-month follow-up.	
20									
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22		Standard physiotherapy +							
23		additional qualified PT				Qualified PT group (n=94)			
24		therapy				Median BI 6 (IQR 3-9)			
25		vs							
26	Lincoln et al.	Standard physiotherapy +		PTs/ PTAs	BI^	PTA group (n=93)	RMA- arm scale,	No differences between the groups	Low
27	1999 <sup>11</sup>	additional PTA therapy	5 weeks			Median BI 6 (IQR 4-8)	ARAT, THPT, grip	across all outcomes	
28		vs					strength, mAS, BI,		
29		Standard physiotherapy				Standard PT group (n=95)	MCA		
30						Median BI 7 (IQR 3-9)			
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35		Acupuncture + systemic				Acupuncture group (n=30)			
36		functional exercise		Not reported	BI*	Mean BI 27.28 (SD 5.41)	FMA, BI	Acupuncture group demonstrated	
37	Min et al.	vs	? 3 months					greater improvements in FMA and BI	Very low
38	2008 <sup>12</sup>	Systemic functional				Systemic exercise group		compared to the systemic exercise	
39		exercise				(n=30)		group	
40						Mean BI 28.01 (SD 4.48)			
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4		Robot-assisted treadmill				Robot-assisted group			
5		gait training + standard				(n=13) Median FAC 0 (IQR			
6	Ochi et al.	physiotherapy				0-1)			
7	2015 <sup>13</sup>	vs	4 weeks	Robot-assisted	FIM mobility	Median FIM mobility 7 (IQR	FAC, FMA, LL	Robot-assisted gait training group	Low
8		Conventional overground		gait training-	FAC	6-10)	muscle torque,	demonstrated greater improvements	
9		gait training + standard		Conventional			10MWT, FIM	in FAC and peak LL muscle torque	
10		physiotherapy		gait training-		Conventional group (n=13)	(mobility scores)	compared to the conventional group	
11				PTs		Median FAC 1 (IQR 0-1)			
12						Median FIM mobility 7 (IQR			
13						7-9)			
14									
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16		Wrist and finger NMES +		NMES- staff		NMES group (n=31)		No differences in ARAT, BI or wrist	
17	Rosewilliam	usual care	6 weeks	group not	BI^	Mean BI 4.4 (SD 3.9)	ARAT, BI, wrist	AROM between groups.	Moderate
18	et al. 2012 <sup>14</sup>	vs		reported,		Mean ARAT 0.0 (SD 0.0)	AROM, wrist	Improvements in wrist extensor and	
19		Usual care		patients and		Usual care group (n=36)	strength, grip	grip strength in the NMES group	
20				carers		Mean BI 2.5 (SD 2.9)	strength	post-intervention but not maintained	
21				Usual care- PTs		Mean ARAT 0.6 (SD 3.5)		at follow-up.	
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25		Functionally targeted				Functional techniques		Functionally targeted physiotherapy	
26		physiotherapy techniques +				group (n=5)		group demonstrated greater	
27	Sanchez-	conventional physiotherapy		PTs	BI*	Mean BI 13 (SD 10.95)	BI	improvement compared to the	Very low
28	Sanchez	vs	Not			Conventional therapy group		conventional physiotherapy group	
29	et al. 2014 <sup>15</sup>	Conventional	reported			(n=8)		when using functional principal	
30		physiotherapy				Mean BI 11.43 (SD 13.13)		component analysis	
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34		Contemporary Bobath				Early contemporary group		Improvements in STREAM and BBS in	
35		approach with early sitting,				(n=24)		the contemporary Bobath approach	Low
36	Tang et al.	standing and walking				Mean STREAM 1.4 (SD 1.0)	STREAM, BBS	with early mobilisation group	
37	2014 <sup>16</sup>	vs	8 weeks	PTs		Mean BBS 0 (SD 0)			
38		Contemporary Bobath				Contemporary group (n=24)			
39		approach				Mean STREAM 1.3 (SD 0.9)			
40						Mean BBS 0 (SD 0)			
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Supplementary Table 2- Studies conducted in the acute – late subacute (&lt;6 months) phase post-stroke

Study	Intervention Description	Intervention Duration	Intervention Delivered By	Stroke Severity Measure	Sample Size and Characteristics	Main Outcome Measures	Main Results	Quality of Evidence
Bai et al. 2014 <sup>17</sup>	Staged physical rehabilitation interventions + routine care vs Routine care	6 months	PTs and OTs	BI*	Staged rehab group (n=83) Mean BI 28 (range 24-31) Routine care group (n=82) Mean BI 23 (range 19-27)	BI, mAS	Staged rehab group demonstrated higher BI scores than the routine care group at 1, 3- and 6-months post-stroke. 42.9% of patients in the routine care group demonstrated spasticity in at least one body part compared to 36.4% of patients in the staged rehab group.	Low
Calabrò et al. 2015 <sup>18</sup>	Robotic verticalisation + standard physiotherapy vs Physiotherapy-assisted verticalisation + standard physiotherapy	6 weeks	PTs	PASS LL FMA	Robotic group (n=10) Mean PASS 3 (SD 1) Mean LL FMA 13 (SD 3) Physiotherapy group (n=10) Mean PASS 3 (SD 3) Mean LL FMA 12 (SD 6)	PASS, LL FMA, MRC, vertical posture tolerance	Both interventions were well tolerated. Robotic group demonstrated greater improvements in MRC, LL FMA and PASS compared to the physiotherapy group	Very low
Chaiyawat and Kulkantrakorn 2012 <sup>19,20</sup>	Home based physiotherapy programme vs Usual care	6 months	PTs	BI*	Home PT group (n=30) Mean BI 31.7 (SD 5.9) Mean NIHSS 16.4 (SD 4.1) Usual care group (n=30) Mean BI 33.2 (SD 4.8) Mean NIHSS 17.8 (SD 3.9)	BI, HADS, mRS, EQ-5D	Home therapy group demonstrated greater improvements in BI, HADS, mRS and EQ-5D compared to the usual care group which were maintained at 2-year follow-up.	Very low
Jongbloed et al. 1989 <sup>21</sup>	Functional treatment approach vs Sensorimotor integrative treatment approach	8 weeks	OTs	BI*	Functional treatment group (n=13) Mean BI 31.5 Sensorimotor integrative treatment group (n=9) Mean BI 30	BI, meal preparation, eight subtests of Sensorimotor Integration Test Battery	No differences between groups on all outcome measures	Very low

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6	Kwakkel et al.	Additional UL training + usual care	20 weeks	PTs and OTs	BI <sup>^</sup>	UL training group (n=33) Median BI 5 (IQR 3-7) LL training (n=31) Median BI 6 (IQR 3-8) Splint control group (n=37) Median BI 5.5 (IQR 3-7)	BI, FAC, ARAT, 10MWT, SIP, NHP, FAI	LL training group had significantly higher BI, FAC, walking speed and ARAT than splint control group post- intervention. UL training group had significantly higher ARAT than splint control group post-intervention. No significant differences in all outcomes were seen between groups from 6 months onwards up until 12-month follow-up.	Moderate
7	1999 <sup>22</sup>	vs							
8	2002 <sup>23</sup>	Additional LL training + usual care							
9	2002 <sup>24</sup>	vs							
10		UL/LL pressure splint immobilisation + usual care							
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27		Robot-assisted BWS treadmill gait training + standard physiotherapy							
28		vs							
29	Morone et al.	Conventional gait training + standard physiotherapy	3 months	PTs	BI*	Robotic groups Low motricity (n=12) Mean BI 14.2 (SD 11.8) High motricity (n=12) Mean BI 20.0 (SD 17.2)	FAC, LL AS, RMI, MI, TCT, CNS, BI, RS, 6MWT, 10MWT	LL training group had significantly higher comfortable walking speed than UL and splint control groups post-intervention. No differences were seen for the mean CRP of arm/leg movements between groups.	
30	2011 <sup>25</sup>								
31	2012 <sup>26</sup>								
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4	Yang et al.	Acupuncture +	8 weeks	Acupuncture-	NIHSS	Acupuncture group (n=33)			
5	2014 <sup>27</sup>	rehabilitation training		not reported	BI*	Mean NIHSS 25.5 (SD 2.4)	NIHSS, FMA, BI	Acupuncture group demonstrated	
6		vs				Mean BI 39.4 (SD 3.9)		higher scores on all outcome	Very low
7		Rehabilitation training		Rehabilitation-		Rehabilitation group (n=31)		measures compared to the	
8				PTs		Mean NIHSS 24.1 (SD 3.1)		rehabilitation group	
9						Mean BI 38.1 (SD 4.3)			
10									
11	Yue et al.	Acupressure treatment				Acupressure group (n=35)		Acupressure group demonstrated	
12	2012 <sup>28</sup>	+ routine care	3 months	Nurses	BI*	Mean BI 26.8 (SD 15.2)	FMA, BI	greater improvements in BI and FMA	Very low
13		vs				Routine care group (n=34)		only at 3-month time frame	
14		Routine care				Mean BI 24.4 (SD 16.8)			
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S3 Table- Studies conducted in the chronic (&gt;6 months) phase post-stroke

Study	Intervention Description	Intervention Duration	Intervention Delivered By	Stroke Severity Measure	Sample Size and Characteristics	Main Outcome Measures	Main Results	Quality of Evidence
Rodrigues et al. 2017 <sup>29</sup>	Robot-assisted BWS treadmill gait training with progressively increased speeds vs Robot-assisted bodyweight supported treadmill gait training with progressively decreased speeds	6 weeks	Not reported	LL FMA FAC	Faster speed group (n=10) Median FAC 1.5 (1–2) Mean LL FMA 19.5 (SD 4.6)  Slower speed group (n=10) Median FAC 1 (1–2) Mean LL FMA 17.5 (SD 2.8)	FAC, TUG, 6MWT, 10MWT, BBS, LL FMA	Improvements in FAC, FMA, TUG and 6MWT in the slower speed group compared to the faster speed group.	Very low
Sackley et al. 2015 <sup>30</sup>	OT intervention vs Usual care	3 months	OTs	BI <sup>^</sup>	OT intervention group- BI 0-4 n=268 BI 5-9 n=129  Usual care group- BI 0-4 n=234 BI 5-9 n=104	BI, RMI, GDS, EQ-5D-3L	No differences between the groups on any outcome measure at 3-, 6- and 12-months post-randomisation. Higher fall rate per resident in OT intervention group at 3 months.	High
Volpe et al. 2008 <sup>31</sup>	Intensive standard UL therapy vs Intensive robot-assisted UL therapy	6 weeks	Therapists	NIHSS	Therapist group (n=10) Mean NIHSS 17 (SD 1)  Robot group (n=11) Mean NIHSS 17 (SD 1)	FMA- UL, MRC-shoulder/ elbow, mAS, UL PROM, SIS, ARAT, BDS, shoulder dislocation, pain	No difference between groups in shoulder and elbow strength and motor function. No improvements in other outcome measures for both groups.	Very low
Zhang and Li 2014 <sup>32</sup>	Trunk acupuncture + rehabilitation training vs Rehabilitation training alone	16 weeks	Not reported	BI*	Acupuncture group (n=30) Mean BI 22.50 (SD 6.79)  Rehabilitation group (n=29) Mean BI 24.48 (SD 7.23)	BI, BBS	Acupuncture group demonstrated higher scores on BI and BBS compared to the rehabilitation group.	Very low

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3 ARAT- Action Research Arm Test, AROM- active range of movement, AS- Ashworth Scale, BBS- Berg Balance Scale, BDS- Becks Depression Scale, BI\*- Barthel Index (original version scored  
4 out of 100), BI^ - Barthel Index(revised version score out of 20), BS- Borg Scale, BWS- bodyweight supported, CNS- Canadian Neurological Scale, CRP- continuous relative phase, CSI-  
5 Caregiver Strain Index, EQ-5D-3L- EuroQoL questionnaire, FAC- Functional Ambulation Category, FAI- Frenchay Activities Index, FIM- Functional Independence Measure, FMA- Fugl-Meyer  
6 Assessment, FTHUE- Functional Test for the Hemiplegic Upper Extremity, GDS- Geriatric Depression Scale, GHQ-28- General Health Questionnaire-28, HADS- Hospital Anxiety and Depression  
7 Scale, LL- lower limb, MAS- Motor Assessment Scale, mAS- Modified Ashworth Scale, MCA- Motor Club Assessment, MI- Motricity Index, mMAS- Modified Motor Assessment Scale, MMSE-  
8 Mini-Mental State Examination, mNIHSS- Modified National Institutes of Health Stroke Scale, mRS- Modified Rankin Scale, MRC- Medical Research Council Scale for Muscle Strength, NEADL-  
9 Nottingham Extended Activities of Daily Living, NHP- Nottingham Health Profile, NIHSS- National Institutes of Health Stroke Scale, OT- occupational therapist, PASS- Postural Assessment  
10 Scale for Stroke Patients, PROM- passive range of movement, PT- physiotherapist, PTA- physiotherapy assistant, RMA- Rivermead Motor Assessment, RMI- Rivermead Mobility Index, RS-  
11 Rankin Scale, SIP- Stroke Impact Profile, SIS- Stroke Impact Scale, ST- speech therapist, STREAM- Stroke Rehabilitation Assessment of Movement, TCT- Trunk Control Test, THPT- Ten-Hole  
12 Peg Test, TUG- Timed Up and Go, UL- upper limb, WHS- Walking Handicap Scale, 6MWT- 6 minute walk test, 10MWT- 10 metre walk test  
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## Supplementary Results- Outcomes Supported by Low or Very Low-Quality Evidence

### Body function

#### Cardiorespiratory Function

Two studies explored participants' cardiorespiratory response to different types of treadmill gait training within the acute to early subacute phase post-stroke.<sup>4,8</sup> There was low-quality evidence that 2 weeks of robot-assisted bodyweight supported treadmill gait training delivered in the first 6 weeks post-stroke improved peak  $\text{VO}_2$  compared to conventional gait training.<sup>4</sup> There was low-quality evidence that a 4-week course of bodyweight supported treadmill training delivered in the first 3 months post-stroke was not perceived to be more effortful than conventional gait training.<sup>8</sup>

#### Neurological Impairment

Three studies evaluated changes in neurological function.<sup>6,25,27</sup> In the acute to early subacute phase post-stroke, there was very low-quality evidence that there was no difference in an intensive or ordinary 2-week acute physical rehabilitation programme on reducing neurological impairment at 2 weeks and 6 months post-stroke.<sup>6</sup> In the acute to late subacute phase post-stroke, there was very low-quality evidence that a 3-month course of robot-assisted bodyweight supported treadmill gait training commenced within the first 6 weeks post-stroke was just as effective as conventional gait training on improving neurological function.<sup>25</sup> There was very low-quality evidence that an 8-week course of acupuncture provided in conjunction with rehabilitation during the subacute phase of stroke reduced neurological impairment compared to rehabilitation alone.<sup>27</sup>

#### Sensorimotor Function

Sixteen studies evaluated changes in sensorimotor function. Nine studies were performed in the acute to early subacute phase post-stroke,<sup>3-5,7,8,10-13</sup> five studies in the acute to late subacute phase post-stroke,<sup>18,21,25,27,28</sup> and two studies in the chronic phase post-stroke.<sup>29,31</sup> In the acute to early subacute phase post-stroke, there was low quality evidence from two studies that thermal stimulation in conjunction with standard rehabilitation resulted in improvements in lower limb sensorimotor function and strength when compared to standard rehabilitation alone.<sup>5,10</sup> Improvements in lower limb sensorimotor function were maintained at 12 months post-intervention. There was low quality evidence that 2 weeks of robot-assisted bodyweight supported treadmill gait training resulted in improvements in lower limb sensorimotor function but not strength compared to conventional gait training.<sup>4</sup> There was low quality evidence that there was no difference between: 4 weeks of robot-assisted treadmill gait training and conventional gait training on improving lower limb sensorimotor function;<sup>13</sup> wearing a cueing wristwatch and wearing a sham wristwatch for 3 hours per weekday for 3 weeks during rehabilitation on improving upper limb sensorimotor function and number of arm movements;<sup>7</sup> a 4-week course of bodyweight supported treadmill training and conventional overground gait training on improving lower limb strength;<sup>8</sup> and a 5-week course of additional upper limb therapy provided by a qualified physiotherapist or a physiotherapy assistant and standard physiotherapy on improving upper limb motor activity and grip strength.<sup>11</sup> There was very low-quality evidence that a thrice weekly, 6-week course of electromyography (EMG) biofeedback combined with conventional physiotherapy had no

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3 effect on improving lower limb active range of movement when compared to conventional  
4 physiotherapy alone.<sup>3</sup> There was very low-quality evidence that a 3-month course of  
5 acupuncture in conjunction with rehabilitation resulted in better upper and lower limb  
6 sensorimotor function when compared to rehabilitation alone.<sup>12</sup>

7  
8 In the acute to late subacute phase post-stroke, there was very low quality evidence that a  
9 6-week course of robotic tilt-table verticalisation that combines cyclic leg movements and  
10 FES and used in conjunction with standard physiotherapy resulted in better lower limb  
11 strength and sensorimotor function compared to physiotherapy-assisted verticalisation  
12 using a standard tilt-table and used in conjunction with standard physiotherapy.<sup>18</sup> There was  
13 very low-quality evidence that an 8-week course of acupuncture provided in conjunction  
14 with rehabilitation resulted in improvements in upper and lower limb sensorimotor function  
15 compared to rehabilitation alone.<sup>27</sup> There was very low-quality evidence that a 3-month  
16 course of nurse-led acupressure resulted in improvements in upper and lower limb motor  
17 function compared to routine care.<sup>28</sup> There was very low quality evidence that there was no  
18 difference between: a functionally-orientated and a sensorimotor integrative occupational  
19 therapy treatment approach delivered over 8 weeks on improving upper limb sensorimotor  
20 function;<sup>21</sup> and a 3-month course of robot-assisted bodyweight supported treadmill gait  
21 training and conventional gait training on improving lower limb power.<sup>25</sup>

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23 In the chronic phase post-stroke, there was very low-quality evidence that a 6-week course  
24 of robot-assisted bodyweight supported treadmill gait training using slower treadmill speeds  
25 resulted in improvements in lower limb sensorimotor function compared to similar treadmill  
26 training using faster treadmill speeds.<sup>29</sup> There was very low-quality evidence that either an  
27 intensive therapist-driven UL protocol or an intensive robotic-driven UL protocol delivered  
28 thrice weekly for 6 weeks resulted in an improvement in shoulder and elbow sensorimotor  
29 function.<sup>31</sup>

## 34 Activity

### 35 Activities of Daily Living

36 Sixteen studies explored independence and ability to perform activities of daily living (ADLs).  
37 Nine studies were completed in the acute to early subacute phase,<sup>2,6-8,10-13,15</sup> six studies  
38 were completed in acute to late subacute phase<sup>17,19-21,25,27,28</sup> and one study was completed  
39 in the chronic phase.<sup>32</sup>

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41 In the acute to early subacute phase, there was low quality evidence that a 6-week course  
42 of thermal stimulation used in conjunction with standard rehabilitation resulted in  
43 improvements in ADL independence 3 months post-stroke compared to standard  
44 rehabilitation alone, although improvements were not seen at 6 months post-stroke.<sup>10</sup>  
45 There was low quality evidence that there was no difference between: regular  
46 physiotherapy and regular physiotherapy in conjunction with use of an Oswestry standing  
47 frame delivered over 14 consecutive weekdays in the first 3 months post-stroke on ADL  
48 independence;<sup>2</sup> wearing a cueing wristwatch and wearing a sham wristwatch for 3 hours per  
49 weekday for 3 weeks during rehabilitation on ADL independence;<sup>7</sup> a 4-week course of  
50 bodyweight supported treadmill training and conventional overground gait training on  
51 improving ADL independence;<sup>8</sup> a 5-week course of additional upper limb therapy provided  
52 by a qualified physiotherapist or a physiotherapy assistant and standard physiotherapy on  
53 improving ADL independence;<sup>11</sup> and 4 weeks of robot-assisted treadmill gait and  
54 conventional overground gait training on ADL independence.<sup>13</sup>

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3 There was very low-quality evidence that there was no difference in an intensive or ordinary  
4 2-week acute physical rehabilitation programme in improving ADL independence at 2 weeks  
5 and 6 months post-stroke.<sup>6</sup> There was very low-quality evidence that a 3-month course of  
6 acupuncture in conjunction with rehabilitation resulted in better ADL independence when  
7 compared to rehabilitation alone.<sup>12</sup> There was very low-quality evidence that providing  
8 additional physiotherapy in conjunction to regular rehabilitation in the first few weeks post-  
9 stroke resulted in improvements in ADL independence at 6 months post-stroke compared to  
10 regular rehabilitation alone.<sup>15</sup>

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13 In the acute to late subacute phase, there was low quality evidence that a 6-month course  
14 of a staged physical rehabilitation programme resulted in greater improvements in ADL  
15 independence compared to usual care that did not involve formal rehabilitation.<sup>17</sup> There  
16 was very low-quality evidence that a monthly home-based physiotherapy programme  
17 delivered over 6 months resulted in improvements in ADL independence compared to  
18 standard care.<sup>19,20</sup> There was very low-quality evidence that there was no difference  
19 between a functionally orientated or a sensorimotor integrative occupational therapy  
20 treatment approach delivered over 8 weeks on ADL independence.<sup>21</sup> There was very low-  
21 quality evidence that a 3-month course of robot-assisted bodyweight supported treadmill  
22 gait training resulted in improvements in ADL independence compared to conventional gait  
23 training.<sup>25</sup> Improvements were only seen in the cohort of participants who demonstrated  
24 significant motor impairment. Improvements were maintained at the 2-year follow-up.<sup>26</sup>  
25 There was very low-quality evidence that an 8-week course of acupuncture provided in  
26 conjunction with rehabilitation during the subacute phase of stroke improved ADL  
27 independence compared to rehabilitation alone.<sup>27</sup> There was very low-quality evidence that  
28 a 3-month course of nurse-led acupressure resulted in improvements in ADL independence  
29 compared to routine care.<sup>28</sup>

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32 In the chronic phase, there was very low-quality evidence that a 16-week course of trunk  
33 acupuncture combined with rehabilitation training resulted in greater improvements in ADL  
34 independence compared to rehabilitation training alone.<sup>32</sup>

### 35 36 37 38 39 Balance and Postural Control

40 Eight studies investigated balance and postural control. Four studies were completed in the  
41 acute to early subacute phase,<sup>2,5,10,16</sup> two studies were completed in the acute to late  
42 subacute phase<sup>18,25</sup> and two studies were completed in the chronic phase.<sup>29,32</sup>

43 In the acute to early subacute phase, there was low quality evidence that a 6-week course  
44 of thermal stimulation in conjunction with standard rehabilitation resulted in improvements  
45 in trunk postural control but not balance compared to standard rehabilitation alone.<sup>5</sup> In a  
46 separate study, there was low quality evidence that a 6-week course of thermal stimulation  
47 in conjunction with standard rehabilitation resulted in improvements in balance 3 months  
48 post-stroke compared to standard rehabilitation alone, although improvements were not  
49 seen at 6 months post-stroke.<sup>10</sup> There was low quality evidence that there was no difference  
50 between regular physiotherapy and regular physiotherapy in conjunction with use of an  
51 Oswestry standing frame delivered over 14 consecutive weekdays in the first 3 months post-  
52 stroke on trunk postural control.<sup>2</sup> There was low quality evidence that an 8-week course of  
53 physiotherapy involving early mobilisation combined with the Bobath approach resulted in  
54 improvements in balance when compared to physiotherapy just involving the Bobath  
55 approach.<sup>16</sup>

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In the acute to late subacute phase, there was very low quality evidence that a 6-week course of robotic tilt-table verticalisation that combines cyclic leg movements and FES and used in conjunction with standard physiotherapy resulted in improved postural control during different activities compared to physiotherapy-assisted verticalisation using a standard tilt-table and used in conjunction with standard physiotherapy.<sup>18</sup> There was very low-quality evidence that a 3-month course of robot-assisted bodyweight supported treadmill gait training resulted in improvements in trunk control compared to conventional gait training.<sup>25</sup> Improvements were only seen in the cohort of participants who demonstrated significant motor impairment.

In the chronic phase, there was very low-quality evidence that a 6-week course of robot-assisted bodyweight supported treadmill gait training resulted in improvements in balance regardless if slower or faster treadmill training speeds were used.<sup>29</sup> There was very low-quality evidence that a 16-week course of trunk acupuncture combined with rehabilitation training resulted in greater improvements in balance compared to rehabilitation training alone.<sup>32</sup>

### Gait

Eight studies investigated gait, which included gait ability and gait speed. Six studies were performed in the acute to early subacute phase,<sup>3-5,8,10,13</sup> one study was performed in the acute to late subacute phase<sup>25</sup> and one study was performed in the chronic phase.<sup>29</sup> In the acute to early subacute phase, there was low quality evidence from two studies that a 6-week course of thermal stimulation in conjunction with standard rehabilitation resulted in improvements in gait ability compared to standard rehabilitation alone.<sup>5,10</sup> There was low quality evidence that 4 weeks of robot-assisted treadmill gait training resulted in better gait ability than conventional gait training.<sup>13</sup> There was low quality evidence that there was no difference between: a 2-week course of robot-assisted bodyweight supported treadmill gait training and conventional gait training delivered in the first 6 weeks post-stroke on improving gait ability;<sup>4</sup> a 4-week course of bodyweight supported treadmill training and conventional overground gait training on improving gait ability;<sup>8</sup> and a thrice weekly, 6-week course of EMG biofeedback combined with conventional physiotherapy and conventional physiotherapy alone in improving gait speed.<sup>3</sup> In the acute to late subacute phase, there was very low-quality evidence that a 3-month course of robot-assisted bodyweight supported treadmill gait training resulted in improvements in gait ability compared to conventional gait training.<sup>25</sup> Improvements were only seen in the cohort of participants who demonstrated significant motor impairment. Improvements were maintained at the 2-year follow-up.<sup>26</sup> In the chronic phase, there was very low-quality evidence that a 6-week course of robot-assisted bodyweight supported treadmill gait training using slower treadmill speeds resulted in improvements gait ability compared to similar treadmill training using faster treadmill speeds.<sup>29</sup>

### General Physical Activity

Seven studies examined the effects of different interventions on improving general physical activity. Six studies were performed in the acute to early subacute phase<sup>2,3,5,10,11,16</sup> and one study was performed in the acute to late subacute phase.<sup>25</sup> In the acute to early subacute phase, there was low quality evidence from two studies that thermal stimulation in conjunction with standard rehabilitation resulted in improvements in physical activity when compared to standard rehabilitation alone.<sup>5,10</sup> Improvements were seen up until 3 months

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3 post-intervention but disappeared at the 6-month follow-up. There was low quality  
4 evidence that an 8-week course of physiotherapy involving early mobilisation combined  
5 with the Bobath approach resulted in improvements in physical activity when compared to  
6 physiotherapy just involving the Bobath approach.<sup>16</sup> There was low quality evidence that  
7 there was no difference between: regular physiotherapy and regular physiotherapy in  
8 conjunction with use of an Oswestry standing frame delivered over 14 consecutive  
9 weekdays in the first 3 months post-stroke on physical activity;<sup>2</sup> and a 5-week course of  
10 additional upper limb therapy provided by a qualified physiotherapist or a physiotherapy  
11 assistant and standard physiotherapy on improving physical activity.<sup>11</sup> There was very low-  
12 quality evidence that there was no difference between a thrice weekly, 6-week course EMG  
13 biofeedback combined with conventional physiotherapy and conventional physiotherapy  
14 alone on improving physical activity.<sup>3</sup>

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18 In the acute to late subacute phase, there was very low-quality evidence that a 3-month  
19 course of robot-assisted bodyweight supported treadmill gait training resulted in  
20 improvements in physical activity compared to conventional gait training.<sup>25</sup> Improvements  
21 were only seen in the cohort of participants who demonstrated significant motor  
22 impairment. Improvements were maintained at the 2-year follow-up.<sup>26</sup>

#### 23 24 25 Upper Limb Function

26 Two studies investigated changes in upper limb function.<sup>11,31</sup> In the acute to early subacute  
27 phase, there was low quality evidence that a 5-week course of additional upper limb  
28 therapy provided by a qualified physiotherapist was no more effective at improving upper  
29 limb function than additional upper limb therapy provided by a physiotherapy assistant or  
30 to standard physiotherapy.<sup>11</sup> In the chronic phase, there was very low-quality evidence that  
31 there was no improvement in upper limb function with either an intensive therapist-driven  
32 UL protocol or an intensive robotic-driven UL protocol delivered thrice weekly for 6 weeks.<sup>31</sup>

#### 33 34 35 Participation

##### 36 37 Extended Activities of Daily Living

38 Four studies investigated the effect of different interventions on extended ADLs.<sup>2,3,9,21</sup> In the  
39 acute to early subacute phase, there was low quality evidence that there was no difference  
40 between: regular physiotherapy and regular physiotherapy in conjunction with use of an  
41 Oswestry standing frame delivered over 14 consecutive weekdays on ability to perform  
42 extended ADLs at 6 months post-stroke,<sup>2</sup> and an 8-week course of rehabilitation with the  
43 addition of a leg cycling machine compared to regular rehabilitation alone on extended ADLs  
44 6 months post stroke.<sup>9</sup> There was very low-quality evidence that there was no difference  
45 between a thrice weekly, 6-week course of electromyography (EMG) biofeedback combined  
46 with conventional physiotherapy and conventional physiotherapy alone in improving  
47 performance in extended ADLs time.<sup>3</sup>

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51 In the acute to late subacute phase, there was very low-quality evidence that there was no  
52 difference between a functionally orientated or a sensorimotor integrative occupational  
53 therapy treatment approach delivered over 8 weeks on the ability to prepare meals.<sup>21</sup>

##### 54 55 Perceived Health Status

56 Two studies explored carers' and patients' perceived health status.<sup>2,31</sup> In the acute to early  
57 subacute phase, there was low quality evidence that there was no difference between  
58 regular physiotherapy and regular physiotherapy in conjunction with use of an Oswestry  
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3 standing frame delivered over 14 consecutive weekdays on carer's perceived health status  
4 at 12 weeks and 6 months post-stroke.<sup>2</sup> In the chronic phase, there was very low-quality  
5 evidence that there was no change in patient's perceived health status with the provision of  
6 either an intensive therapist-driven UL protocol or an intensive robotic-driven UL protocol  
7 delivered thrice weekly for 6 weeks.<sup>31</sup>  
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#### 10 Quality of Life

11 There was very low-quality evidence that a monthly home-based physiotherapy programme  
12 delivered over 6 months resulted in an improvement in quality of life compared to standard  
13 care.<sup>19</sup>  
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#### 16 Complications

##### 17 Caregiver Burden

18 There was low quality evidence that there was no difference between regular physiotherapy  
19 and regular physiotherapy in conjunction with use of an Oswestry standing frame delivered  
20 over 14 consecutive weekdays in the first 3 months post-stroke on caregiver strain and  
21 psychological well-being at 12 weeks and 6 months post-stroke.<sup>2</sup>  
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##### 25 Depression

26 Three studies explored changes in depression.<sup>2,20,31</sup> In the acute to early subacute phase,  
27 there was low quality evidence that there was no difference between regular physiotherapy  
28 and regular physiotherapy in conjunction with use of an Oswestry standing frame delivered  
29 over 14 consecutive weekdays on depression at 12 weeks and 6 months post-stroke.<sup>2</sup> In the  
30 acute to late subacute phase, there was very low-quality evidence that a monthly home-  
31 based physiotherapy programme delivered over 6 months resulted in a reduction in level of  
32 depression compared to standard care.<sup>20</sup> In the chronic phase, there was very low-quality  
33 evidence that there was no difference between an intensive therapist-driven UL protocol  
34 and an intensive robotic-driven UL protocol delivered thrice weekly for 6 weeks in reducing  
35 depression.<sup>31</sup>  
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##### 40 Shoulder Pain/Dislocation

41 There was very low-quality evidence that either an intensive therapist-driven UL protocol or  
42 an intensive robotic-driven UL protocol delivered thrice weekly for 6 weeks had no effect on  
43 shoulder pain nor caused any shoulder dislocation when delivered to participants in the  
44 chronic phase post-stroke.<sup>31</sup>  
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##### 47 Spasticity

48 Six studies explored the effect of different interventions on spasticity.<sup>3,8,11,17,25,31</sup> In the acute  
49 to early subacute phase, there was low quality evidence that there was no difference  
50 between: bodyweight supported treadmill training and conventional overground gait  
51 training delivered over 4 weeks on reducing lower limb spasticity;<sup>8</sup> and a 5-week course of  
52 additional upper limb therapy provided by a qualified physiotherapist or a physiotherapy  
53 assistant and standard physiotherapy on reducing upper limb spasticity.<sup>11</sup> There was very  
54 low-quality evidence that there was no reduction in spasticity with a 6-week course of  
55 conventional physiotherapy with or without EMG biofeedback.<sup>3</sup>  
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58 In the acute to late subacute phase, there was low quality evidence that a 6-month course  
59 of a staged physical rehabilitation programme resulted in a lower incidence of upper and  
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3 lower limb spasticity compared to usual care that did not involve formal rehabilitation.<sup>17</sup>  
4 There was very low-quality evidence that a 3-month course of either robot-assisted  
5 bodyweight supported treadmill training or conventional gait training had no effect on  
6 reducing lower limb spasticity.<sup>25</sup>  
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8 In the chronic phase, there was very low-quality evidence that there was no difference  
9 between an intensive therapist-driven UL protocol and an intensive robotic-driven UL  
10 protocol delivered thrice weekly for 6 weeks in reducing UL spasticity.<sup>31</sup>  
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# BMJ Open

## The effect of rehabilitation interventions on physical function and immobility-related complications in severe stroke- a systematic review

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3 The effect of rehabilitation interventions on physical function and immobility-related  
4 complications in severe stroke- a systematic review  
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## Abstract

Objective: To evaluate the effectiveness of rehabilitation interventions on physical function and immobility-related complications in severe stroke.

Design: Systematic review of electronic databases (MEDLINE, EMBASE, CINAHL, AMED, PEDro, DORIS, CENTRAL) searched between January 1987 and November 2018.

Methods: The PRISMA statement guided the review. Randomised controlled trials comparing the effect of one type of rehabilitation intervention to another intervention, usual care or no intervention on physical function and immobility-related complications for patients with severe stroke were included. Studies that recruited participants with all levels of stroke severity were included only if subgroup analysis based on stroke severity was performed. Two reviewers screened search results, selected studies using pre-defined selection criteria, extracted data and assessed risk of bias for selected studies using piloted proformas. Marked heterogeneity prevented meta-analysis and a descriptive review was performed. The GRADE approach was used to assess evidence strength.

Results: 28 studies (n=2,677, mean age 72.7 years, 49.3% male) were included in the review. 24 studies were rated low or very low quality due to high risk of bias and small sample sizes. There was high quality evidence that very early mobilisation (i.e. mobilisation with 24 hours post-stroke) and occupational therapy in care homes were no more effective than usual care. There was moderate quality evidence supporting short-term benefits of wrist and finger neuromuscular electrical stimulation in improving wrist extensor and grip strength, additional upper limb training on improving upper limb function and additional lower limb training on improving upper limb function, independence in activities of daily living, gait speed, and gait independence.

Conclusions: There is a paucity of high-quality evidence to support the use of rehabilitation interventions to improve physical function and reduce immobility-related complications after severe stroke. Future research investigating more commonly used rehabilitation interventions, particularly to reduce post-stroke complications, is required.

PROSPERO registration number: CRD42017077737

Keywords: stroke rehabilitation, physiotherapy, occupational therapy

### Strengths and Limitations of this Study

- This is the first systematic review to investigate rehabilitation interventions specifically to survivors of severe stroke
- The review included outcomes on physical function and immobility-related post-stroke complications, of which the latter contribute to high levels of caregiver burden and are less commonly reported outcomes in stroke rehabilitation research
- Marked heterogeneity of included studies prevented meta-analysis
- Most included studies were rated as low or very low-quality evidence due to unclear or high risk of bias as well as recruitment of very small samples

## INTRODUCTION

Despite advances in stroke management over recent decades, stroke remains one of the most common causes of death and disability globally. |1,2| The mainstay of treating stroke is stroke rehabilitation, which aims to enable a person to achieve their optimal physical, cognitive, communicative, emotional and social level of function. |3-5| Rehabilitation of physical function comprises a large component of stroke rehabilitation programmes delivered by health-care professionals, such as physiotherapists and occupational therapists. |6-8| Whilst several systematic reviews support the use of rehabilitation interventions to improve aspects of physical function, such as motor function, balance, walking speed and activities of daily living, |9-11| it is not clear from these reviews if these interventions are effective for survivors of differing levels of stroke severity, particularly severe stroke.

Severe stroke can be understood as a stroke resulting in a significant amount of brain tissue damage and multiple neurological impairments, which leads to a significant loss of function and residual disability. |12| Dependent upon how it is measured, 14 - 31% of people who sustain a stroke globally are classified as having a severe stroke, |13-18| a cohort of the stroke population that experiences worse outcomes compared to survivors of less severe stroke. |19-30| In the initial hospitalisation phase post-stroke, they are more likely to develop acute medical complications, which are negatively associated with functional recovery. |19| Three month mortality can be as high as 40%, compared to just under 5% for those patients with mild stroke. |20-22| Survivors of severe stroke spend longer in hospital, resulting in increased hospital costs, and demonstrate slower and less functional recovery, resulting in greater dependency when they are discharged from hospital. |14,15,23,25| For those discharged from hospital, survivors of severe stroke are at least eight times more likely to be discharged to a nursing home. |25,26| Longer-term care costs, which mostly support survivors of severe stroke, represent 49% of total stroke care spending globally. |27| In the first year post severe stroke, mortality can be as high as 60% |20| and survivors of severe stroke also experience very high levels of immobility-related complications, such as falls, contracture, pain, and pressure sores. |28,29| Due to this residual disability, the physical assistance provided by caregivers to look after survivors of



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3 severe stroke as well as the psychosocial and emotional impact of the stroke on caregivers  
4 result in high levels of caregiver burden. |30|  
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9 As there are a number of significant issues faced by survivors of severe stroke, rehabilitation  
10 of severe stroke should focus on addressing these poor outcomes, particularly reduced  
11 physical function and its associated complications. However, the extent to which  
12 rehabilitation can address these outcomes is not clear. A previous systematic review  
13 demonstrated positive benefits of inpatient stroke rehabilitation, such as reduced mortality  
14 and hospital length of stay, and uncertain benefit on improving functional recovery. |31|  
15 However, this review did not explore the effect of specific interventions delivered within  
16 inpatient rehabilitation on improving physical function or on reducing immobility-related  
17 complications. Most trials investigating the efficacy of rehabilitation interventions on  
18 physical function have either not recruited survivors of severe stroke or not reported results  
19 specifically for survivors of severe stroke. |9-11| Therefore, it is not known if research  
20 findings are applicable to survivors of severe stroke. It is not clear whether rehabilitation  
21 should focus more on functional restoration, which may be incomplete or not possible, or  
22 reducing immobility-related complications, which may lessen longer-term burden for  
23 caregivers of severe stroke survivors. Due to this lack of clarity, there is an urgent need to  
24 summarise evidence-based rehabilitation interventions designed to optimise physical  
25 function and reduce immobility-related complications for this cohort of the stroke  
26 population.  
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43 This systematic review aims to establish the effectiveness of rehabilitation interventions on  
44 physical function and immobility-related complications for survivors of severe stroke and  
45 identify areas for future rehabilitation research for these patients.  
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## 50 **METHODS**

51 The systematic review has been reported according to the Preferred Reporting Items for  
52 Systematic Reviews and Meta-analysis (PRISMA) statement (see Supplementary File 1). |32|  
53 The protocol for the systematic review has been published previously. |33|  
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## Study design

The systematic review included randomised controlled trials (RCTs). The systematic review excluded quasi-experimental, correlational and descriptive study designs. Studies were selected according to the PICO (participant, intervention, comparator and outcome) format. The systematic review protocol provides full details of the PICO components<sup>[33]</sup> and a brief summary of the components is reported below. There were no deviations from the protocol PICO.

### Participants

The review included studies of adult ( $\geq 18$  years) stroke patients with severe stroke. Stroke severity was defined using a score on a validated and routinely used outcome measure (e.g. National Institutes of Health Stroke Scale (NIHSS), Functional Independence Measure (FIM), Barthel Index (BI)).<sup>[34-36]</sup>

### Interventions

The review included studies that involved the provision of rehabilitation interventions used to manage problems relating to physical function or immobility-related complications post-stroke. A rehabilitation intervention was defined as any non-surgical or non-pharmacological intervention used in current clinical practice as part of the usual rehabilitative care of stroke patients.

### Comparators

The review included studies that had a comparator, which included any of the following: another type of rehabilitation intervention, usual care or no intervention. Usual care was defined as the rehabilitation that the patient would normally receive as part of undergoing stroke rehabilitation.

### Outcomes

The review included studies that focused on the primary outcomes of physical function and post-stroke complications. As per the definition of function in the International Classification of Functioning, Disability and Health, physical function was assessed using measures of body function (e.g. Fugl-Meyer Assessment), activity (e.g. BI), and participation (e.g. Stroke

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3 Impact Scale). [37, 38] An immobility-related complication was defined as any medical  
4 problem arising after a stroke because of immobility or reduced physical activity. [39]  
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## 10 **Search strategy**

### 11 Information sources

12 Electronic searches of the following databases were conducted: MEDLINE, EMBASE,  
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14 Cumulative Index to Nursing and Allied Health Literature (CINAHL), Allied and  
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16 Complementary Medicine Database (AMED), Physiotherapy Evidence Database (PEDro),  
17  
18 Database of Research in Stroke (DORIS) and the Cochrane Central Register of Controlled  
19  
20 Trials (CENTRAL). An example search strategy is shown in Supplementary File 2. Databases  
21  
22 were searched from January 1987 to November 2018. The search timeframe was guided by  
23  
24 a scoping review of the literature (demonstrating very few published RCTs before 2000) and  
25  
26 a consideration to include studies reflecting current clinical practice. Ongoing studies were  
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28 identified by searching the Stroke Trials Registry ([www.strokecenter.org/trials/](http://www.strokecenter.org/trials/)) and  
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30 clinicaltrials.gov. These sources were searched from 2012 to 2018 as it was assumed that  
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32 studies before these dates would have been completed and published. References from  
33  
34 included studies were hand searched and any potentially relevant study was included for  
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36 review. Forward citation checks of included studies were also performed. To avoid language  
37  
38 or cultural bias, studies in any language or geographical location were included.  
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### 42 **Data management and study selection**

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44 The results from the literature search were uploaded to a reference management  
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46 programme (Refworks) and duplicate references were removed. A final list of non-  
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48 duplicated references was generated by one author (MM). The titles and abstracts of the  
49  
50 search results were screened independently by two review authors (MM and JJ) and full text  
51  
52 articles were obtained for relevant studies. Full text articles were reviewed by the same two  
53  
54 authors (MM and JJ) independently to determine if studies met the inclusion criteria using  
55  
56 an inclusion/exclusion checklist previously piloted. Two review authors (MM and JJ)  
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58 independently performed data extraction for all eligible articles using a data extraction  
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60 proforma previously piloted. Any differences in opinion between the two authors at any

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3 stage of the study selection and data extraction process were resolved by a third review  
4 author (CS).  
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### 9 **Risk of bias and quality assessment**

10 Risk of bias was assessed by two review authors independently (MM and JJ) using the  
11 Cochrane Collaboration tool for assessing the risk of bias across six main domains (sequence  
12 generation, allocation concealment, blinding, incomplete outcome data, selective outcome  
13 reporting, other bias). [40] A risk of bias judgement of 'high', 'low' or 'unclear' was  
14 determined for each of these main domains. The strength of evidence was assessed using  
15 the Grading of Recommendations Assessment, Development and Evaluation (GRADE)  
16 approach. [40] The five criteria considered by the GRADE approach included risk of bias,  
17 inconsistencies between studies, indirectness, imprecision and publication bias. Studies  
18 were given a baseline rating of 'high' and downgraded if any of the five criteria were  
19 present. The quality of the evidence was ranked 'high', 'medium', 'low' or 'very low' by two  
20 review authors independently (MM and JJ). Any differences in opinion between the two  
21 authors at any stage of the study selection and data extraction process were resolved by a  
22 third reviewer (CS).  
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### 37 **Data analysis**

38 Due to the limited number of studies investigating each individual intervention and the  
39 marked heterogeneity of the selected studies, it was not appropriate to undertake a meta-  
40 analysis. Heterogeneity was seen in the rehabilitation interventions (type, dosage, method  
41 of delivery, timeframe completed post-stroke) as well as outcomes (type and timeframe  
42 completed post-stroke). Therefore, a descriptive review of results was performed. As there  
43 may be differences in recovery rates and outcomes according to the time post-stroke,  
44 studies were grouped into three timeframes post-stroke based on when participants were  
45 recruited to the study and when the study finished. These timeframes were the acute to  
46 early subacute stage (up to 3 months post-stroke), acute to late-subacute stage (up to 6  
47 months post-stroke) and chronic stage (greater than 6 months post-stroke). These  
48 timeframes were chosen based on recommendations for the standardised measurement of  
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3 sensorimotor recovery in stroke trials. |41| Study findings were presented according to  
4 these three timeframes.  
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### 8 **Patient and public involvement**

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10 There was no patient involvement in this study.  
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## 13 **RESULTS**

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15 The initial literature review identified 7589 articles (Figure 1). After removing duplicates and  
16 screening titles and abstracts, 1083 full text articles were assessed for eligibility. 28 studies  
17 were included in the systematic review. |42-73| 2677 participants were recruited to these  
18 studies- mean participant age was 72.7 years, 49.3% were male and 87% of patients  
19 sustained a cerebral infarction. The main reasons for excluding studies were due to not  
20 recruiting participants with severe stroke, not providing results separately for participants  
21 with severe stroke or not providing sufficient information to determine if the participants  
22 had sustained a severe stroke. There was an excellent level of agreement between the two  
23 authors in selecting the included articles (Cohen's  $\kappa$  0.93, percentage of agreement 97.7%).  
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34 The characteristics of the included studies are provided in Supplementary File 2  
35 (Supplementary Tables 1 – 3, Supplemental References). 16 studies were completed within  
36 the acute-early subacute phase, eight studies were completed within the acute-late  
37 subacute phase and four studies were completed within the chronic phase post-stroke. 20  
38 different interventions were evaluated across the 28 studies. The assessment of risk of bias  
39 for each study is presented in Figure 2.  
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### 48 **Outcomes**

49 60 measures of physical function and immobility-related post-stroke complications were  
50 identified across the studies. The measures were classified as measures of body function  
51 (n=18), activity (n=26), participation (n=8) and post-stroke complications (n=8). These  
52 measures were grouped together as 16 different outcomes. An overview of these measures  
53 and outcomes have been included in Supplementary File 2 (Supplementary Table 4).  
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3 For each outcome, there was usually only one study investigating the effectiveness of a  
4 specific rehabilitation intervention in each time frame post-stroke. Most of these studies  
5 were rated as providing very low or low-quality evidence for these outcomes (see  
6 Supplementary File 2). Outcomes which were supported by studies providing moderate or  
7 high quality of evidence are reported in this section. Outcomes which were supported by  
8 studies providing low or very low quality of evidence are reported in Supplementary File 2  
9 (Supplementary Results, Supplemental References).  
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## 18 Body function

### 19 *Sensorimotor Function*

20 Seventeen studies evaluated changes in sensorimotor function. Ten studies were completed  
21 in the acute to early subacute phase post-stroke, | 44-46,48,49,51-55 | five studies were  
22 completed in the acute to late subacute phase post-stroke | 59,62,66,68,69 | and two studies  
23 were completed in the chronic phase post-stroke. | 70,72 | The most frequently used  
24 outcome measures of sensorimotor function were the Fugl-Meyer Assessment, used in 11  
25 studies, | 45,46,48,51,53,54,59,68-70,72 | and the MRC scale for muscle strength, used in 5  
26 studies. | 46,51,52,59,72 |  
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29 In the acute to early subacute phase post-stroke, there was moderate quality evidence from  
30 one study that a 6-week course of neuromuscular electrical stimulation (NMES) applied to  
31 the wrist and finger extensors in conjunction with usual therapy resulted in no improvement  
32 in wrist active movement compared to usual therapy. | 55 | Wrist strength and grip strength  
33 improved in the NMES group during the treatment period although these improvements  
34 were not evident at the 9-month follow-up.  
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## 47 Activity

### 48 *Activities of Daily Living*

49 Twenty studies explored independence and ability to perform activities of daily living (ADLs).  
50 Eleven studies were completed in the acute to early subacute phase, | 42,43,47-49,51-56 |  
51 seven studies were completed in acute to late subacute phase | 58,60-63,66-69 | and two  
52 studies were completed in the chronic phase. | 71,73 | Eighteen studies used the Barthel  
53 Index as the main outcome measure to assess independence in ADLs. | 43,47,49,51-  
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3 53,55,56,58,60-63,66-69,71,73 | Four studies used the Modified Rankin Scale | 42,49,60,61 |  
4 and three studies used the Functional Independence Measure. | 48,50,54 |

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7 In the acute to early subacute phase, there was high quality evidence that frequent, very  
8 early mobilisation (median of 6.5 times per day) commencing within 24 hours post-stroke  
9 did not result in more patients being less dependent in ADLs at 3 months post-stroke  
10 compared to usual care, which traditionally started more than 24 hours post-stroke and  
11 averaged 3 times per day. | 42 | However, caution is required with interpreting this finding as  
12 the sub-group analysis of patients with severe stroke was not powered for this outcome.  
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14 There was moderate quality evidence that a 6-week course of NMES applied to the wrist  
15 and finger extensors in conjunction with usual therapy resulted in no difference in ADL  
16 independence compared to usual care. | 55 |

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19 In the acute to late subacute phase, there was moderate quality evidence that additional  
20 lower limb (LL) therapy in conjunction with regular physical rehabilitation performed in the  
21 first 20 weeks post-stroke improved ADL independence whilst the intervention was being  
22 delivered when compared to regular physical rehabilitation alone. | 63 | However, these  
23 improvements were not seen 6 months post-stroke.

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26 In the chronic phase, there was high quality evidence that a 3-month occupational therapy  
27 (OT) intervention provided to residents in care homes resulted in no difference in ADL  
28 independence compared to usual care. | 71 | Similar caution is required with interpreting this  
29 finding as the sub-group analysis of patients who were severely or very severely disabled  
30 was not powered for this outcome.  
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#### 44 *Gait*

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46 Nine studies investigated gait, which included gait ability and gait speed. Six studies were  
47 performed in the acute to early subacute phase, | 44-46,49,51,54 | two studies were  
48 performed in the acute to late subacute phase | 63,66 | and one study was performed in the  
49 chronic phase. | 70 | The Functional Ambulation Classification was used in eight studies,  
50 making it the most frequently used outcome measure of gait  
51 ability. | 45,46,49,51,54,63,66,70 | The 10-metre walk test was used in five studies, making it  
52 the most frequently used outcome measure of gait speed. | 44,49,54,66,70 |

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58 Only one study demonstrated moderate quality evidence. | 63 | In the acute to late subacute  
59 phase, additional LL therapy in conjunction with regular physical rehabilitation performed in  
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3 the first 20 weeks post-stroke improved gait ability and speed when compared to regular  
4 physical rehabilitation alone. | | However, these improvements were not seen 6 months  
5 post-stroke.  
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### 10 11 12 13 14 *General Physical Activity*

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16 Eight studies examined the effects of different interventions on improving general physical  
17 activity. Six studies were performed in the acute to early subacute  
18 phase, |43,44,46,51,52,57| one study was performed in the acute to late subacute  
19 phase |66| and one study was performed in the chronic phase. |71| General physical activity  
20 was defined as a composite of multiple physical tasks completed within one assessment,  
21 such as upper limb (UL) or LL function, transfers, gait and balance. Outcome measures used  
22 to assess general physical activity included the Rivermead Mobility Index, Rivermead  
23 Mobility Assessment and Motor Assessment Scale. Only one study demonstrated high  
24 quality evidence. |71| In the chronic phase, a 3-month OT intervention provided to residents  
25 in care homes resulted in no difference in physical activity compared to usual care.  
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### 36 *Upper Limb Function*

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38 Four studies investigated changes in UL function, |52,55,63,72| of which two provided  
39 moderate quality evidence. |55,63| In the acute to early subacute phase, a 6-week course of  
40 NMES applied to the wrist and finger extensors in conjunction with usual therapy resulted in  
41 no difference in UL function compared to usual care. |55| In the acute to late subacute  
42 phase, additional UL or LL therapy in conjunction with regular physical rehabilitation  
43 performed in the first 20 weeks post-stroke improved UL function 6 months post-stroke  
44 when compared to regular rehabilitation. |63|  
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### 53 *Participation*

#### 54 *Instrumental Activities of Daily Living*

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56 Five studies investigated the effect of different interventions on instrumental  
57 ADLs, |43,44,50,62,63| of which one provided moderate quality evidence. Instrumental  
58 ADLs are those activities that enable an individual to live independently within their  
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3 community. In the acute to late subacute phase, additional UL or LL therapy in conjunction  
4 with regular physical rehabilitation performed in the first 20 weeks post-stroke improved  
5 performance in instrumental ADLs 6 months post-stroke when compared to regular  
6 rehabilitation. |63|  
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### 10 11 12 *Quality of Life*

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14 Three studies examined quality of life, |60,63,71| of which two were moderate or high  
15 quality. |63,71| In the acute to late subacute phase, there was moderate quality evidence  
16 that there was no benefit of additional UL or LL therapy to regular physical rehabilitation  
17 performed in the first 20 weeks post-stroke on improving quality of life 6 months post-  
18 stroke. |63| In the chronic phase, there was high quality evidence that a 3-month OT  
19 intervention provided to residents in care homes resulted in no difference in quality of life  
20 compared to usual care. |71|  
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### 29 *Complications*

#### 30 *Depression*

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32 Four studies explored changes in depression, |43,61,71,72| of which one was high  
33 quality. |71| In the chronic phase, a 3-month OT intervention provided to residents in care  
34 homes resulted in no difference in depression compared to usual care. |71|  
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#### 40 *Mortality*

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42 One study investigated the effect of very early mobilisation on mortality. |42| There was  
43 high quality evidence that frequent, higher dose, very early mobilisation commencing within  
44 24 hours post-stroke did not result in more patients dying at 3 months when compared to  
45 usual care, which traditionally started more than 24 hours post-stroke.  
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#### 50 *Other Outcomes*

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52 There was low quality of evidence for cardiorespiratory function (2 studies) |45,49| and  
53 caregiver burden (1 study). |43| There was very low to low quality of evidence for  
54 neurological impairment (3 studies), |47,66,68| balance and postural control (8  
55 studies), |43,46,51,57,59,66,70,73| perceived health status (2 studies), |43,72| shoulder  
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3 pain and dislocation (1 study), |72| and spasticity (6 studies). |44,49,52,58,66,72| Further  
4 details of these outcome and studies are included in Supplementary File 2.  
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## 8 **DISCUSSION**

### 9 **Main Findings**

10 Although 28 RCTs investigating 20 different rehabilitation interventions were identified in  
11 this review, there was a paucity of high-quality evidence to support the use of these  
12 interventions to improve physical function and reduce immobility-related complications  
13 after severe stroke. Most studies were rated as low or very low-quality evidence due to  
14 unclear or high risk of bias as well as recruitment of very small samples (refer to  
15 Supplementary Table 1). However, compared to data from national (United Kingdom) and  
16 global estimates of stroke incidence and prevalence, participants recruited to these studies  
17 were similar in terms of stroke type and gender but slightly younger (median age of stroke  
18 in the United Kingdom is 77 years). |1,2,18| Therefore, participants were generally  
19 representative of the wider stroke population.  
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### 32 **Physical Function**

33 Two large, multi-centre studies provided high quality evidence that their respective  
34 treatment interventions were no more effective at improving different aspect of physical  
35 function than usual care. |42,71| However, patients with severe stroke or severe disability  
36 post-stroke comprised a smaller sample within these larger trials. Analyses of data from  
37 these sub-groups may not be powered to detect changes between the treatment and usual  
38 care interventions and therefore caution is required in interpreting the studies' findings.  
39 In AVERT (A Very Early Rehabilitation Trial), |42| very early and frequent mobilisation  
40 commencing within 24 hours post-stroke did not result in more patients being less  
41 dependent in ADLs 3 months post-stroke compared to usual care, which traditionally started  
42 more than 24 hours post-stroke. Although the data seemed to favour usual care practice for  
43 patients with severe stroke, this finding did not achieve statistical significance. It could be  
44 argued that patients with severe stroke may be less likely to tolerate very early and  
45 intensive therapy in the first few days after stroke due to fatigue and reduced exercises  
46 tolerance. |74| This would suggest that mobilising patients less intensively after 24 hours  
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3 may be more beneficial at improving functional recovery than very early and frequent  
4 mobilisation. However, this finding was not seen in AVERT.

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7 In the OT in care home trial, [71] a 3-month, goal-orientated OT intervention for stroke  
8 survivors living in care homes did not result in improved ADL ability or quality of life up to 1-  
9 year post-intervention. The authors hypothesised that the lack of treatment effect may have  
10 been due to the care home residents' disability severity, which may have limited their  
11 engagement in therapy. However, a content analysis of the OT intervention by the research  
12 team revealed that the mean number of OT visits over the period was 5.1 (SD 3.0), the  
13 median session time was 30 minutes (IQR 15-60 minutes) and only 15% of OT time was used  
14 to provide ADL and mobility training. Although session length and duration were dependent  
15 upon the care home resident's ability to engage, it is possible that a more frequent OT  
16 intervention that focussed more on ADL and mobility training may have resulted in different  
17 findings.

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20 Two additional studies provided moderate quality evidence that their respective treatment  
21 interventions were effective at improving different aspects of physical function. In both  
22 studies, improvements were seen in different aspects of physical function that were  
23 specifically trained with the treatment intervention. Kwakkel et al. demonstrated that,  
24 compared to usual care, a 20-week course of additional upper limb therapy resulted in  
25 improvements in upper limb function and additional lower limb training resulted in  
26 improvements in upper limb function, independence in ADLs, gait speed and gait  
27 independence. [63] However, these improvements were not maintained after 6 months  
28 post-stroke once the additional therapy had discontinued. [64] Rosewilliam et al.  
29 demonstrated that the addition of wrist and finger neuromuscular electrical stimulation to  
30 usual therapy care resulted in improvements in wrist extensor and grip strength but no  
31 difference in upper limb function nor independence in ADLs. [55] As the electrical  
32 stimulation provided to patients was limited to cyclical movements of the wrist and did not  
33 involve multiple limb segments, it seems reasonable that upper limb function and  
34 independence in ADLs, which were not specifically trained for with the neuromuscular  
35 stimulation, did not improve.

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58 **Immobility-Related Complications**  
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3 As demonstrated in Supplementary Table 2, there were relatively fewer complication  
4 outcomes investigated across all studies compared to physical function outcomes. This  
5 observation may reflect that the primary focus of stroke rehabilitation is to optimise  
6 functional recovery. [3-5] Therefore, the primary focus of stroke rehabilitation research  
7 investigating the effectiveness of rehabilitation interventions may be on improving  
8 functional recovery post-stroke rather than reducing immobility-related complications.  
9 Only two high-quality studies investigated the effectiveness of their respective interventions  
10 at reducing immobility-related complications. In AVERT, very early and frequent  
11 mobilisation commencing within 24 hours post-stroke did not result in more patients dying  
12 at 3 months post-stroke compared to usual care. [42] Whilst this finding is obviously  
13 positive, very early and frequent mobilisation did not result in less patient dependency as  
14 reported earlier in the discussion. Therefore, the optimal time and frequency to commence  
15 the mobilisation of patients with severe stroke is not clear.

16  
17 In the OT in care home trial, [71] a 3-month, goal-orientated OT intervention for stroke  
18 survivors living in care homes did not result in reduced depression up to 1-year post-  
19 intervention. Whilst post-stroke depression has a multi-factorial cause, it has been reported  
20 that mental distress associated with residual disability may contribute to the development  
21 of post-stroke depression. [75] Therefore, reductions in residual disability may alleviate  
22 depressive symptoms post-stroke. As the OT intervention did not result in improved ADL  
23 ability, it is possible that depression did not significantly change due to the lack of  
24 improvement in ADL ability.

### 25 26 27 **Implications for Practice and Research**

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29 In light of these findings, it may be necessary to re-evaluate the design of future trials  
30 investigating rehabilitation interventions in severe stroke. As it is not known if survivors of  
31 severe stroke respond to interventions in the same ways as survivors of milder stroke, there  
32 may be a need for more proof of concept studies to understand the mechanisms of recovery  
33 in severe stroke more fully. The high number of small, low-quality, single-centre RCTs  
34 investigating a broad range of interventions may suggest that larger, high-quality multi-  
35 centre RCTs investigating fewer interventions are warranted. However, outcome  
36 evaluations alone are insufficient to understand why certain interventions do or do not  
37 work. It is recommended that evaluations of complex interventions, such as stroke  
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3 rehabilitation, use process evaluations alongside outcome evaluations. |76| Process  
4 evaluations enable an understanding of how to implement an intervention as well as how  
5 participants respond to and interact with the intervention. Therefore, future trials should be  
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7 guided by more proof of concept research and involve both outcome and process  
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9 evaluations.  
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12 In this review, the most frequently investigated outcomes were functional tasks, such as  
13 ADLs and gait ability. However, Pereira et al. has suggested that individuals with severe  
14 stroke are likely to make limited functional improvement with inpatient rehabilitation in the  
15 their review of rehabilitation after severe stroke. |31| They also advocated more focus on  
16 discharge planning and reducing post-stroke complications during inpatient rehabilitation  
17 for patients with severe stroke. Whilst the extent to which patients can improve functionally  
18 after severe stroke is not clear, there is merit in further exploring the effect of rehabilitation  
19 in the prevention and management of post-stroke complications in severe stroke. Sackley et  
20 al. investigated the prevalence of immobility-related complications in the first year after  
21 severely disabling stroke and found a very high prevalence of falls, contractures, pain and  
22 pressure sores. |28| However, with the exception of spasticity, there was very little focus on  
23 the prevention or management of post-stroke complications in the studies selected for our  
24 systematic review. In addition to a lack of focus on immobility-related complications, only  
25 one study explored caregiver burden, known to be very high amongst carers looking after  
26 survivors of severe stroke. |30| Future research in the rehabilitation of severe stroke should  
27 therefore focus more on the effectiveness of rehabilitation interventions in the prevention  
28 and management of immobility-related complications in severe stroke.  
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31 This review identified several studies investigating technological interventions, such as  
32 treadmill training and robot-assistive devices, and more novel interventions, such as  
33 thermal stimulation. However, it is not clear how commonly used these interventions are in  
34 clinical practice. Additionally, there were no trials studies of interventions commonly used  
35 with survivors of severe stroke, such as positioning, sitting balance and seating. |77| This  
36 mismatch between available research evidence, which may not reflect current practice, and  
37 clinical practice, which may have limited research evidence to support its use, may present a  
38 dilemma for therapists, who are expected to base healthcare decisions on the best available  
39 and relevant evidence. |78| Therefore, future research is required to understand what  
40 interventions are currently being used in clinical practice. Knowledge of currently used  
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3 rehabilitation interventions may guide future trials investigating their efficacy in improving  
4 physical function and reducing immobility-related post-stroke complications.  
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### 8 **Strengths and Limitations**

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10 In terms of strengths, this is the first systematic review to investigate rehabilitation  
11 interventions specifically to survivors of severe stroke, who tend to be underrepresented in  
12 stroke rehabilitation research, and the identification of topics for future rehabilitation  
13 research will hopefully guide much needed research for this cohort of the stroke population.  
14 As well, the outcomes of the review focussed on not just physical function but immobility-  
15 related post-stroke complications, which are known to be higher in the severe stroke  
16 population and contribute to high levels of caregiver burden. |28-30| In terms of limitations,  
17 it has been reported that the defining severe stroke is difficult due to different criteria used  
18 to classify severity. |79| The use of objective scores on validated outcome measures to  
19 classify stroke severity in our systematic review was deemed necessary to ensure that  
20 participants had actually sustained a severe stroke. In our review, the BI was the most  
21 commonly used measure to classify stroke severity, reported in 17 out of 28 studies. Using a  
22 pre-specified score on the BI to classify severe stroke ( $\leq 9/20$  or  $\leq 45/100$ ) |33| enabled the  
23 identification of patients with severely disabling stroke. However, the use of an alternative  
24 measure of stroke severity, such as the NIHSS, may have resulted in the inclusion of a study  
25 with participants with a slightly different clinical presentation than participants measured  
26 with the BI. Alternatively, we may have excluded studies that used a different scoring  
27 system to classify stroke severity. However, these studies were discussed in detail amongst  
28 three review authors to determine suitability for inclusion and therefore it is likely that the  
29 number of relevant studies excluded from the review was minimal. Another limitation is the  
30 use of data from subgroups within larger clinical trials. As subgroup analyses may not be  
31 powered to detect changes between groups, caution is required in the interpretation of  
32 findings from these trials.  
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### 54 **CONCLUSION**

55  
56 There was a paucity of high-quality evidence to support the use of rehabilitation  
57 interventions to improve physical function and reduced immobility-related complications  
58 after severe stroke. Two high quality studies suggested that very early mobilisation and  
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3 occupational therapy in care homes were no more effective than usual care. One moderate  
4 quality study supported wrist and finger neuromuscular electrical stimulation in improving  
5 wrist extensor and grip strength. One moderate quality study supported that use of  
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7 additional upper limb training on improving upper limb function and additional lower limb  
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9 training on improving upper limb function, independence in ADLs, gait speed and gait  
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11 independence. Future research should be guided by more proof of concept studies and  
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13 involve outcome and process evaluations to more fully understand the impact of different  
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15 interventions on patients with severe stroke. Future research should investigate the effect  
16  
17 of more clinically used interventions, such as positioning, sitting balance and seating. Future  
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19 research should also investigate the effect of interventions on post-stroke complications  
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21 known to be high after severe stroke, such as contracture, pressure sores and caregiver  
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23 burden.  
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### 26 27 **Authors' Contributions**

28  
29 MM is the guarantor of the review. MM, CS and CM were involved in the design of the  
30  
31 protocol and systematic review. MM conducted scoping searches. MM and JJ piloted the  
32  
33 inclusion/exclusion form. MM piloted the data extraction form. MM was the first reviewer  
34  
35 and JJ was the second reviewer for the systematic review. AD provided statistical support  
36  
37 for the systematic review. MM drafted the manuscript. All authors read and approved the  
38  
39 final manuscript.  
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### 42 **Competing Interests**

43  
44 None declared.  
45  
46

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48  
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50  
51 number RT62/0116]. The funder has had no input on the design of the protocol and will  
52  
53 have no input on the analysis and interpretation of the results of the systematic review, or  
54  
55 publication of the systematic review.  
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### 58 **Patient consent**

59  
60 Not required.

### Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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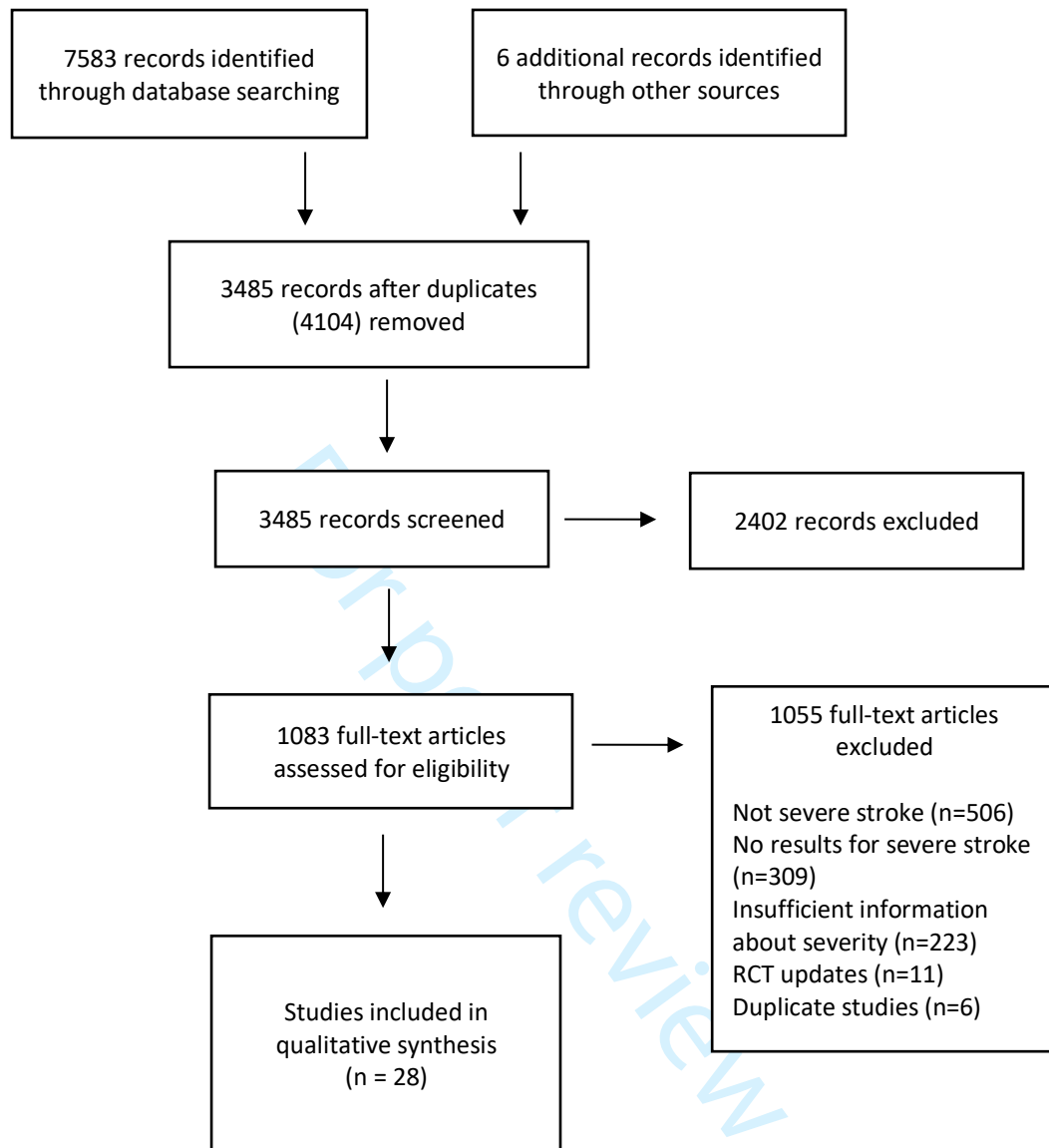
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#### FIGURE LEGENDS

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26 Figure 1- Flow chart of studies  
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28 Figure 2- Risk of bias of individual domains in the included studies  
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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
AVERT Triallists' Colloboration 2015	+	+	+	+	+	+	?
Bagley et al. 2005	+	+	-	+	+	?	-
Bai et al. 2014	+	?	-	+	+	-	-
Bradley et al. 1998	+	?	-	+	?	?	+
Calabro et al. 2015	+	?	?	+	?	?	+
Chaiyawat and Kulkantrakorn 2012	+	+	-	-	+	?	-
Chang et al. 2012	+	+	?	+	+	?	+
Chen et al. 2011	+	+	?	+	+	?	+
di Lauro et al. 2003	+	+	?	+	+	?	-
Fong et al. 2013	+	+	?	+	+	?	+
Franceschini et al. 2009	+	?	?	+	-	?	?
Jongbloed et al. 1989	+	?	+	+	?	?	+
Katz-Leurer et al. 2003	+	?	?	+	?	?	+
Kwakkel et al. 1999	+	+	+	+	+	?	+
Liang et al. 2012	+	+	?	+	+	?	+
Lincoln et al. 1999	+	+	-	+	?	?	+
Min et al. 2008	?	?	-	?	?	?	+
Morone et al. 2011	+	?	?	+	+	?	+
Ochi et al. 2015	+	+	?	+	+	?	+
Rodrigues et al. 2017	+	+	?	+	?	?	+
Rosewilliam et al. 2012	+	+	?	+	+	?	?
Sackley et al. 2015	+	+	+	+	+	+	+
Sanchez-Sanchez et al. 2014	+	?	-	+	?	?	-
Tang et al. 2014	+	+	+	+	+	?	+
Volpe et al. 2008	?	?	?	+	+	?	+
Yang et al. 2014	+	?	-	?	+	?	+
Yue et al. 2012	+	+	-	?	+	?	+
Zhang et al. 2014	-	?	-	?	?	?	+



# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract page
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Abstract page, 2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary file
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3, 4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3, 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	N/A





# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplementary file
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary file, 6-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12, 13
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

**Supplementary File 2**

## Supplementary Material- Medline Search Strategy

1. exp Stroke/
2. severe stroke.mp.
3. stroke severit\*.mp.
4. stroke disabilit\*.mp.
5. exp Physical Therapy Modalities/
6. exp Occupational Therapy/
7. exp Nursing Care/
8. physical rehabilitation.mp.
9. exp Stroke Rehabilitation/
10. exp Patient Positioning/
11. exp Posture/
12. exp Exercise/
13. exp Exercise Therapy/
14. passive exercise.mp.
15. exp "Range of Motion, Articular"/
16. manual technique.mp.
17. active exercise.mp.
18. Resistance Training/
19. exp Muscle Stretching Exercises/
20. exp Electric Stimulation/
21. exp Electric Stimulation Therapy/
22. exp Wheelchairs/
23. seat?.mp.
24. exp "Equipment and Supplies"/
25. exp Teaching/
26. exp Education/
27. exp Motor Skills/
28. exp Movement/
29. motor function.mp.
30. motor recovery.mp.
31. exp "Recovery of Function"/
32. exp "Activities of Daily Living"/
33. functional independence.mp.
34. physical independence.mp.
35. complicatio\*.mp.
36. exp Pain/
37. exp Contracture/
38. exp Pressure Ulcer/
39. exp Respiratory Tract Infections/
40. exp Urinary Tract Infections
41. Muscle Spasticity/
42. Venous Thrombosis/
44. exp Pulmonary Embolism/
44. exp Accidental Falls/
45. exp Fatigue/
46. exp Depression/
47. 1 or 2 or 3 or 4

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For peer review only

Supplementary Table 1- Studies conducted in the acute – early subacute (&lt;3 months) phase post-stroke

Study	Intervention Description	Intervention Duration	Intervention Delivered By	Stroke Severity Measure	Sample Size and Characteristics	Main Outcome Measures	Main Results	Quality of Evidence
AVERT trial collaboration group 2015 <sup>1</sup>	Very early mobilisation vs Usual care	Up to 14 days	PT and nursing staff	NIHSS	Very early mobilisation group NIHSS >16 (n=147)  Usual care group NIHSS >16 (n=144)	Favourable outcome (mRS 0-2) and mortality at 3 months	No difference in favourable outcome or mortality between groups	High
Bagley et al. 2005 <sup>2</sup>	Oswestry standing frame + standard physiotherapy vs Standard physiotherapy	14 daily sessions	PTs	BI <sup>^</sup>	Oswestry group (n=71) Median BI 1 (IQR 0-3)  Control group (n=69) Median BI 2 (IQR 1-3)	RMI, BI, HADS, NEADL, RMA, MAS (balance, sit to stand sections), TCT, CSI, GHQ-28	No differences between groups for all outcome measures. No differences in number of treatment sessions between groups or number of staff members required to treat each patient.	Low
Bradley et al. 1998 <sup>3</sup>	EMG biofeedback + conventional physiotherapy vs Placebo EMG + conventional physiotherapy	6 weeks	PTs	RMI	EMG group RMI ≤3 (n=7)  Conventional PT group RMI ≤3 (n=6)	MBS, mAS, 10MWT, RMI, sensation, proprioception  NEADL	No differences between groups for MBS, RMI, NEADL and 10MWT. No improvements in mAS, sensation and proprioception for both groups.	Very low
Chang et al. 2012 <sup>4</sup>	Robot-assisted BWS treadmill gait training + conventional physiotherapy vs Conventional physiotherapy	2 weeks	PTs	FAC LL FMA	Robot-assisted group (n=20) Mean FAC 0.5 (SD 0.5) Mean LL FMA 17.2 (SD 5.5)  Conventional group (n=17) Mean FAC 0.4 (SD 0.5) Mean LL FMA 16.8 (SD 5.7)	FAC, LL MI, LL FMA, Peak VO <sub>2</sub>	Improvements in LL FMA and peak VO <sub>2</sub> in robot-assisted gait training group. No improvements in LL MI and FAC for both groups.	Low

1						Thermal stimulation group (n=17)		Thermal stimulation group	
2						Median FAC 0 (IQR 0-1)	LL FMA, LL MRC,	demonstrated greater recovery gains	
3		Thermal stimulation +	6 weeks	Thermal stimulation- PTs	FAC	Median LL FMA 7 (4-11.5)	mAS, mMAS, PASS	compared to standard rehabilitation	Low
4	Chen et al. 2011 <sup>5</sup>	standard rehabilitation vs Standard rehabilitation		Standard rehabilitation- PTs and OTs	LL FMA		(trunk control items), BBS, FAC	group in all outcomes except PASS.	
5						Standard rehab group (n=16)		No difference between groups in	
6						Median FAC 0 (IQR 0-1)		MAS.	
7						Median LL FMA 6 (4.3-12.0)			
8									
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12		Intensive rehabilitative treatment vs Ordinary rehabilitative treatment	14 days	Therapists and nursing staff	BI^	Intensive rehab group (n=29)	BI, mNIHSS	No differences between groups in BI or mNIHSS	Very low
13	Di Lauro et al. 2003 <sup>6</sup>					Mean BI 1.4 (SD 1.4)			
14						Ordinary rehab group (n=31)			
15						Mean BI 1.5 (SD 1.5)			
16									
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22		Cueing wristwatch + conventional rehabilitation vs Sham wristwatch + conventional rehabilitation	3 weeks	Wristwatch- OTs	Motor FIM	Cueing wristwatch group (n=19) Mean motor FIM 25.6 (SD 8.3)	UL FMA, FTHUE, motor FIM, total number of UL movements	No differences between groups for UL FMA, FTHUE and motor FIM. More total UL movements in cueing wristwatch group but not significantly different between groups.	Low
23	Fong et al. 2013 <sup>7</sup>			Conventional rehab- OT, PT, ST		Sham wristwatch group (n=16)			
24						Mean motor FIM 28.2 (SD 10.0)			
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34		BWS treadmill gait training + conventional treatment vs Conventional treatment	4 weeks	PTs	BI^	Treadmill training group (n=52)	MI, TCT, mRS, BI, FAC, AS, LL proprioception,	No differences between groups. All patients were able to walk at discharge.	Low
35	Franceschini et al. 2009 <sup>8</sup>					Median BI 6 (IQR 3-9)	6MWT, 10MWT, BS, WHS		
36						Median FAC 0 (IQR 0-0)			
37						Conventional group (n=45)			
38						Median BI 5 (IQR 3-7)			
39						Median FAC 0 (IQR 0-0)			
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2	Katz-Leurer et	Leg cycle ergometer +		Leg cycle		Leg cycle ergometer and			
3	al. 2003 <sup>9</sup>	regular therapy	8 weeks	ergometer- PTs	SSS	regular rehabilitation	FAI	No differences in decline in FAI	Low
4		vs		Regular		groups- actual number of		between groups	
5		Regular therapy		therapy- PT, OT,		(SSS <30) not reported			
6				ST					
7									
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11								Improvements in LL FMA, LL MRC,	
12		Thermal stimulation +		Thermal		Thermal stimulation group		FAC and mMAS in thermal	
13	Liang et al.	standard rehabilitation	6 weeks	stimulation- PTs	BI*	(n=15)	LL FMA, LL MRC,	stimulation group post-intervention	
14	2012 <sup>20</sup>	vs		Standard		Mean BI 30.3 (SD 11.1)	FAC, BBS, mMAS, BI	and at 3-month follow-up.	Low
15		Standard rehabilitation		rehabilitation-		Standard rehab group		Improvements in BBS and BI in	
16				PTs and OTs		(n=15)		thermal stimulation group only at 3-	
17						Mean BI 27.7 (SD 14.3)		month follow-up. Except for LL-FMA,	
18								all improvements disappeared at 6-	
19								month and 12-month follow-up.	
20									
21									
22		Standard physiotherapy +							
23		additional qualified PT				Qualified PT group (n=94)			
24		therapy				Median BI 6 (IQR 3-9)			
25		vs							
26	Lincoln et al.	Standard physiotherapy +	5 weeks	PTs/ PTAs	BI^	PTA group (n=93)	RMA- arm scale,	No differences between the groups	Low
27	1999 <sup>11</sup>	additional PTA therapy				Median BI 6 (IQR 4-8)	ARAT, THPT, grip	across all outcomes	
28		vs					strength, mAS, BI,		
29		Standard physiotherapy				Standard PT group (n=95)	MCA		
30						Median BI 7 (IQR 3-9)			
31									
32									
33									
34									
35		Acupuncture + systemic				Acupuncture group (n=30)			
36		functional exercise	? 3 months	Not reported	BI*	Mean BI 27.28 (SD 5.41)	FMA, BI	Acupuncture group demonstrated	Very low
37	Min et al.	vs						greater improvements in FMA and BI	
38	2008 <sup>12</sup>	Systemic functional				Systemic exercise group		compared to the systemic exercise	
39		exercise				(n=30)		group	
40						Mean BI 28.01 (SD 4.48)			
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3		Robot-assisted treadmill				Robot-assisted group			
4		gait training + standard				(n=13) Median FAC 0 (IQR			
5		physiotherapy				0-1)			
6	Ochi et al.	vs	4 weeks	Robot-assisted	FIM mobility	Median FIM mobility 7 (IQR	FAC, FMA, LL	Robot-assisted gait training group	Low
7	2015 <sup>13</sup>	Conventional overground		gait training-	FAC	6-10)	muscle torque,	demonstrated greater improvements	
8		gait training + standard		Conventional			10MWT, FIM	in FAC and peak LL muscle torque	
9		physiotherapy		gait training-		Conventional group (n=13)	(mobility scores)	compared to the conventional group	
10				PTs		Median FAC 1 (IQR 0-1)			
11						Median FIM mobility 7 (IQR			
12						7-9)			
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16	Rosewilliam	Wrist and finger NMES +		NMES- staff	BI^	NMES group (n=31)	ARAT, BI, wrist	No differences in ARAT, BI or wrist	
17	et al. 2012 <sup>14</sup>	usual care	6 weeks	group not		Mean BI 4.4 (SD 3.9)	AROM, wrist	AROM between groups.	Moderate
18		vs		reported,		Mean ARAT 0.0 (SD 0.0)	strength, grip	Improvements in wrist extensor and	
19		Usual care		patients and			strength	grip strength in the NMES group	
20				carers		Usual care group (n=36)		post-intervention but not maintained	
21						Mean BI 2.5 (SD 2.9)		at follow-up.	
22				Usual care- PTs		Mean ARAT 0.6 (SD 3.5)			
23									
24									
25									
26		Functionally targeted				Functional techniques		Functionally targeted physiotherapy	
27	Sanchez-	physiotherapy techniques +				group (n=5)		group demonstrated greater	
28	Sanchez	conventional physiotherapy		PTs	BI*	Mean BI 13 (SD 10.95)	BI	improvement compared to the	Very low
29	et al. 2014 <sup>15</sup>	vs	Not					conventional physiotherapy group	
30		Conventional	reported			Conventional therapy group		when using functional principal	
31		physiotherapy				(n=8)		component analysis	
32						Mean BI 11.43 (SD 13.13)			
33									
34									
35		Contemporary Bobath				Early contemporary group		Improvements in STREAM and BBS in	
36	Tang et al.	approach with early sitting,				(n=24)		the contemporary Bobath approach	Low
37	2014 <sup>16</sup>	standing and walking	8 weeks	PTs	STREAM	Mean STREAM 1.4 (SD 1.0)	STREAM, BBS	with early mobilisation group	
38		vs			BBS	Mean BBS 0 (SD 0)			
39		Contemporary Bobath							
40		approach				Contemporary group (n=24)			
41						Mean STREAM 1.3 (SD 0.9)			
42						Mean BBS 0 (SD 0)			

Supplementary Table 2- Studies conducted in the acute – late subacute (&lt;6 months) phase post-stroke

Study	Intervention Description	Intervention Duration	Intervention Delivered By	Stroke Severity Measure	Sample Size and Characteristics	Main Outcome Measures	Main Results	Quality of Evidence
Bai et al. 2014 <sup>17</sup>	Staged physical rehabilitation interventions + routine care vs Routine care	6 months	PTs and OTs	BI*	Staged rehab group (n=83) Mean BI 28 (range 24-31)  Routine care group (n=82) Mean BI 23 (range 19-27)	BI, mAS	Staged rehab group demonstrated higher BI scores than the routine care group at 1, 3- and 6-months post-stroke. 42.9% of patients in the routine care group demonstrated spasticity in at least one body part compared to 36.4% of patients in the staged rehab group.	Low
Calabrò et al. 2015 <sup>18</sup>	Robotic verticalisation + standard physiotherapy vs Physiotherapy-assisted verticalisation + standard physiotherapy	6 weeks	PTs	PASS LL FMA	Robotic group (n=10) Mean PASS 3 (SD 1) Mean LL FMA 13 (SD 3)  Physiotherapy group (n=10) Mean PASS 3 (SD 3) Mean LL FMA 12 (SD 6)	PASS, LL FMA, MRC, vertical posture tolerance	Both interventions were well tolerated. Robotic group demonstrated greater improvements in MRC, LL FMA and PASS compared to the physiotherapy group	Very low
Chaiyawat and Kulkantrakorn 2012 <sup>19,20</sup>	Home based physiotherapy programme vs Usual care	6 months	PTs	BI*	Home PT group (n=30) Mean BI 31.7 (SD 5.9) Mean NIHSS 16.4 (SD 4.1)  Usual care group (n=30) Mean BI 33.2 (SD 4.8) Mean NIHSS 17.8 (SD 3.9)	BI, HADS, mRS, EQ-5D	Home therapy group demonstrated greater improvements in BI, HADS, mRS and EQ-5D compared to the usual care group which were maintained at 2-year follow-up.	Very low
Jongbloed et al. 1989 <sup>21</sup>	Functional treatment approach vs Sensorimotor integrative treatment approach	8 weeks	OTs	BI*	Functional treatment group (n=13) Mean BI 31.5  Sensorimotor integrative treatment group (n=9) Mean BI 30	BI, meal preparation, eight subtests of Sensorimotor Integration Test Battery	No differences between groups on all outcome measures	Very low



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6	Kwakkel et al.	Additional UL training + usual care	20 weeks	PTs and OTs	BI <sup>^</sup>	UL training group (n=33) Median BI 5 (IQR 3-7) LL training (n=31) Median BI 6 (IQR 3-8) Splint control group (n=37) Median BI 5.5 (IQR 3-7)	BI, FAC, ARAT, 10MWT, SIP, NHP, FAI	LL training group had significantly higher BI, FAC, walking speed and ARAT than splint control group post- intervention. UL training group had significantly higher ARAT than splint control group post-intervention. No significant differences in all outcomes were seen between groups from 6 months onwards up until 12-month follow-up.	Moderate
7	1999 <sup>22</sup>	vs							
8	2002 <sup>23</sup>	Additional LL training + usual care							
9	2002 <sup>24</sup>	vs							
10		UL/LL pressure splint immobilisation + usual care							
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27		Robot-assisted BWS treadmill gait training + standard physiotherapy							
28		vs							
29	Morone et al.	Conventional gait training + standard physiotherapy	3 months	PTs	BI*	CRP sub-study UL training group (n=18) Mean BI 5.0 (SD 2.0) LL training (n=17) Mean BI 6.3 (SD 2.7) Splint control group (n=18) Mean BI 5.3 (SD 2.7)	10MWT, mean CRP of arm/leg movements	LL training group had significantly higher comfortable walking speed than UL and splint control groups post-intervention. No differences were seen for the mean CRP of arm/leg movements between groups.	
30	2011 <sup>25</sup>								
31	2012 <sup>26</sup>								
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2					Acupuncture group (n=33)				
3					Mean NIHSS 25.5 (SD 2.4)				
4	Yang et al.	Acupuncture +	8 weeks	Acupuncture-	Mean BI 39.4 (SD 3.9)	NIHSS, FMA, BI	Acupuncture group demonstrated	Very low	
5	2014 <sup>27</sup>	rehabilitation training		not reported					
6		vs			Rehabilitation group (n=31)		measures compared to the		
7		Rehabilitation training		Rehabilitation-	Mean NIHSS 24.1 (SD 3.1)		rehabilitation group		
8				PTs	Mean BI 38.1 (SD 4.3)				
9									
10					Acupressure group (n=35)				
11	Yue et al.	Acupressure treatment			Mean BI 26.8 (SD 15.2)	FMA, BI	Acupressure group demonstrated	Very low	
12	2012 <sup>28</sup>	+ routine care	3 months	Nurses					
13		vs			Routine care group (n=34)		only at 3-month time frame		
14		Routine care			Mean BI 24.4 (SD 16.8)				
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Supplementary Table 3- Studies conducted in the chronic (&gt;6 months) phase post-stroke

Study	Intervention Description	Intervention Duration	Intervention Delivered By	Stroke Severity Measure	Sample Size and Characteristics	Main Outcome Measures	Main Results	Quality of Evidence
Rodrigues et al. 2017 <sup>29</sup>	Robot-assisted BWS treadmill gait training with progressively increased speeds vs Robot-assisted bodyweight supported treadmill gait training with progressively decreased speeds	6 weeks	Not reported	LL FMA FAC	Faster speed group (n=10) Median FAC 1.5 (1–2) Mean LL FMA 19.5 (SD 4.6)  Slower speed group (n=10) Median FAC 1 (1–2) Mean LL FMA 17.5 (SD 2.8)	FAC, TUG, 6MWT, 10MWT, BBS, LL FMA	Improvements in FAC, FMA, TUG and 6MWT in the slower speed group compared to the faster speed group.	Very low
Sackley et al. 2015 <sup>30</sup>	OT intervention vs Usual care	3 months	OTs	BI <sup>^</sup>	OT intervention group- BI 0-4 n=268 BI 5-9 n=129  Usual care group- BI 0-4 n=234 BI 5-9 n=104	BI, RMI, GDS, EQ-5D-3L	No differences between the groups on any outcome measure at 3-, 6- and 12-months post-randomisation. Higher fall rate per resident in OT intervention group at 3 months.	High
Volpe et al. 2008 <sup>31</sup>	Intensive standard UL therapy vs Intensive robot-assisted UL therapy	6 weeks	Therapists	NIHSS	Therapist group (n=10) Mean NIHSS 17 (SD 1)  Robot group (n=11) Mean NIHSS 17 (SD 1)	FMA- UL, MRC-shoulder/ elbow, mAS, UL PROM, SIS, ARAT, BDS, shoulder dislocation, pain	No difference between groups in shoulder and elbow strength and motor function. No improvements in other outcome measures for both groups.	Very low
Zhang and Li 2014 <sup>32</sup>	Trunk acupuncture + rehabilitation training vs Rehabilitation training alone	16 weeks	Not reported	BI*	Acupuncture group (n=30) Mean BI 22.50 (SD 6.79)  Rehabilitation group (n=29) Mean BI 24.48 (SD 7.23)	BI, BBS	Acupuncture group demonstrated higher scores on BI and BBS compared to the rehabilitation group.	Very low

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3 ARAT- Action Research Arm Test, AROM- active range of movement, AS- Ashworth Scale, BBS- Berg Balance Scale, BDS- Becks Depression Scale, BI\*- Barthel Index (original version scored  
4 out of 100), BI^ - Barthel Index(revised version score out of 20), BS- Borg Scale, BWS- bodyweight supported, CNS- Canadian Neurological Scale, CRP- continuous relative phase, CSI-  
5 Caregiver Strain Index, EQ-5D-3L- EuroQoL questionnaire, FAC- Functional Ambulation Category, FAI- Frenchay Activities Index, FIM- Functional Independence Measure, FMA- Fugl-Meyer  
6 Assessment, FTHUE- Functional Test for the Hemiplegic Upper Extremity, GDS- Geriatric Depression Scale, GHQ-28- General Health Questionnaire-28, HADS- Hospital Anxiety and Depression  
7 Scale, LL- lower limb, MAS- Motor Assessment Scale, mAS- Modified Ashworth Scale, MCA- Motor Club Assessment, MI- Motricity Index, mMAS- Modified Motor Assessment Scale, MMSE-  
8 Mini-Mental State Examination, mNIHSS- Modified National Institutes of Health Stroke Scale, mRS- Modified Rankin Scale, MRC- Medical Research Council Scale for Muscle Strength, NEADL-  
9 Nottingham Extended Activities of Daily Living, NHP- Nottingham Health Profile, NIHSS- National Institutes of Health Stroke Scale, OT- occupational therapist, PASS- Postural Assessment  
10 Scale for Stroke Patients, PROM- passive range of movement, PT- physiotherapist, PTA- physiotherapy assistant, RMA- Rivermead Motor Assessment, RMI- Rivermead Mobility Index, RS-  
11 Rankin Scale, SIP- Stroke Impact Profile, SIS- Stroke Impact Scale, ST- speech therapist, STREAM- Stroke Rehabilitation Assessment of Movement, TCT- Trunk Control Test, THPT- Ten-Hole  
12 Peg Test, TUG- Timed Up and Go, UL- upper limb, WHS- Walking Handicap Scale, 6MWT- 6 minute walk test, 10MWT- 10 metre walk test  
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Supplementary Table 4- Overview of Measures of Physical Function and Immobility-Related Complications

<b>Body Function</b>	<b>Activity</b>	<b>Participation</b>	<b>Complications</b>
<b>Cardiorespiratory Function</b>	<b>Activities of Daily Living</b>	<b>Instrumental Activities of Daily Living</b>	<b>Adverse Effects</b>
Aerobic capacity	Barthel Index	Frenchay Activities Index	Pain
Borg scale	Functional Independence Measure- motor	Nottingham Extended ADL Scale	Shoulder dislocation
Cardiovascular response	Functional Independence Measure- total	Meal preparation	
Ventilatory response	Modified Rankin Scale		<b>Caregiver Burden</b>
		<b>Perceived Health Status</b>	Caregiver Strain Index
<b>Neurological Impairment</b>	<b>Balance and Postural Control</b>	Stroke Impact Scale	
Canadian Neurological Scale	Berg Balance Scale	General Health Questionnaire-28	
National Institutes of Health Stroke Scale	Postural Assessment Scale for Stroke		<b>Depression</b>
	Trunk Control Test		Beck Depression Scale
	Vertical Posture Test	<b>Quality of Life</b>	Geriatric Depression Scale
<b>Sensorimotor Function</b>		EQ-5D	Hospital and Depression Scale
Active range of movement- UL		Nottingham Health Profile	
Grip strength	<b>Gait</b>	Sickness Impact Profile	
Fugl Meyer- UL	Continuous relative phase between UL/LL movement		<b>Mortality</b>
Fugl Meyer- LL	Comfortable/maximal walking speed		Mortality
Fugl Meyer- UL and LL	Functional Ambulation Category		
Motricity Index	Number of independent walkers		
Medical Research Council strength- UL	Time taken to walk 50 metres independently		<b>Spasticity</b>
Medical Research Council strength- LL	Walking Handicap Scale		Modified Ashworth Scale
Medical Research Council strength- UL and LL	6 minutes walking test		
Number of upper limb movements	10 metre walking test		
Sensation/proprioception			
Sensorimotor integration test			
	<b>General Physical Activity</b>		
	Modified Bobath Scale		
	Motor Assessment Scale		
	Rivermead Motor Assessment		
	Rivermead Mobility Index		
	Stroke Rehabilitation Assessment of Movement		
	Timed Up and Go		
	<b>Upper Limb Function</b>		
	Action Research Arm Test		
	Functional Test for Hemiplegic Upper Extremity		
	9 Hole Peg Test		
	10 Hole Peg Test		

## Supplementary Results- Outcomes Supported by Low or Very Low-Quality Evidence

### Body function

#### Cardiorespiratory Function

Two studies explored participants' cardiorespiratory response to different types of treadmill gait training within the acute to early subacute phase post-stroke.<sup>4,8</sup> There was low-quality evidence that 2 weeks of robot-assisted bodyweight supported treadmill gait training delivered in the first 6 weeks post-stroke improved peak VO<sub>2</sub> compared to conventional gait training.<sup>4</sup> There was low-quality evidence that a 4-week course of bodyweight supported treadmill training delivered in the first 3 months post-stroke was not perceived to be more effortful than conventional gait training.<sup>8</sup>

#### Neurological Impairment

Three studies evaluated changes in neurological function.<sup>6,25,27</sup> In the acute to early subacute phase post-stroke, there was very low-quality evidence that there was no difference in an intensive or ordinary 2-week acute physical rehabilitation programme on reducing neurological impairment at 2 weeks and 6 months post-stroke.<sup>6</sup> In the acute to late subacute phase post-stroke, there was very low-quality evidence that a 3-month course of robot-assisted bodyweight supported treadmill gait training commenced within the first 6 weeks post-stroke was just as effective as conventional gait training on improving neurological function.<sup>25</sup> There was very low-quality evidence that an 8-week course of acupuncture provided in conjunction with rehabilitation during the subacute phase of stroke reduced neurological impairment compared to rehabilitation alone.<sup>27</sup>

#### Sensorimotor Function

Sixteen studies evaluated changes in sensorimotor function. Nine studies were performed in the acute to early subacute phase post-stroke,<sup>3-5,7,8,10-13</sup> five studies in the acute to late subacute phase post-stroke,<sup>18,21,25,27,28</sup> and two studies in the chronic phase post-stroke.<sup>29,31</sup> In the acute to early subacute phase post-stroke, there was low quality evidence from two studies that thermal stimulation in conjunction with standard rehabilitation resulted in improvements in lower limb sensorimotor function and strength when compared to standard rehabilitation alone.<sup>5,10</sup> Improvements in lower limb sensorimotor function were maintained at 12 months post-intervention. There was low quality evidence that 2 weeks of robot-assisted bodyweight supported treadmill gait training resulted in improvements in lower limb sensorimotor function but not strength compared to conventional gait training.<sup>4</sup> There was low quality evidence that there was no difference between: 4 weeks of robot-assisted treadmill gait training and conventional gait training on improving lower limb sensorimotor function;<sup>13</sup> wearing a cueing wristwatch and wearing a sham wristwatch for 3 hours per weekday for 3 weeks during rehabilitation on improving upper limb sensorimotor function and number of arm movements;<sup>7</sup> a 4-week course of bodyweight supported treadmill training and conventional overground gait training on improving lower limb strength;<sup>8</sup> and a 5-week course of additional upper limb therapy provided by a qualified physiotherapist or a physiotherapy assistant and standard physiotherapy on improving upper limb motor activity and grip strength.<sup>11</sup> There was very low-quality evidence that a thrice weekly, 6-week course of electromyography (EMG) biofeedback combined with conventional physiotherapy had no effect on improving lower limb active range of movement when compared to conventional

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2  
3 physiotherapy alone.<sup>3</sup> There was very low-quality evidence that a 3-month course of  
4 acupuncture in conjunction with rehabilitation resulted in better upper and lower limb  
5 sensorimotor function when compared to rehabilitation alone.<sup>12</sup>

6  
7 In the acute to late subacute phase post-stroke, there was very low quality evidence that a  
8 6-week course of robotic tilt-table verticalisation that combines cyclic leg movements and  
9 FES and used in conjunction with standard physiotherapy resulted in better lower limb  
10 strength and sensorimotor function compared to physiotherapy-assisted verticalisation  
11 using a standard tilt-table and used in conjunction with standard physiotherapy.<sup>18</sup> There was  
12 very low-quality evidence that an 8-week course of acupuncture provided in conjunction  
13 with rehabilitation resulted in improvements in upper and lower limb sensorimotor function  
14 compared to rehabilitation alone.<sup>27</sup> There was very low-quality evidence that a 3-month  
15 course of nurse-led acupuncture resulted in improvements in upper and lower limb motor  
16 function compared to routine care.<sup>28</sup> There was very low quality evidence that there was no  
17 difference between: a functionally-orientated and a sensorimotor integrative occupational  
18 therapy treatment approach delivered over 8 weeks on improving upper limb sensorimotor  
19 function;<sup>21</sup> and a 3-month course of robot-assisted bodyweight supported treadmill gait  
20 training and conventional gait training on improving lower limb power.<sup>25</sup>

21  
22 In the chronic phase post-stroke, there was very low-quality evidence that a 6-week course  
23 of robot-assisted bodyweight supported treadmill gait training using slower treadmill speeds  
24 resulted in improvements in lower limb sensorimotor function compared to similar treadmill  
25 training using faster treadmill speeds.<sup>29</sup> There was very low-quality evidence that either an  
26 intensive therapist-driven UL protocol or an intensive robotic-driven UL protocol delivered  
27 thrice weekly for 6 weeks resulted in an improvement in shoulder and elbow sensorimotor  
28 function.<sup>31</sup>

## 33 Activity

### 34 Activities of Daily Living

35 Sixteen studies explored independence and ability to perform activities of daily living (ADLs).  
36 Nine studies were completed in the acute to early subacute phase,<sup>2,6-8,10-13,15</sup> six studies  
37 were completed in acute to late subacute phase<sup>17,19-21,25,27,28</sup> and one study was completed  
38 in the chronic phase.<sup>32</sup>

39  
40 In the acute to early subacute phase, there was low quality evidence that a 6-week course  
41 of thermal stimulation used in conjunction with standard rehabilitation resulted in  
42 improvements in ADL independence 3 months post-stroke compared to standard  
43 rehabilitation alone, although improvements were not seen at 6 months post-stroke.<sup>10</sup>  
44 There was low quality evidence that there was no difference between: regular  
45 physiotherapy and regular physiotherapy in conjunction with use of an Oswestry standing  
46 frame delivered over 14 consecutive weekdays in the first 3 months post-stroke on ADL  
47 independence;<sup>2</sup> wearing a cueing wristwatch and wearing a sham wristwatch for 3 hours per  
48 weekday for 3 weeks during rehabilitation on ADL independence;<sup>7</sup> a 4-week course of  
49 bodyweight supported treadmill training and conventional overground gait training on  
50 improving ADL independence;<sup>8</sup> a 5-week course of additional upper limb therapy provided  
51 by a qualified physiotherapist or a physiotherapy assistant and standard physiotherapy on  
52 improving ADL independence;<sup>11</sup> and 4 weeks of robot-assisted treadmill gait and  
53 conventional overground gait training on ADL independence.<sup>13</sup>

54  
55 There was very low-quality evidence that there was no difference in an intensive or ordinary  
56 2-week acute physical rehabilitation programme in improving ADL independence at 2 weeks  
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3 and 6 months post-stroke.<sup>6</sup> There was very low-quality evidence that a 3-month course of  
4 acupuncture in conjunction with rehabilitation resulted in better ADL independence when  
5 compared to rehabilitation alone.<sup>12</sup> There was very low-quality evidence that providing  
6 additional physiotherapy in conjunction to regular rehabilitation in the first few weeks post-  
7 stroke resulted in improvements in ADL independence at 6 months post-stroke compared to  
8 regular rehabilitation alone.<sup>15</sup>

9  
10 In the acute to late subacute phase, there was low quality evidence that a 6-month course  
11 of a staged physical rehabilitation programme resulted in greater improvements in ADL  
12 independence compared to usual care that did not involve formal rehabilitation.<sup>17</sup> There  
13 was very low-quality evidence that a monthly home-based physiotherapy programme  
14 delivered over 6 months resulted in improvements in ADL independence compared to  
15 standard care.<sup>19,20</sup> There was very low-quality evidence that there was no difference  
16 between a functionally orientated or a sensorimotor integrative occupational therapy  
17 treatment approach delivered over 8 weeks on ADL independence.<sup>21</sup> There was very low-  
18 quality evidence that a 3-month course of robot-assisted bodyweight supported treadmill  
19 gait training resulted in improvements in ADL independence compared to conventional gait  
20 training.<sup>25</sup> Improvements were only seen in the cohort of participants who demonstrated  
21 significant motor impairment. Improvements were maintained at the 2-year follow-up.<sup>26</sup>  
22 There was very low-quality evidence that an 8-week course of acupuncture provided in  
23 conjunction with rehabilitation during the subacute phase of stroke improved ADL  
24 independence compared to rehabilitation alone.<sup>27</sup> There was very low-quality evidence that  
25 a 3-month course of nurse-led acupressure resulted in improvements in ADL independence  
26 compared to routine care.<sup>28</sup>

27  
28 In the chronic phase, there was very low-quality evidence that a 16-week course of trunk  
29 acupuncture combined with rehabilitation training resulted in greater improvements in ADL  
30 independence compared to rehabilitation training alone.<sup>32</sup>

### 36 Balance and Postural Control

37 Eight studies investigated balance and postural control. Four studies were completed in the  
38 acute to early subacute phase,<sup>2,5,10,16</sup> two studies were completed in the acute to late  
39 subacute phase<sup>18,25</sup> and two studies were completed in the chronic phase.<sup>29,32</sup>

40 In the acute to early subacute phase, there was low quality evidence that a 6-week course  
41 of thermal stimulation in conjunction with standard rehabilitation resulted in improvements  
42 in trunk postural control but not balance compared to standard rehabilitation alone.<sup>5</sup> In a  
43 separate study, there was low quality evidence that a 6-week course of thermal stimulation  
44 in conjunction with standard rehabilitation resulted in improvements in balance 3 months  
45 post-stroke compared to standard rehabilitation alone, although improvements were not  
46 seen at 6 months post-stroke.<sup>10</sup> There was low quality evidence that there was no difference  
47 between regular physiotherapy and regular physiotherapy in conjunction with use of an  
48 Oswestry standing frame delivered over 14 consecutive weekdays in the first 3 months post-  
49 stroke on trunk postural control.<sup>2</sup> There was low quality evidence that an 8-week course of  
50 physiotherapy involving early mobilisation combined with the Bobath approach resulted in  
51 improvements in balance when compared to physiotherapy just involving the Bobath  
52 approach.<sup>16</sup>

53 In the acute to late subacute phase, there was very low quality evidence that a 6-week  
54 course of robotic tilt-table verticalisation that combines cyclic leg movements and FES and  
55 used in conjunction with standard physiotherapy resulted in improved postural control  
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3 during different activities compared to physiotherapy-assisted verticalisation using a  
4 standard tilt-table and used in conjunction with standard physiotherapy.<sup>18</sup> There was very  
5 low-quality evidence that a 3-month course of robot-assisted bodyweight supported  
6 treadmill gait training resulted in improvements in trunk control compared to conventional  
7 gait training.<sup>25</sup> Improvements were only seen in the cohort of participants who  
8 demonstrated significant motor impairment.  
9

10 In the chronic phase, there was very low-quality evidence that a 6-week course of robot-  
11 assisted bodyweight supported treadmill gait training resulted in improvements in balance  
12 regardless if slower or faster treadmill training speeds were used.<sup>29</sup> There was very low-  
13 quality evidence that a 16-week course of trunk acupuncture combined with rehabilitation  
14 training resulted in greater improvements in balance compared to rehabilitation training  
15 alone.<sup>32</sup>  
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### 18 19 Gait

20 Eight studies investigated gait, which included gait ability and gait speed. Six studies were  
21 performed in the acute to early subacute phase,<sup>3-5,8,10,13</sup> one study was performed in the  
22 acute to late subacute phase<sup>25</sup> and one study was performed in the chronic phase.<sup>29</sup> In the  
23 acute to early subacute phase, there was low quality evidence from two studies that a 6-  
24 week course of thermal stimulation in conjunction with standard rehabilitation resulted in  
25 improvements in gait ability compared to standard rehabilitation alone.<sup>5,10</sup> There was low  
26 quality evidence that 4 weeks of robot-assisted treadmill gait training resulted in better gait  
27 ability than conventional gait training.<sup>13</sup> There was low quality evidence that there was no  
28 difference between: a 2-week course of robot-assisted bodyweight supported treadmill gait  
29 training and conventional gait training delivered in the first 6 weeks post-stroke on  
30 improving gait ability;<sup>4</sup> a 4-week course of bodyweight supported treadmill training and  
31 conventional overground gait training on improving gait ability;<sup>8</sup> and a thrice weekly, 6-week  
32 course of EMG biofeedback combined with conventional physiotherapy and conventional  
33 physiotherapy alone in improving gait speed.<sup>3</sup> In the acute to late subacute phase, there was  
34 very low-quality evidence that a 3-month course of robot-assisted bodyweight supported  
35 treadmill gait training resulted in improvements in gait ability compared to conventional gait  
36 training.<sup>25</sup> Improvements were only seen in the cohort of participants who demonstrated  
37 significant motor impairment. Improvements were maintained at the 2-year follow-up.<sup>26</sup>  
38 In the chronic phase, there was very low-quality evidence that a 6-week course of robot-  
39 assisted bodyweight supported treadmill gait training using slower treadmill speeds resulted  
40 in improvements gait ability compared to similar treadmill training using faster treadmill  
41 speeds.<sup>29</sup>  
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### 48 49 General Physical Activity

50 Seven studies examined the effects of different interventions on improving general physical  
51 activity. Six studies were performed in the acute to early subacute phase<sup>2,3,5,10,11,16</sup> and one  
52 study was performed in the acute to late subacute phase.<sup>25</sup> In the acute to early subacute  
53 phase, there was low quality evidence from two studies that thermal stimulation in  
54 conjunction with standard rehabilitation resulted in improvements in physical activity when  
55 compared to standard rehabilitation alone.<sup>5,10</sup> Improvements were seen up until 3 months  
56 post-intervention but disappeared at the 6-month follow-up. There was low quality  
57 evidence that an 8-week course of physiotherapy involving early mobilisation combined  
58 with the Bobath approach resulted in improvements in physical activity when compared to  
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3 physiotherapy just involving the Bobath approach.<sup>16</sup> There was low quality evidence that  
4 there was no difference between: regular physiotherapy and regular physiotherapy in  
5 conjunction with use of an Oswestry standing frame delivered over 14 consecutive  
6 weekdays in the first 3 months post-stroke on physical activity;<sup>2</sup> and a 5-week course of  
7 additional upper limb therapy provided by a qualified physiotherapist or a physiotherapy  
8 assistant and standard physiotherapy on improving physical activity.<sup>11</sup> There was very low-  
9 quality evidence that there was no difference between a thrice weekly, 6-week course EMG  
10 biofeedback combined with conventional physiotherapy and conventional physiotherapy  
11 alone on improving physical activity.<sup>3</sup>

12  
13  
14 In the acute to late subacute phase, there was very low-quality evidence that a 3-month  
15 course of robot-assisted bodyweight supported treadmill gait training resulted in  
16 improvements in physical activity compared to conventional gait training.<sup>25</sup> Improvements  
17 were only seen in the cohort of participants who demonstrated significant motor  
18 impairment. Improvements were maintained at the 2-year follow-up.<sup>26</sup>

### 21 Upper Limb Function

22  
23 Two studies investigated changes in upper limb function.<sup>11,31</sup> In the acute to early subacute  
24 phase, there was low quality evidence that a 5-week course of additional upper limb  
25 therapy provided by a qualified physiotherapist was no more effective at improving upper  
26 limb function than additional upper limb therapy provided by a physiotherapy assistant or  
27 to standard physiotherapy.<sup>11</sup> In the chronic phase, there was very low-quality evidence that  
28 there was no improvement in upper limb function with either an intensive therapist-driven  
29 UL protocol or an intensive robotic-driven UL protocol delivered thrice weekly for 6 weeks.<sup>31</sup>

### 32 Participation

#### 33 Instrumental Activities of Daily Living

34  
35 Four studies investigated the effect of different interventions on instrumental ADLs.<sup>2,3,9,21</sup> In  
36 the acute to early subacute phase, there was low quality evidence that there was no  
37 difference between: regular physiotherapy and regular physiotherapy in conjunction with  
38 use of an Oswestry standing frame delivered over 14 consecutive weekdays on ability to  
39 perform instrumental ADLs at 6 months post-stroke,<sup>2</sup> and an 8-week course of rehabilitation  
40 with the addition of a leg cycling machine compared to regular rehabilitation alone on  
41 instrumental ADLs 6 months post stroke.<sup>9</sup> There was very low-quality evidence that there  
42 was no difference between a thrice weekly, 6-week course of electromyography (EMG)  
43 biofeedback combined with conventional physiotherapy and conventional physiotherapy  
44 alone in improving performance in instrumental ADLs.<sup>3</sup>

45  
46 In the acute to late subacute phase, there was very low-quality evidence that there was no  
47 difference between a functionally orientated or a sensorimotor integrative occupational  
48 therapy treatment approach delivered over 8 weeks on the ability to prepare meals.<sup>21</sup>

#### 51 Perceived Health Status

52  
53 Two studies explored carers' and patients' perceived health status.<sup>2,31</sup> In the acute to early  
54 subacute phase, there was low quality evidence that there was no difference between  
55 regular physiotherapy and regular physiotherapy in conjunction with use of an Oswestry  
56 standing frame delivered over 14 consecutive weekdays on carer's perceived health status  
57 at 12 weeks and 6 months post-stroke.<sup>2</sup> In the chronic phase, there was very low-quality  
58 evidence that there was no change in patient's perceived health status with the provision of  
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3 either an intensive therapist-driven UL protocol or an intensive robotic-driven UL protocol  
4 delivered thrice weekly for 6 weeks.<sup>31</sup>  
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#### 7 Quality of Life

8 There was very low-quality evidence that a monthly home-based physiotherapy programme  
9 delivered over 6 months resulted in an improvement in quality of life compared to standard  
10 care.<sup>19</sup>  
11  
12

#### 13 Complications

##### 14 Caregiver Burden

15 There was low quality evidence that there was no difference between regular physiotherapy  
16 and regular physiotherapy in conjunction with use of an Oswestry standing frame delivered  
17 over 14 consecutive weekdays in the first 3 months post-stroke on caregiver strain and  
18 psychological well-being at 12 weeks and 6 months post-stroke.<sup>2</sup>  
19  
20

##### 21 Depression

22 Three studies explored changes in depression.<sup>2,20,31</sup> In the acute to early subacute phase,  
23 there was low quality evidence that there was no difference between regular physiotherapy  
24 and regular physiotherapy in conjunction with use of an Oswestry standing frame delivered  
25 over 14 consecutive weekdays on depression at 12 weeks and 6 months post-stroke.<sup>2</sup> In the  
26 acute to late subacute phase, there was very low-quality evidence that a monthly home-  
27 based physiotherapy programme delivered over 6 months resulted in a reduction in level of  
28 depression compared to standard care.<sup>20</sup> In the chronic phase, there was very low-quality  
29 evidence that there was no difference between an intensive therapist-driven UL protocol  
30 and an intensive robotic-driven UL protocol delivered thrice weekly for 6 weeks in reducing  
31 depression.<sup>31</sup>  
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##### 36 Shoulder Pain/Dislocation

37 There was very low-quality evidence that either an intensive therapist-driven UL protocol or  
38 an intensive robotic-driven UL protocol delivered thrice weekly for 6 weeks had no effect on  
39 shoulder pain nor caused any shoulder dislocation when delivered to participants in the  
40 chronic phase post-stroke.<sup>31</sup>  
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##### 43 Spasticity

44 Six studies explored the effect of different interventions on spasticity.<sup>3,8,11,17,25,31</sup> In the acute  
45 to early subacute phase, there was low quality evidence that there was no difference  
46 between: bodyweight supported treadmill training and conventional overground gait  
47 training delivered over 4 weeks on reducing lower limb spasticity;<sup>8</sup> and a 5-week course of  
48 additional upper limb therapy provided by a qualified physiotherapist or a physiotherapy  
49 assistant and standard physiotherapy on reducing upper limb spasticity.<sup>11</sup> There was very  
50 low-quality evidence that there was no reduction in spasticity with a 6-week course of  
51 conventional physiotherapy with or without EMG biofeedback.<sup>3</sup>  
52 In the acute to late subacute phase, there was low quality evidence that a 6-month course  
53 of a staged physical rehabilitation programme resulted in a lower incidence of upper and  
54 lower limb spasticity compared to usual care that did not involve formal rehabilitation.<sup>17</sup>  
55 There was very low-quality evidence that a 3-month course of either robot-assisted  
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bodyweight supported treadmill training or conventional gait training had no effect on reducing lower limb spasticity.<sup>25</sup>

In the chronic phase, there was very low-quality evidence that there was no difference between an intensive therapist-driven UL protocol and an intensive robotic-driven UL protocol delivered thrice weekly for 6 weeks in reducing UL spasticity.<sup>31</sup>

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