The Effectiveness, Economic Cost and Adoption of Robotic Rehabilitation for Mobility and Functional Ability in Adult Stroke Patients

Kenneth Lo

The Joanna Briggs Institute, Faculty of Health and Medical Sciences,
The University of Adelaide

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Table of Contents

Abstract

Robotic rehabilitation devices have been developed to assist therapists to rehabilitate stroke patients based on intensive, high repetitions of task specific exercises to train the impaired limbs of patients. In contrast, conventional therapy is labour intensive and places physical strain on therapists when sustaining intense exercises. Hence it is hoped that with robotic assistive devices, better rehabilitation progress can be achieved for patients, together with alleviation of time and physical demands on therapists.

However, there are still uncertainties regarding the use of robotic devices. Studies on the clinical effectiveness of robotic devices have presented a mixed picture. Robotic devices are high capital cost items and its economic cost effectiveness is unclear. The adoption of robotic devices into clinical settings is also an area lacking clarity, as these devices do not work alone but are part of a wider spectrum of clinical care that involves clinicians, patients, hospital administrators and device manufacturers. Inadequate, or incomplete interconnection across these domains of clinical care could affect adoption into clinical settings.

Given these uncertainties, the aim of this thesis was to examine and investigate the clinical effectiveness, economic cost, and clinical adoption of robotic rehabilitation. The specific research questions were:

- Can robotic devices help adult stroke patients to regain motor movement of their upper and lower limbs?
- Can robotic devices rehabilitate adult stroke patients cost economically?
- What are the clinical views and experiences of utilizing robotic rehabilitation? What are the factors to consider when introducing robotic devices into the clinical care environment?
- How can findings from the effectiveness, economic cost and adoption studies be aggregated to create a conceptual framework of providing robotic rehabilitation?

To determine the effectiveness and cost effectiveness of robotic rehabilitation, two systematic reviews were conducted according to the JBI review methodology. To seek insights regarding its clinical adoption, qualitative descriptive interviews were conducted with therapists to understand their experiences working with robotic devices.

The findings of our research show that robotic rehabilitation is not only clinically effective but also economically cost effective, and especially for severely impaired lower limb patients robotic therapy provides better outcomes. The adoption study, which bridges the gap between the effectiveness and economic evidence from systematic reviews and translation into clinical practice, has uncovered a multitude of factors that need to be taken into consideration when introducing robotic rehabilitation into practice. These factors involve not just simply user training for these devices, but also aspects such as workflow processes, interfacing systems, communication strategies to influence adoption, perceived benefits, and attitudes and motivations of users. From the understandings gained from these various streams of research, a conceptual framework on implementing robotic rehabilitation was developed in order to facilitate translation of the research evidence into practice.

This thesis contributes new evidence on effectiveness, cost-effectiveness and clinical integration to the global knowledge base about the use of robotic rehabilitation, and ultimately will lead to stroke patients benefiting from robotic rehabilitation and gaining better health outcomes.

Thesis Declarations

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Dated: October 2019

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- And to my family and friends who have shown patience and understanding when I needed time to work on the thesis.

Chapter One: Introduction

This chapter describes the nature of stroke in adults: its causes, impairment effects, and rehabilitation methods. From the concept of neuroplasticity and the use of intensive therapy to regain functional improvements, the application of robotic devices in rehabilitation is introduced. We then discuss uncertainties surrounding robotic rehabilitation which leads to the aim of this thesis, that is to determine the clinical and cost effectiveness, and adoption considerations of robotic rehabilitation in clinical settings. Lastly, we outline the composition of subsequent chapters contained in this thesis that answer the research questions posed.

Incidence of stroke

Stroke is a leading cause of long-term disability and is the third most common cause of mortality in developed countries with 15 million people suffering a stroke yearly.[1] The annual incidence of stroke is around 2 per 1000 in developed countries and the incidence of stroke rises steeply with increasing age, with the average age of stroke patients at 75 years old.[2] In terms of gender, men are 25% to 30% more likely to suffer a stroke compared to women, and people in lower socio-economic strata are 60% more likely than those in higher strata to suffer a stroke.[2] The mortality risk within three months after a stroke incident is around 30%, and even if they survive a stroke incident, stroke survivors are commonly left with long-term impairments (physical, speech and cognitive deficits).[2]

In Australia, stroke is also a leading cause of disability, with 65% of stroke survivors unable to carry out daily living activities unassisted.[3] In 2017 there were around 475,000 people living with the effects of stroke and this is predicted to increase to one million by 2050.[3] In terms of the financial cost (health system cost, direct and indirect costs) of stroke in Australia, it is estimated to be around $5 billion each year.[3]

Causes and effects of stroke

Stroke is an acute neurologic deficit and is caused by cerebrovascular aetiology, when the flow of blood to the brain is interrupted. Oxygen is carried from the lungs to tissues in the body by the protein haemoglobin in red blood cells, and an interruption of oxygen supply for a few minutes to the brain will cause neuronal death (cerebral infarction).[4] This leads to a loss of neurological functions, which manifest as physical, speech and cognitive impairments. When an infarction occurs, there is a central area of dead brain

tissue, which is surrounded by brain tissue that is ischemic (i.e. with restricted blood supply) but not yet dead. Further from the central infarction area, the brain becomes less ischemic. Recovery of neurological functions within this ischemic penumbra, together with the ability of unaffected parts of the brain taking over the affected parts (i.e. neuroplasticity), are the likely mechanisms that contribute to the therapeutic rehabilitation of stroke patients.[2]

There are two types of stroke: ischemic and haemorrhagic. Ischemic stroke is caused by blockage of blood vessels (vascular occlusion or stenosis) and haemorrhagic stroke by rupture of blood vessels (vascular rupture). Ischemic stroke is the main type of stroke and accounts for 80% of stroke cases.[5]

Two types of ischemic strokes exist.[5] They are:

- Embolic
    - Stroke that is caused by a clot that is formed elsewhere in the body and is transported via the blood stream to the brain. In the brain, the clot reaches an artery which is too small for it to pass through and becomes embedded, thus limiting blood flow.
- Thrombotic
    - Stroke that is caused by cholesterol deposits on the inner walls of blood vessels. Over time, the deposit grows in size and leads to a narrowing and eventual blockage of the artery.

Haemorrhagic strokes can also be classified into two types:[5]

- Intracerebral
    - Haemorrhage that is caused when an artery within the brain bursts and blood flows out of the blood vessel into the brain tissue.
- Subarachnoid
    - Haemorrhage that is caused by blood flow into the meninges of the brain.

Stroke-like symptoms can also occur in what is known as ‘Transient Ischemic Attack’ (TIA).[5] TIA is mainly caused by clots that initially block the flow of blood but which dissolves and allows blood flow again. TIA can also be caused by a sudden drop in blood pressure that reduces blood flow to the brain. Symptoms of TIA are sudden onset of numbness, loss of movement or weakness in the face, arm or leg (usually on one side of the body), vision changes or inability to speak. These symptoms gradually reduce as blood flow is restored and last for less than 24 hours. TIA is a warning sign of a possible

future stroke incident (a very high risk of stroke in the first month after the TIA event and up to one year thereafter).[6]

The number-one cause of stroke is high blood pressure.[7] High blood pressure, in turn, is affected by factors such as smoking, excessive alcohol consumption, obesity, and high intake of fatty or salty food. When blood pressure is high, it causes more stress on the walls of blood vessels, thus weakening them. Eventually it could lead to a rupture causing a haemorrhagic stroke. High blood pressure can also cause blood clots or plaque (formed from cholesterol or fat-like substances) to be broken off from the inner walls of blood vessels. These clots can then travel to a brain artery where it blocks off the flow of blood, causing an ischemic stroke. Another cause of stroke is diabetes. Diabetes can cause blood vessels to harden and narrow, increasing the risk of stroke. A medical condition, Fibromuscular Dysplasia (FMD), is also a cause of stroke.[8] FMD is a condition whereby fibrous tissue is formed in the walls of arteries, causing narrowing of the arteries. As a result, blood flow through the arteries decreases. FMD usually affects arteries to the kidney but it can also affect the carotid (neck) arteries that supply blood to the brain. Cardiovascular diseases, such as abnormal heart rhythms (e.g. atrial fibrillation) and heart valve problems can cause blood clots to form. When these clots block an artery in the brain, stroke can occur.

Different parts of the brain control different bodily functions. If a person survives a stroke and depending on the location of brain damage, severity and duration of the stroke, it can have various effects. Broadly, the impairment effects of stroke can be physical or cognitive related. The most common physical effect of stroke is the loss of motor abilities of the limbs. The upper or lower limbs can experience weakness (paresis) or paralysis (plegia), and this physical impairment can affect one side of the body or just an arm or leg. The most common type of limb impairment is hemiparesis which affects eight out of ten stroke survivors[7]. The affected side is usually on the opposite side of where the brain damage is, due to the cross-over of the motor and sensory tracts of the nervous system from one side to the other. Hemiparesis patients will experience weakness to the arms, hands, legs and facial muscles. Consequently, patients have difficulties performing everyday activities such as walking, eating or dressing. Another physical effect of stroke is the loss of visual fields or vision perception. Under visual field loss, stroke patients usually experience blindness on one side of both eyes. If the left side of the brain is damaged (left hemisphere stroke), visual fields on the right side of both eyes will be affected (this symptom is called homonymous hemianopia). Another type of visual field loss is blindness in the outer half of the visual field, which results in the loss of peripheral

vision (i.e. tunnel vision). Stroke patients with loss of vision perception experience challenges gauging depth and distances, double vision of seeing two of a thing, or shifting of the centre line of sight to either left or right side. This visual midline shift can result in the loss of balance and tilting of the body more to the left or right. Another type of visual perception is called visual neglect, where the patient does not register objects in a certain area. Under this condition, patients may only take food from only one half of the plate. Other physical impairments caused by stroke are difficulty swallowing (dysphagia), apraxia of speech, incontinence, joint pain or neuropathic pain (caused by inability of the brain to correctly interpret sensory signals in response to stimuli to the affected limbs).[7]

Cognitive effects of stroke are aphasia, memory loss and vascular dementia.[7] Stroke patients can lose the ability to understand speech or the capacity to read, think or reason. Normal mental tasks can present big challenges to stroke patients and can affect their quality of life. Patients may not be able to follow instructions, remember directions, dates or time; or demonstrate a lack of rationale when undertaking tasks that are not safe.

The drastic changes in physical and cognitive abilities caused by stroke can lead to emotional effects for stroke patients. Stroke survivors can experience depression after stroke when they encounter problems in doing tasks that they could easily do pre-stroke. Along with depression, they can experience a lack of motivation and mental fatigue. Another emotional effect of stroke is the sudden and uncontrollable onset of laughing and crying, which can occur even though the patient does not have such emotions internally. This involuntary outburst is called Pseudobulbar Affect (PBA) and is caused by damage to parts of the brain that control emotion.[7]

Rehabilitation of stroke survivors

For post-stroke survivors, rehabilitation is the pathway to regaining or managing their impaired functions.[9] There is no definite end to recovery but most rapid improvement is within the first 6-months post stroke.[10] Before a patient undergoes rehabilitation, an assessment is first done to determine if a patient is medically stable and fit for a rehabilitation program.[11,12] If the patient is assessed to be suitable, then depending on the level of rehabilitative supervision required, the patient could undergo rehabilitation in various settings: as an inpatient/outpatient (at either a hospital or nursing facility) or at home.[9,13-15]

Rehabilitation is administered by a multi-disciplinary team of physiotherapist, occupational therapist, speech therapist and neuropsychologist, who work together to offer an integrated, holistic rehabilitation therapy.[9,12,16] Depending on the type of impairment, rehabilitation specialists will assess the appropriate therapies needed and set realistic goals for patients to achieve. Generally, stroke patients are given a minimum of 45 minutes for each therapy over at least 5 days per week, so long as the patient can tolerate the rehabilitation regime[6].

One of the main goals in stroke rehabilitation is the restoration of physical motor skills and this involves the patient undergoing repetitive, high intensity, task-specific exercises that enables them to regain their motor and functional abilities.[17] It is theorized that the brain is plastic in nature and that repetitive exercises over long periods can enable the brain to adapt and regain the motor functionality that has been repeatedly stimulated. This involves the formation of new neuronal interconnections that enable the re-transmission of motor signals[18]. It has been shown in animal studies that test subjects regained motor abilities after intensive and repetitive task training.[19] This was associated with a reorganization of the undamaged motor cortex to enable recovery of motor abilities of the affected limbs.[20] Such 'neuroplasticity' is the underlying principle of motor learning involving repetitive, high intensity, task-specific exercises.[21]

Robotic rehabilitation

To facilitate 'neuroplasticity' motor learning, robotic devices have been developed to assist therapists to rehabilitate patients based on high repetitions of task specific exercises.[22] These robotic devices provide intensive, consistent and repetitive cycles over long periods to train the impaired limbs of patients. There are two main types of robotic devices: exoskeletons or end-effectors. Exoskeletons are devices that wrap around limbs and are able to assist each limb joint to move. End-effectors are devices that assist only the extremities of a limb (either hands or feet).[23] Regardless of design mechanism, one key feature of robotic devices is the ability to automatically assist patients to move their limbs when they are unable to do so by themselves. This automated assistive feature enables high repetitions to be achieved.

In contrast, to achieve the high repetitions needed for 'neuroplasticity', conventional therapy can be labour intensive and places physical strain on therapists when sustaining intense exercises.[23] Coupled with the requirements of stroke patients for medical care and intensive rehabilitation exercises (which frequently entails one-to-one manual

interaction with therapists), therapist time and organizational budget would face difficulties to provide an optimal rehabilitation program.[23] Therefore, it is hoped that with robotic assistive devices, better rehabilitation progress can be achieved for patients together with alleviation of time and physical demands on therapists. With the assistance of robots, therapists could concentrate more on functional rehabilitation during individual training sessions or be able to supervise multiple patients simultaneously during robot assisted therapy sessions. This approach would maximize the expertise and time of therapists, thus improving the effectiveness of the rehabilitation program.[23]

There have been clinical studies to determine the effectiveness of robotic assistive devices in the rehabilitation of stroke patients.[24] However, these studies presented a mixed picture of the effectiveness of robotic devices. One study on lower limbs reported an improvement in a motor movement scale (Fugl-Meyer Assessment lower-extremity score) but not for another motor scale (leg score of Motricity Index) and also stated no improvement on a walking scale (Functional Ambulation Category).[25] Others reported that there was no statistically significant difference between robotic assisted therapy and conventional therapy,[26,27] while one study that investigated walking speeds and distance found that conventional therapy was more effective than robotic assisted therapy.[28] The inconclusive findings and diverse outcomes in the existing evidence base, unfortunately, do not provide a clear determination of the effectiveness of robotic rehabilitation.

Besides the clinical effectiveness, there is also a need to evaluate the economic cost of robotic rehabilitation. Robotic devices enable a high intensity training regime, but the devices incur a significant capital outlay for healthcare providers. Some of the robotic training equipment can cost up to several hundred thousand dollars per device.[29] Despite its high cost, robotic devices may increase the work efficiency of therapists, meaning that more patients can be treated and this could lead to an overall reduction in cost of treatment per patient.[30,31] Hence, the decision to introduce robotic devices into clinical settings and offer robotic stroke rehabilitation to patients is a major economic cost consideration for hospitals, and it is important to identify appropriate treatment methods that can not only reduce the disability experienced by stroke survivors but are also economically viable.

Another consideration is the adoption of robotic rehabilitation devices into clinical settings. One of the end goals of rehabilitation is to improve the functional ability of patients. For physical disability this requires gradual training of minimal movements and progressing to more complex task specific actions.[16] Therapy also focuses on improving

strength, endurance, precision and speed of movements. Coupled with the various types of robotic devices with different therapeutic modalities (active, passive, active-assist training modes), it is important to determine how therapists and robotics can work together to improve the physical functionality of patients. Robotic devices also do not work alone but are part of a wider spectrum of clinical care that involves clinicians, patients, hospital administrators and device manufacturers. This interconnection to other parties could affect its adoption into a clinical setting in diverse ways, raising questions such as the work scope of therapists when robotic devices are doing the rehabilitation, the responses of patients to robotic treatment that has less human contact, and the optimal treatment protocols that can best combine the benefits of conventional and robotic training. The presence of robotic devices could change the way clinicians work and how patients are handled in a rehabilitation unit. Therefore, the clinical, organisational and human behavioural dimensions could present challenges to the adoption of robotic devices.

Objective of thesis

It is the aim of this thesis to examine and investigate the abovementioned aspects of robotic rehabilitation in terms of its clinical effectiveness, economic cost, and adoption into clinical settings. The specific research questions to be addressed are:

- Can robotic devices help adult stroke patients to regain motor movement of their upper and lower limbs?
- Can robotic devices rehabilitate adult stroke patients cost economically?
- What are the clinical views and experiences of utilizing robotic rehabilitation? What are the factors to consider when introducing robotic devices into the clinical care environment?
- How can findings from the effectiveness, economic cost and adoption studies be aggregated to create a conceptual framework of providing robotic rehabilitation?

This thesis is organized into seven chapters and has been undertaken through a series of publications. Chapter one introduces the topic and outlines the aims and the composition of the thesis. Chapter two is a systematic review that examined the clinical effectiveness of robotic rehabilitation, and chapter three supplements the systematic review by analysing the sources of heterogeneity that was encountered during the systematic review. Chapter four investigates the economic cost perspectives of robotic rehabilitation via an economic systematic review, and chapter five introduces a supplemental method to extend the hierarchical decision matrix used in the economic

systematic review. This supplemental method was applied in order to gain a more differentiating analysis of the economic systematic review. Both systematic reviews for effectiveness and economic cost have been conducted according to the review methodology of the Joanna Briggs Institute (JBI). Each review has been peer reviewed and subsequently published in the JBI Database of Systematic Reviews and Implementation Reports.

The systematic review methodology has been applied in our research as it enables a comprehensive and objective assessment of evidence in order to answer the specific questions, namely the clinical and cost effectiveness of robotic rehabilitation for adult stroke patients. With the large volume of research literature available regarding a clinical question, robust methods for systematically finding and reviewing the available evidence, and to undertake meta-analyses of the results of such evidence is needed.[32] Here, for the two systematic reviews, the review methodology of JBI has been applied. The JBI methodology, through its defined PICO (Participant, Intervention, Comparator, Outcome) inclusion criteria, allows for a comprehensive and yet informed selection of studies that best address the research question. Without the PICO inclusion criteria of a systematic review, the large volume of information would not be manageable and be digestible for analysis.[33] The structured and rigorous assessment of risks of bias (i.e. methodological quality) also contributes to the reliability and quality of the review findings.[32,34] The detection of the levels of heterogeneity and use of sub-group analysis in a systematic review further ensures a robust interpretation of review findings.[35] Lastly, through the use of meta-analysis, systematic reviews offer increased power and precision in estimates of effect sizes by statistically pooling all available data of included studies.[32,33] In view of these benefits, systematic review is the most appropriate method to answer the specific clinical and cost effectiveness questions posed in this thesis.

Chapter six details the qualitative findings from interviews with rehabilitation therapists on their perspectives and experiences adopting and working with robotic devices in clinical settings. Ethics approval has been obtained to conduct the interviews (HREC approval number: H-2017-151). In chapter six, the method applied for this study was based on qualitative description analysis.[36] This method involves the identification of findings that are close to the data (i.e. straight and largely unadorned answers), and with minimal transformation (i.e. with little imputation of meaning by researchers).[36] This descriptive analysis approach enabled us to identify and extract data that described specific adoption considerations, such as what worked/did not work as expressed by participants, i.e. manifest context is described with low interpretation of data.[36]

Qualitative descriptive analysis also facilitated our data collection method of semi-structured interviews with individual clinicians. The semi-structured interview format not only allowed us to tap into the knowledge, past experiences and learning points of clinicians, but also enabled the collection of further information to uncover and probe deeper into specific points during the interviews. We used the qualitative descriptive analysis as it allowed us to understand the actual nature of the situations faced by those involved, thereby giving us a sharper resolution of the events that were being encountered on the ground, without any loss of details or contextual meaning.[36] This then enabled us to identify specific adoption findings.

In chapter seven, the findings from prior studies are amalgamated to generate a conceptual framework for implementing robotic rehabilitation for adult stroke patients, which takes into account the findings from the effectiveness and economic reviews, and the qualitative adoption study. Implications of the thesis findings are also discussed, and key clinical and economic cost domains that should be considered when introducing robotic training are identified.

Ultimately, it is hoped that stroke patients can benefit from robotic rehabilitation and gain better health outcomes from the thesis research.

Chapter Two: Effectiveness Systematic Review (Paper One and Two – Published)

Paper 1: Lo K, Stephenson M, Lockwood C. Effectiveness of robotic assisted rehabilitation for mobility and functional ability in adult stroke patients: a systematic review. JBI Database System Rev Implement Rep. 2017;15(12):3049-91.

Paper 2: Lo K, Stephenson M, Lockwood C. Effectiveness of robotic assisted rehabilitation for mobility and functional ability in adult stroke patients: a systematic review protocol. JBI Database System Rev Implement Rep. 2017;15(1):39-48.

Statement of Contribution

Kenneth Lo (Candidate)

I was responsible for the overall creation of this paper. As the primary author I developed the protocol, conducted the literature searches, retrieved papers, and assessed each paper for their eligibility. I subsequently undertook critical appraisal, data extraction and data analysis. I was also responsible for responses to reviewers and revisions to the paper. The review was conducted using tools provided by the Joanna Briggs Institute.

Statement of Authorship

Title of Paper	Effectiveness of robotic assisted rehabilitation for mobility and functional ability in adult stroke patients: a systematic review.
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Principal Author

Name of Principal Author (Candidate)	Kenneth Lo		
Contribution to the Paper	I was responsible for the overall creation of this paper. As the primary author I developed the protocol, conducted the literature searches, retrieved papers, and assessed each paper for their eligibility. I subsequently undertook critical appraisal, data extraction and data analysis. I was also responsible for responses to reviewers and revisions to the paper. The review was conducted using tools provided by the Joanna Briggs Institute.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	October 2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr. Matthew Stephenson		
Contribution to the Paper	Supervisor: provided conceptualization and methodological guidance to the manuscript. Contributed to the writing and revision of the paper, including responding to peer review comments, and reviewing the findings and conclusion.		
Signature		Date	October 2019

Name of Co-Author	Assoc. Prof. Craig Lockwood		
Contribution to the Paper	Supervisor: provided conceptualization and methodological guidance to the manuscript. Contributed to the writing and revision of the paper, including responding to peer review comments, and reviewing the findings and conclusion.		
Signature		Date	October 2019

Please cut and paste additional co-author panels here as required.

Effectiveness of robotic assisted rehabilitation for mobility and functional ability in adult stroke patients: a systematic review

Kenneth Lo • Matthew Stephenson • Craig Lockwood

The Joanna Briggs Institute, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, Australia

EXECUTIVE SUMMARY

Background
Stroke is a leading cause of long-term disability, and rehabilitation, involving repetitive, high intensity, task-specific exercises, is the pathway to restoring motor skills. Robotic assistive devices are increasingly being used and it is hoped that with robotic devices, rehabilitation progress can be achieved for patients.

Objectives
To examine the effectiveness of robotic devices in the rehabilitation of stroke patients for upper limb mobility, lower limb mobility, and activities of daily living. The sustainability of treatment effect was also examined.

Inclusion criteria
Types of participants
Adult stroke patients 18 years and over.

Types of intervention(s)
Rehabilitation of stroke patients using robotic devices with assistive automation, compared to conventional physiotherapy.

Outcomes
Motor movements of upper limbs, walking movement of lower limbs and activities of daily living, including follow-up measurements to examine the sustainability of treatment effect.

Types of studies
Randomized and controlled clinical trials.

Search strategy
Published and unpublished studies in English were searched.

Methodological quality
All studies meeting the review inclusion criteria were independently assessed for methodological quality by two reviewers.

Data extraction
Quantitative data were extracted using the standardized data extraction tool from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument.

Data synthesis
Quantitative data were pooled in statistical meta-analysis. Effect sizes expressed as standardized mean difference, 95% confidence intervals and levels of heterogeneity (I^2) were calculated. Where statistical pooling was not possible, the findings were presented in narrative form.

Results
Fifty-one studies with 1798 patients were included in this review. Thirty studies examined upper limb interventions and 21 studies evaluated lower limb gait training. Non-significant results were found for upper limb (SMD 0.07, 95% CI −0.11 to 0.26, $I^2 = 41\%$, $P = 0.45$), lower limb (SMD 0.17, 95% CI −0.15 to 0.48, $I^2 = 75\%$, $P = 0.31$) and activities of

Correspondence: Kenneth Lo, kenneth.lo@adelaide.edu.au

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daily living (SMD 0.11, 95% CI −0.11 to 0.33, $I^2 = 66\%$, P = 0.32). For patients with severely impaired lower limbs, a significant difference was observed in favor of robotics (SMD 0.41, 95% CI 0.19 to 0.63, $I^2 = 28\%$, P = 0.0003). P-value analysis did not show significant results for the sustainability of treatment effect post intervention.

Conclusions

Robotic training is just as effective as conventional training for upper limb motor movement, lower limb walking mobility and for activities of daily living. For lower limb patients with severe impairment, robotic training produces better outcomes than conventional training. The sufficient quantity of studies included and the reasonable quality of Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence support the findings. For treatment sustainability of upper and lower limbs, robotic training is just as effective as conventional training. However, the low quality of GRADE evidence and the lower number of studies included require caution for this finding. For treatment sustainability of activities of daily living, the better quality of GRADE evidence and the larger number of studies analyzed indicate that robotic training is just as effective as conventional training.

Keywords cerebrovascular accident; rehabilitation; robotics; robots; Stroke

JBI Database System Rev Implement Rep 2017; 15(12):3049–3091.

GRADE Summary of Findings

Robotic assisted rehabilitation for mobility and functional ability in adult stroke patients compared to conventional physiotherapy

Bibliography: Kenneth L, Stephenson M, Lockwood C. Effectiveness of robotic assisted rehabilitation for mobility and functional ability in adult stroke patients: a systematic review. JBI Database System Rev Implement Rep 2017; 15(12):3049–3091.

Outcomes	№ of participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with conventional training	Risk difference with robotic training
Upper limb	860 (29 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **0.07 higher** (0.11 lower to 0.26 higher)
Upper Limb - therapy ratio = 0	507 (16 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **0.13 higher** (0.13 lower to 0.39 higher)
Upper limb - follow-up (<=3 months)	293 (9 RCTs)	⨁⨁◯◯ LOW [a,b]	-	-	SMD **0.06 higher** (0.22 lower to 0.33 higher)
Upper limb - follow-up (>3 months)	217 (7 RCTs)	⨁⨁◯◯ LOW [a,b]	-	-	SMD **0** (0.45 lower to 0.45 higher)

Lower limb	701 (15 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **0.17 higher** (0.15 lower to 0.48 higher)
Lower limb - severe	510 (10 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **0.41 higher** (0.19 higher to 0.63 higher)
Lower limb - therapy ratio = 0	207 (6 RCTs)	⨁⨁◯◯ LOW [a,b]	-	-	SMD **0.08 SD lower** (0.74 lower to 0.58 higher)
Lower limb - follow-Up (<=3 months)	259 (5 RCTs)	⨁⨁◯◯ LOW [a,b]	-	-	SMD **0.33 lower** (1.31 lower to 0.65 higher)
Lower limb - follow-up (>3 months)	408 (6 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **0.3 higher** (0.05 lower to 0.65 higher)
Activities of daily living (ADL)	1120 (31 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **0.11 higher** (0.11 lower to 0.33 higher)
ADL - therapy ratio = 0	345 (12 RCTs)	⨁⨁⨁◯ MODERATE [a]	-	-	SMD **0** (0.54 lower to 0.53 higher)
ADL - follow-up (<=3 months)	428 (11 RCTs)	⨁⨁⨁◯ MODERATE [b]	-	-	SMD **0.1 lower** (0.57 lower to 0.38 higher)
ADL - follow-up (>3 months)	481 (9 RCTs)	⨁⨁⨁⨁ HIGH	-	-	SMD **0.14 higher** (0.27 lower to 0.56 higher)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **SMD:** Standardized mean difference
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
a. Imprecision: Sample sizes of experimental and control groups are less than 400
b. Publication Bias: Funnel plot shows a possible bias

Background

Stroke is a leading cause of long-term disability and is the third most common cause of mortality in developed countries, with 15 million people suffering a stroke yearly.[1] Different parts of the brain control different bodily functions. If a person survives a stroke and, depending on the location of brain damage, severity and duration of the stroke, various effects can follow. Broadly, the effects of stroke can be physical, cognitive or emotional in nature. In terms of the physical effects of stroke, the loss of motor abilities of the limbs presents significant challenges for patients, as their mobility and activities of daily living are affected. The upper or lower limbs can experience weakness (paresis) or paralysis (plegia), with the most common type of limb impairment being hemiparesis, which affects eight out of ten stroke survivors.[2] Other physical effects of stroke are loss of visual fields, vision perception, difficulty swallowing (dysphagia), apraxia of speech, incontinence and joint pain or neuropathic pain (caused by inability of the brain to correctly interpret sensory signals in response to stimuli to the affected limbs). Cognitive effects of stroke are aphasia, memory loss and vascular dementia. Stroke patients can lose the ability to understand speech or the capacity to read, think or reason, and normal mental tasks can present big challenges to stroke patients, affecting their quality of life. The drastic changes in physical and cognitive abilities caused by stroke also lead to emotional effects. Stroke survivors can experience depression when they encounter problems in doing tasks that they can easily do pre-stroke. Along with depression, they can experience a lack of motivation and mental fatigue.[2]

For stroke patients, rehabilitation is the pathway to regaining or managing their impaired functions. There is no definite end to recovery but most rapid improvement is within the first six months post stroke.[3] Before a patient undergoes rehabilitation, an assessment is first done to determine if a patient is medically stable and fit for a rehabilitation program.[4] If the patient is assessed to be suitable, then, depending on the level of rehabilitative supervision required, the patient could undergo rehabilitation in various settings: as an inpatient/outpatient (at either a hospital or nursing facility) or at home.[3,4] Rehabilitation should be administered by a multidisciplinary team of physiotherapists, occupational therapist, speech therapist and neuropsychologists, who work together to offer integrated, holistic rehabilitation therapy.[4] Depending on the type of impairment, rehabilitation specialists will assess the appropriate therapies needed and set realistic goals for patients to achieve. Generally, stroke patients should be given a minimum of 45 minutes for each therapy session per day over at least five days per week, so long as the patient can tolerate the rehabilitation regime.[3]

One of the main goals in stroke rehabilitation is the restoration of motor skills and this involves patients undergoing repetitive, high intensity, task-specific exercises that enables them to regain their motor and functional abilities.[5,6] It is theorized that the brain is plastic in nature and that repetitive exercises over long periods can enable the brain to adapt and regain the motor skills that are repeatedly stimulated.[7] This involves the formation of new neuronal interconnections that enable re-transmission of motor signals.[8]

Over the years, a number of robotic assistive devices have been used to rehabilitate patients based on high repetitions of task specific exercises.[9] These robotic assistive devices provide intensive, consistent and repetitive cycles over long periods and help patients train their limbs to keep receiving and sending signals from and back to the brain, and thereby regain their motor abilities. Such devices are complex in nature, involving interactive automation, sensors and dynamic control logic and are able to function without much intervention from physiotherapists. Several devices have been used for rehabilitation of upper limb (e.g. ARMin [Sensory-Motor Systems Lab, ETH Zurich, Switzerland], InMotion ARM™ [Bionik Laboratories], NeReBot [University of Padua, Italy], Armeo®Spring [Hocoma]) and lower limb (e.g. Lokomat® [Hocoma], Gait Trainer™ [Reha-Stim Medtec], G-EO System™ [Reha Technology], Hybrid Assistive Leg® [Cyberdyne]).[10,11] As an example, for patients who are unable to walk, there are gait training devices such as the Lokomat® that help patients to recover their walking ability. Initially the physiotherapist will set up the patient into the device and start a software program that cycles through the various stages of walking.[12] The patient's lower limbs will be moved by the device and the physiotherapist is able to set the pace of simulated walking and amount of guidance force to

assist movement of the legs and extent of body weight support.[12]

In comparison, for conventional rehabilitation of the lower limbs without assistive devices, it would require at least two physiotherapists to train a patient to walk, and the pace and pattern of walking may not be consistent.[13] It is also physically strenuous for the physiotherapists to sustain the exercise over long periods, thus affecting the rehabilitation progress of the patient. The labor-intensive nature of conventional physiotherapy places a great strain on physiotherapists. Coupled with the requirements of stroke patients for medical care and intensive rehabilitation exercises (which frequently entails one-to-one manual interaction with therapists), providing an optimal rehabilitation program would place a huge strain on therapist time and organizational budget.[10] Therefore, it is hoped that with robotic assistive devices, better rehabilitation progress can be achieved for patients, together with the alleviation of time and physical demands on physiotherapists. With the assistance of robots, physiotherapists will be able to concentrate more on functional rehabilitation during individual training sessions and supervision of multiple patients simultaneously during robot assisted therapy sessions. This approach would maximize the expertise and time of physiotherapists, thus improving the effectiveness of rehabilitation programs.[10]

There have been clinical studies to determine the effectiveness of robotic assistive devices in the rehabilitation of stroke patients.[14] However, these studies presented a mixed picture of the effectiveness of robotic devices. One study on lower limbs reported improvement in a motor movement scale (Fugl-Meyer Assessment lower-extremity score) but not in another motor scale (leg score of Motricity Index), and also stated no improvement in a walking scale (Functional Ambulation Category).[15] Others reported that there was no statistically significant difference between robotic assisted therapy and conventional therapy,[16,17] while one study that investigated walking speeds and distance found that conventional therapy was more effective than robotic assisted therapy.[12] There were also various types of study designs. Some studies examined not just robot-assisted rehabilitation but combinations of robot-assisted rehabilitation and non-conventional physiotherapies (e.g. functional electrical simulation [FES], constraint induced therapy [CIT], transcranial direct current stimulation or motor imagery) versus conventional therapies in three-arm studies.[18-20] Other studies involved patients in randomized controlled cross-over trials with or without a wash-out period.[21,22]

A variety of outcomes were used to assess motor movement, motor strength/duration, walking speed or functional activities across the included studies in this systematic review, complicating the analysis.[23] In a trial with multiple outcome measures, this could lead to increased risk of Type I error when multiple simultaneous hypotheses are tested at set p-values.[24] To mitigate this, Feise[24] recommended that researchers facing multiple outcome measures select a primary outcome measure or use a global assessment measure. As robotic devices are primarily designed to enable movement of a particular limb,[10] a suitable outcome measure that reflects the design function of the device is necessary in order to accurately determine the effectiveness of these devices. In view of this, outcomes that measure motor movement of the paretic limbs were considered, such as Fugl-Meyer Scale Assessment (upper extremity) for the upper limbs or Functional Ambulation Category for the lower limbs. The current review also aimed to address the question of sustainability of the treatment effects, for example, is the improved motor movement measured at the end of the intervention period maintained post intervention?

The diverse range of outcomes and study designs in the existing evidence base do not provide a clear determination of the effectiveness of robotic assisted rehabilitation and therefore it was the intent of this review to give clarity to the discussion and offer useful recommendations for clinical practice. In this review, robotic assisted therapies for both upper and lower limbs were studied to gain a detailed understanding of the effectiveness of robotic devices in these two areas, where a large proportion of rehabilitation efforts are devoted. The methods of the review have been described in a previously published protocol.[25]

Objectives

The objective of this review was to synthesize the best available evidence on the effectiveness of robotic assistive devices in the rehabilitation of adult stroke patients for recovery of impairments in the upper and lower limbs. The specific review question to be addressed was: Can robotic assistive devices

help adult stroke patients regain motor movement of their upper and lower limbs?

The secondary objective of this systematic review was to investigate the sustainability of the treatment effect associated with use of robotic devices.

Inclusion criteria

Types of participants

This review considered studies that included adult stroke patients (18 years and over) of all genders, regardless of whether stroke was due to ischemic or hemorrhagic causes. Patients with pre-existing impairments that were not caused by stroke, such as disabilities due to spinal cord injuries, Parkinson's disease, multiple sclerosis and traumatic brain injuries (caused by accidents, falls, infections, tumors or chemical toxins) were excluded. Study participants were new stroke patients or repeat stroke patients at acute, sub-acute or chronic stages of their stroke, as long as they had been accepted into a formal rehabilitation program. Only trials where the rehabilitation setting was either inpatient or outpatient were included. Home rehabilitation patients were excluded due to potential confounding of treatment adherence. The rehabilitation program was conducted at hospitals, nursing facilities or across multi-centers and only physical impairments related to upper and lower limbs were considered.

Types of intervention(s)

This review considered studies that evaluated rehabilitation of stroke patients using interactive, automated electro-mechanical equipment (i.e. assistive robotics) and compared the outcomes to control groups which had conventional physiotherapy. The types of robotic assistive devices were varied (e.g. either robotic exoskeletons or end-effectors for gait training, and unilateral or bilateral arm robotics for upper limb training). Interventions involving the devices below were not considered as robotic rehabilitation devices, as they did not exhibit assistive automation:

- Non-interactive devices that delivered passive motion such as treadmills, static body-weight assisted treadmills, bicycles, static walking aids, static orthoses (such as ankle-foot orthoses addressing foot drop) or pure mechanical trainers (e.g. Reha-Slide™ [Reha-Stim Medtec], Reha-Slide Duo™ [Reha-Stim Medtec]).
- Standalone video games that were controlled solely by patient without automated assistive feature, such as Wii U™ (Nintendo Co. Ltd.).
- Rehabilitation programs using non-conventional therapies such as acupuncture, FES, transcranial direct current stimulation, motor imagery, biofeedback, CIT.

Intervention groups analyzed had a combination of robotic and conventional physiotherapy training in various therapy ratios (i.e. duration of conventional training/duration of robotic training), and in other studies, some intervention groups had purely robotic training and did not include conventional therapy components. The examined intervention groups also did not contain other types of non-conventional therapy (e.g. FES, transcranial direct current stimulation, motor imagery or CIT). For multiple-arm studies, only results of the intervention arm with robotic-assisted rehabilitation was compared to the control arm. The intervention arm with a combination of robotic assistive devices and non-conventional therapy was excluded from analysis.

Outcomes

This review considered studies that included the outcome measure of the amount of motor movement demonstrated by the paretic limbs and only studies that used scales that measure motor movement were considered for the review.

- For the outcome measure of upper limbs, the Fugl-Meyer Assessment[26] (upper extremity score) was the preferred scale. If a study did not use this scale, then an alternative measurement scale that quantified upper limb motor movement (e.g. upper limb Motricity Index[27]) was considered.
- For the outcome measure of lower limbs, the Functional Ambulation Category[28] was the preferred scale. If a study did not use this scale, then an alternative measurement scale that quantified walking was considered, e.g. Barthel Index[29] (ambulation item) or Functional Independence Measure[30] (walking item).

The second outcome of interest that was examined was the level of activities of daily living (ADLs) attained after the intervention. For outcome measure of ADLs, Functional Independence Measure was the preferred scale. If a study did not use this scale, then

an alternative measurement scale that quantified the level of ADLs was considered, e.g. Barthel Index. As ADLs involved usage of both upper and lower limbs, a global ADLs measurement combining both subgroups of upper and lower limbs was considered.

In clinical trials, patient outcomes were measured at different stages of rehabilitation. Usually measures were taken at pre-, mid- and post-intervention stages but some studies continued to take follow-up measurements in the months after the end of the intervention therapy. For this review, measurements taken at pre- and post- intervention therapy were included for analysis. Follow-up measurements taken after interventions had ended were also included to examine the sustainability of the treatment effect.

Types of studies

The review was limited to randomized and controlled clinical trials. For studies with cross-over design, only the first study period (before cross-over) was considered for inclusion.

Search strategy

The search strategy aimed to find both published and unpublished studies. A three-step search strategy was utilized in this review. An initial limited search of PubMed was undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms (modified for goodness of fit with each specific database thesaurus) was then undertaken across all included databases. Thirdly, the reference list of all identified reports and articles was searched for additional studies. Studies published in English were considered for inclusion in this review and a date limit starting from 2000 was set, as automated robotic devices have increasingly been used since 2000, together with an associated increase in the number of studies undertaken. The overall search date range was from January 2000 to June 2016.

The databases searched included: PubMed, Embase, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL) and PEDro (Physiotherapy Evidence Database).

The search for unpublished studies included: MedNar, ProQuest Dissertations and Theses, ClinicalTrials.gov, Google Scholar.

Initial keywords used for PubMed were: Robotics[mh] OR Robot*[tw] OR Exoskeleton Device[mh] OR Exoskeleton*[tw] OR Gait Trainer[tw] OR Lokomat[tw] AND Rehabilitation[mh] OR Rehabilitation[tw] OR Habilitation[tw] AND Stroke[mh] OR Stroke*[tw] OR ''Cerebrovascular Accident'' OR Cerebral[tw] OR ''Cerebral Stroke'' OR ''Cerebrovascular Stroke'' OR ''Acute Stroke'' OR ''Sub-acute Stroke'' OR ''Subacute Stroke''.

The full search strategy is provided in Appendix I.

Assessment of methodological quality

Articles selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using the standardized critical appraisal instrument from the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI).[31] Any disagreements that arose between the reviewers were resolved through discussion, or with a third reviewer. To establish the quality of evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[32] approach and Summary of Findings were used.

The key appraisal criteria to include or exclude studies were questions pertaining to true randomization (Question 1) and whether the treatment groups were treated identically (i.e. both intervention and control groups) were dose matched (Question 7). Studies that received a ''No'' to either of these two questions were excluded.

Two appraisal questions (Questions 4 and 5) were assessed as being not applicable given the rehabilitation context of the trials, where it was not practically feasible to blind participants or treatment therapists.

Data extraction

Data were extracted from papers included in the review using the standardized data extraction tool from JBI SUMARI.[31] The data extracted included specific details about the interventions, populations,

study methods and outcomes of significance to the review question and specific objectives.

Data synthesis

Data were, where possible, pooled in statistical meta-analysis using Review Manager 5 (Copenhagen: The Nordic Cochrane Centre, Cochrane). Effect sizes expressed as standardized mean difference (SMD) for continuous data and their 95% confidence intervals (95% CI) were calculated for analysis. Heterogeneity was assessed statistically using I^2 and the standard Chi-square. Where statistical pooling was not possible the findings have been presented in narrative form including tables and figures to aid in data presentation where appropriate.

Subgroups considered for analysis included:

- Upper limb and lower limb interventions
- Acute/sub-acute patients (less than six months post stroke) and chronic patients (more than or equal to six months post stroke)
- Severe impairment patients and moderate/mild impairment patients
- Intervention groups whereby there is only robotic training and no conventional training (i.e. Therapy Ratio [TR] = 0, TR = Duration of Conventional Training/Duration of Robotic Training)
- Intervention groups with follow-up less than or equal to three months and follow-up more than three months.

The different impairment levels for upper limb are as follows:

- Severe impairment: 0 < Fugl-Meyer (UL) <= 20
  - For patients with severe motor impairment, majority of the scale ratings are unable to perform (rating = 0), with some ratings between partial performance (rating = 1) and near normal performance (rating = 2)[33]
- Moderate impairment: 20 < Fugl-Meyer (UL) <= 40
  - For patients with moderate motor impairment, the bulk of the ratings are between partial performance level (rating = 1) 1) and near normal performance level (rating = 2)[33]
- Mild impairment: 40 < Fugl-Meyer (UL) <= 66
  - For patients with mild motor impairment, the bulk of the ratings are at the near normal performance level (rating = 2).[33]

The different impairment levels for lower limb are as follows:

- Severe impairment: 0 < Functional Ambulation Categorie (FAC) <= 1.5
  - 0: Patient cannot walk or requires help from two or more people[34]
  - 1: Patient requires firm, continuous support from one person who helps with carrying weight and with balance[34]
- Moderate impairment: 1.5 < FAC <= 3.5
  - 2: Patient needs continuous or intermittent support from one person to help with balance or coordination[34]
  - 3: Patient requires verbal supervision or assistance to stand with help from one person without physical contact[34]
- Mild impairment: 3.5 < FAC <= 5
  - 4: Patient can walk independently on level ground, but requires help on stairs, slopes or uneven surfaces[34]
  - 5: Patient can walk independently.[34]

Six studies had data as median values and three of these[35-37] were converted to means and standard deviations using the methods of Wan *et al.*[38] The median data of the other three studies[39-41] were not suitable for conversion, as they had only the interquartile range but did not contain the required quartile 1 and quartile 3 values.

Results

A total of 3048 citations were generated from the final search strategy and 681 were identified from other sources such as MedNar, ProQuest Dissertations and Theses, ClinicalTrials.gov and Google Scholar (Figure 1).[42] After initial screening of titles and abstracts, 158 studies went through the process of verification of study eligibility (Appendix II). Consequently, 51 studies were appraised for quality.

Description of included studies

A total of 51 studies with 1,798 patients were included in this review. There were 30 studies that examined upper limb interventions and 21 studies that evaluated lower limb gait training. Of the included studies, 27 had acute/sub-acute patients and 24 had chronic patients.

The studies came from diverse regions: Americas (USA, Mexico), Europe (Italy, Finland, Germany,

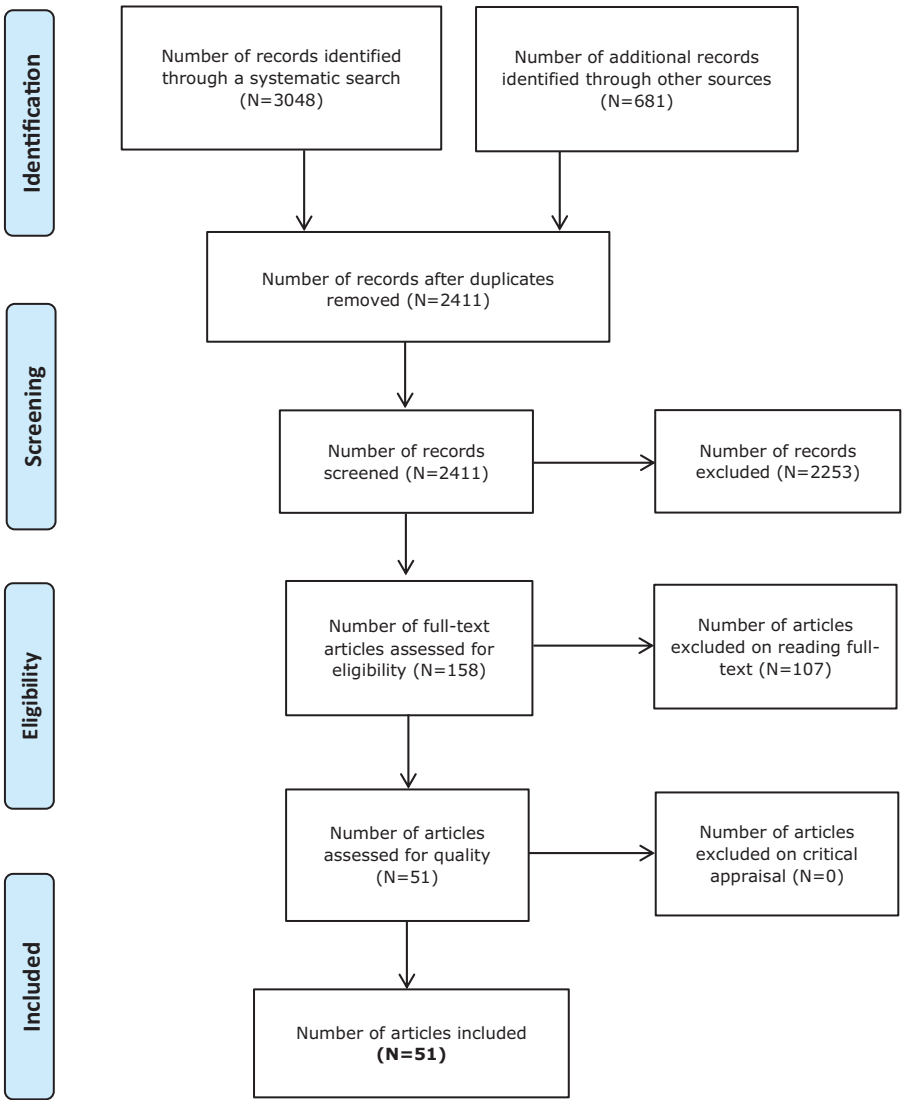

Figure 1: PRISMA flow diagram of study selection and inclusion process[42]

the Netherlands, Portugal, Switzerland), Middle East (Israel) and Asia (Hong Kong, Japan, Singapore, South Korea, Taiwan). Trial participants were all adults and were predominantly around 60 years old. Three trials with the largest sample sizes (Pohl *et al.*,[43] Chua *et al.*[44] and Lo *et al.*[17]) had a majority of male patients (around 80% on average for the three studies). However, the average male percentage over all included studies was 64%. In terms of stroke types, more patients had ischemic stroke (60% to 90%) than hemorrhagic stroke. There were various training durations across studies, with total training hours ranging from four hours to 300 hours. However, within each study, the therapy dosage was the same for intervention and control groups (i.e. groups were dose-matched).

There were 22 studies that compared purely robotic training to purely conventional training (i.e. experimental group had no conventional training component; TR = 0). Of these 22 studies, 16

were for upper limb studies and six were for lower limb studies. The remaining studies had varying amounts of conventional training combined with robotic training in the experimental groups (TR ranges from 0.2 to 6). Further details of the studies are presented in Appendix III.

Methodological quality

Various sources of bias such as selection, performance, detection and attrition biases[45,46] were considered significant in the assessment of the included studies. For this review, the important strategies for assessing attempts to minimize the risk of bias were whether studies were truly randomized, and if experimental and control groups were treated equally in terms of the duration of training given. If studies were not properly randomized, or if trials were not dose-matched, these would be major risks of bias, as the patient group receiving higher training durations would be likely to have better outcomes. An imbalance in this respect would make outcome comparisons meaningless. In these two areas, all included studies were required to score a ''Yes'' to appraisal questions 1 and 7, which significantly reduces the risk of bias.

In terms of homogeneity of patient characteristics between groups at baseline (question 3), the majority of studies (92%) scored a ''Yes''. This indicated that trial subjects were mostly comparable at the start of the study. Due to the rehabilitation nature of the trials, it was not practically feasible for patients and therapists to be blinded and this could have introduced bias into the outcomes.[47] Patients who were in the experimental group with novel robotic training could have felt more motivated than patients in the conventional training and so achieve better outcome measures.[48] Nevertheless, this risk of bias is common for rehabilitation type of trials and do not necessarily mean that the trials were of low quality.[49]

Another potential source of bias is non-blinded assessment.[50] Assessors might have over-rated patients with robotic training in order to show positive results or they themselves might have been pre-disposed towards robotic training. There were 11 out of the 51 studies that did not have blinded assessment and they had a sample size of 354 patients, which is around 20% of the total sample size. In terms of study designs, most trials involved two-arm and three-arm studies, and only two studies had a cross-over design.

Overall, the included studies had good methodological quality with no major sources of bias. For non-blinded assessment, this could be a potential source of bias and was addressed via a sensitivity analysis[46,51] which is described further in the discussion section. Appendix IV outlines the appraisal of methodological quality for the included studies.

Findings of the review

Here we present the findings of the review based on the following three sub-groups: upper limb, lower limb and activities of daily living. For each sub-group, we looked at overall outcomes of the included studies. Then we explored if the outcomes were any different based on comparing robotic therapy alone to conventional therapy alone (i.e. TR = 0) and looking at sustainability of treatment effects. For the three studies[39-41] that were not suitable for meta-analysis, we did a narrative review. As part of the review, we also analyzed for heterogeneity and non-blinded assessment.

Upper limb movement

For the outcome of upper limb movement, 29 studies with a total patient population of 860 were analyzed. Overall, the forest plot showed no significant difference between experimental and control groups (Figure 2). The pooled SMD (random-effects model) was 0.07, 95% CI −0.11 to 0.26, $I^2 = 41\%$, P = 0.45. No evidence for publication bias was found from the funnel plot (Figure 3).

Sub-group analyses for acute/sub-acute patients, chronic patients, severe impairment patients and moderate/mild impairment patients were conducted and these showed no significant differences between experimental and control groups (Acute/Sub-Acute: SMD −0.02, 95% CI −0.42 to 0.39, P = 0.93; Chronic: SMD 0.11, 95% CI −0.06 to 0.28, P = 0.22; Severe: SMD 0.17, 95% CI −0.18 to 0.51, P = 0.34; Moderate/Mild: SMD 0.03, 95% CI −0.19 to 0.26, P = 0.78).

Upper limb movement (TR = 0)

For the comparison of robotic therapy alone to conventional therapy alone (TR = 0), 16 studies with

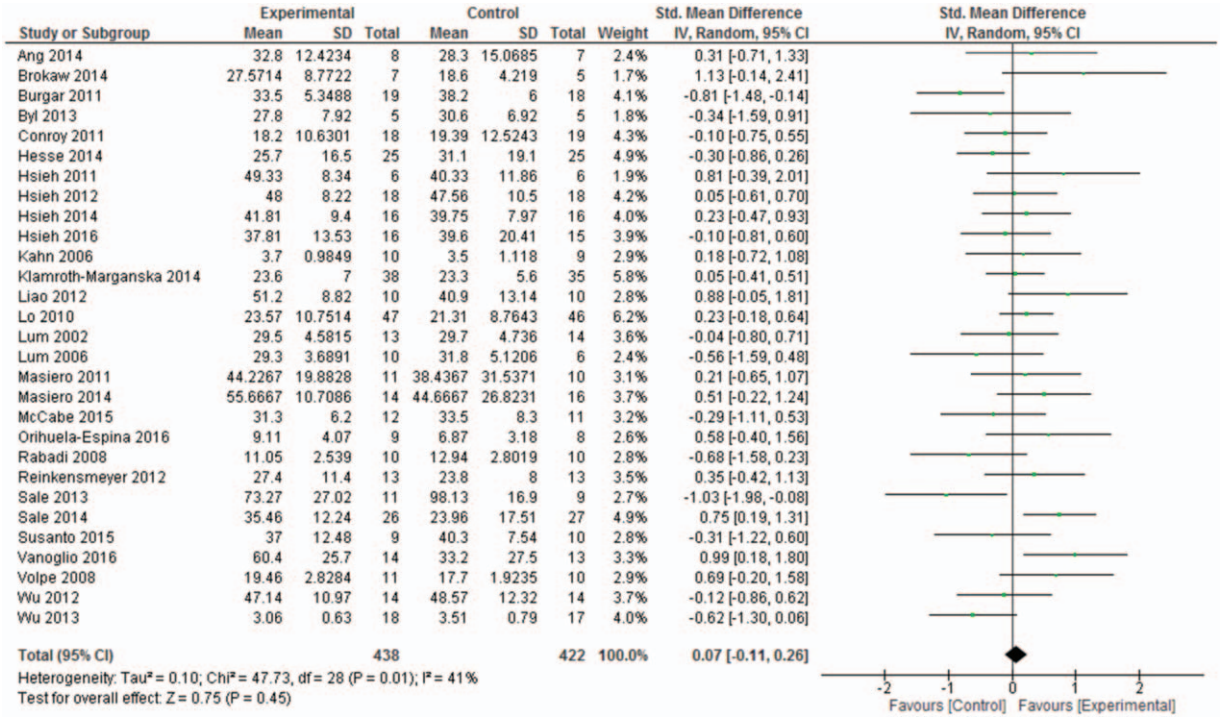

Figure 2: Effect of robotic therapy in experimental group compared with conventional therapy control group on upper limb movement (SD: standard deviation; CI: confidence interval)

a total patient population of 507 were analyzed and the result showed no significant difference between experimental and control groups (Figure 4). The pooled SMD (random-effects model) was 0.13, 95% CI −0.13 to 0.39, $I^2 = 48\%$, P = 0.33. No evidence for publication bias was found from the funnel plot (Figure 5).

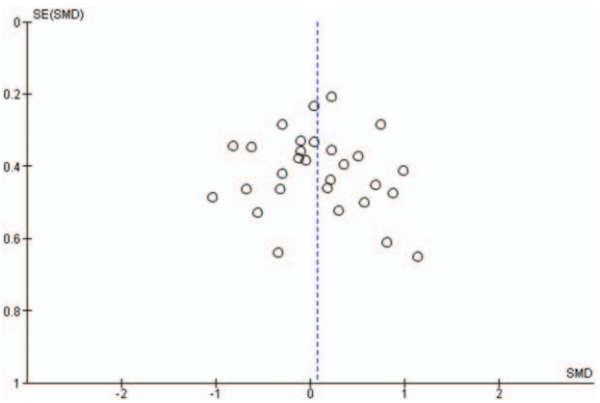

Figure 3: Funnel plot of upper limb studies (SE: standard error; SMD: standard mean difference)

Sub-group analyses for acute/sub-acute patients, chronic patients, severe impairment patients and moderate/mild impairment patients were conducted and these showed no significant differences between experimental and control groups (Acute/Sub-Acute: SMD 0.06, 95% CI −0.60 to 0.73, P = 0.85; Chronic: SMD 0.14, 95% CI −0.07 to 0.36, P = 0.19; Severe: SMD 0.25, 95% CI −0.10 to 0.61, P = 0.16; Moderate/Mild: SMD 0.02, 95% CI −0.37 to 0.42, P = 0.90).

Upper limb movement (sustainability)

To examine the sustainability effects, analyses involving intervention groups with: (i) follow-up in less than or equal to three months, and (ii) follow-up in more than three months were conducted.

Follow-up in less than or equal to three months

Nine studies with a total patient population of 293 were analyzed. The forest plot showed no significant difference between experimental and control groups (Figure 6). The pooled SMD (random-effects model) was 0.06, 95% CI −0.22 to 0.33, $I^2 = 24\%$,

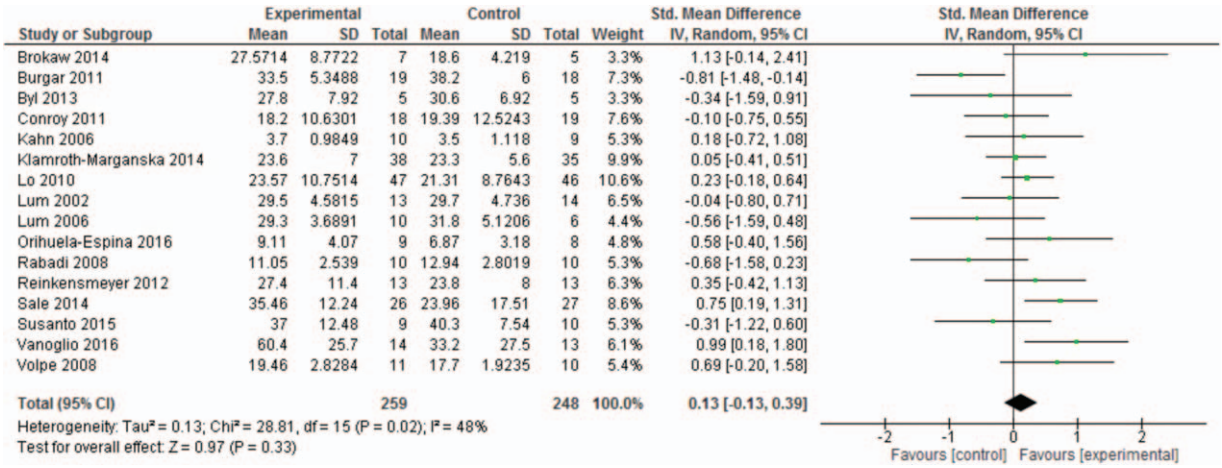

Figure 4: Effect of robotic therapy in experimental group compared with conventional therapy control group on upper limb movement (TR = 0) (SD: standard deviation; CI: confidence interval)

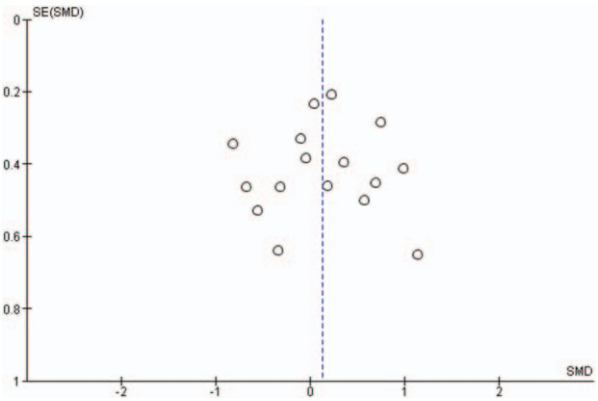

Figure 5: Funnel plot of upper limb studies with TR = 0 (SE: standard error; SMD: standard mean difference)

P = 0.68. A potential for publication bias was found from the funnel plot (Figure 7).

Follow-up in more than three months

Seven studies with a total patient population of 217 were analyzed. The forest plot showed no significant difference between experimental and control groups (Figure 8). The pooled SMD (random-effects model) was 0.00, 95% CI −0.45 to 0.45, $I^2 = 59\%$, P = 1.00. The funnel plot showed a possible publication bias (Figure 9).

Lower limb walking

Fifteen studies with a total patient population of 701 were analyzed. The forest plot showed no significant difference between experimental and control groups

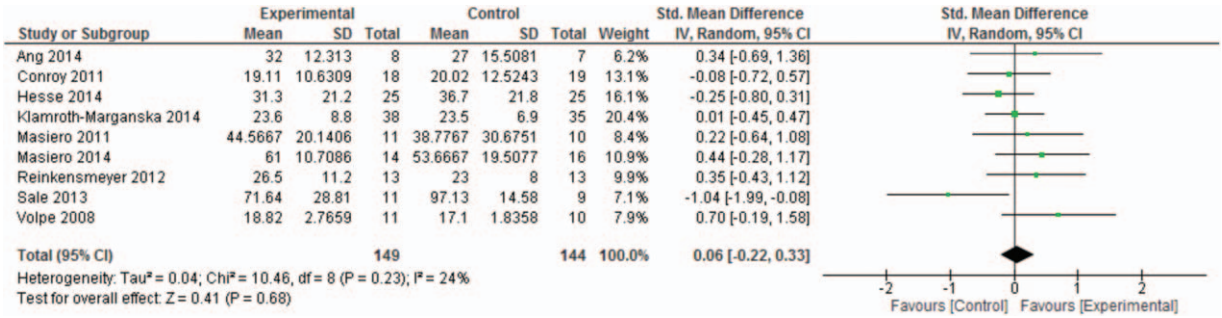

Figure 6: Effect of robotic therapy in experimental group compared with conventional therapy control group on upper limb movement (follow-up in less than or equal to 3 months) (SD: standard deviation; CI: confidence interval)

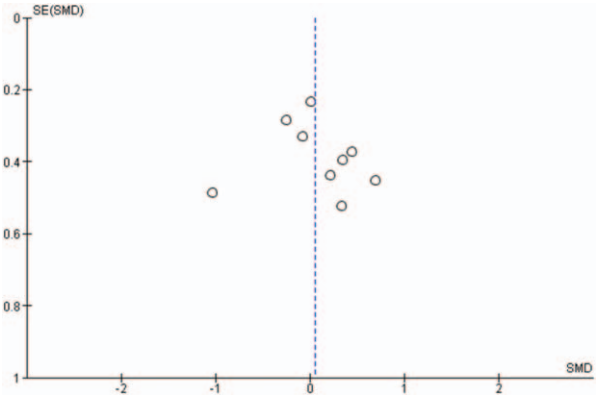

Figure 7: Funnel plot of upper limb studies with follow-up in less than or equal to 3 months (SD: standard deviation; CI: confidence interval)

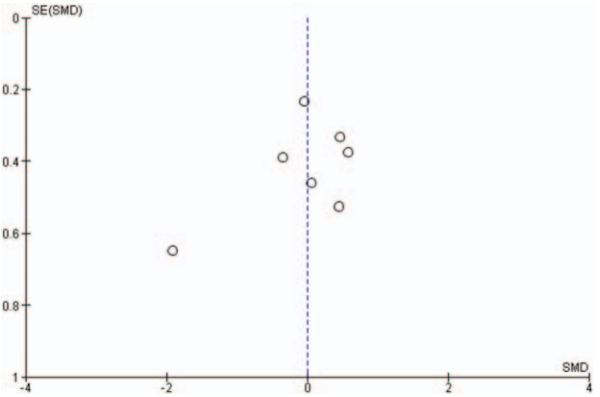

Figure 9: Funnel plot of upper limb studies with follow-up in more than 3 months (SE: standard error; SMD: standard mean difference)

(Figure 10). The pooled SMD (random-effects model) was 0.17, 95% CI −0.15 to 0.48, $I^2 = 75\%$, $P = 0.31$. No evidence for publication bias was found from the funnel plot (Figure 11).

Sub-group analyses for acute/sub-acute patients, chronic patients, severe impairment patients and moderate/mild impairment patients were conducted. For acute/sub-acute patients, chronic patients and

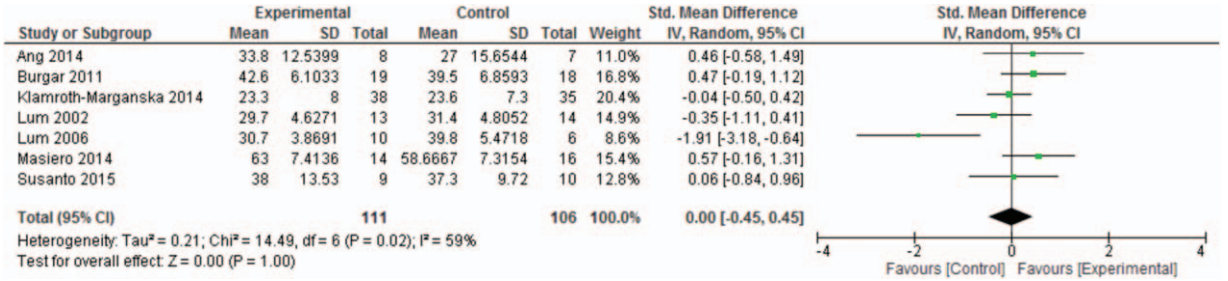

Figure 8: Effect of robotic therapy in experimental group compared with conventional therapy control group on upper limb movement (follow-up in more than 3 months) (SD: standard deviation; CI: confidence interval)

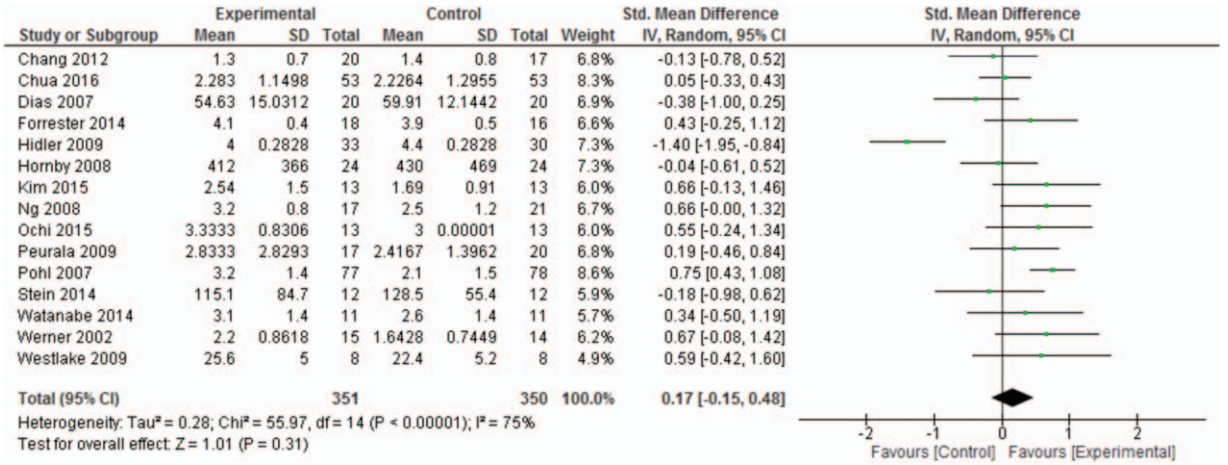

Figure 10: Effect of robotic therapy in experimental group compared with conventional therapy control group on lower limb walking (SD: standard deviation; CI: confidence interval)

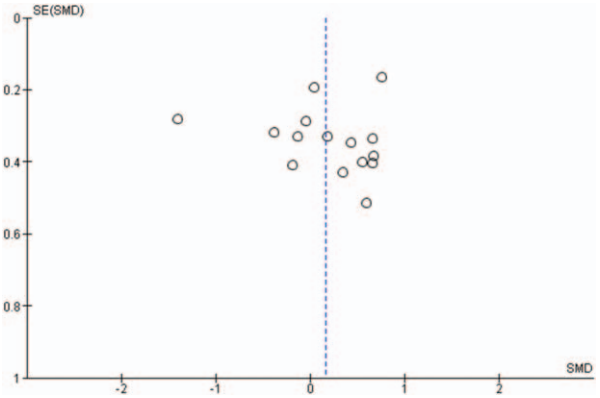

Figure 11: Funnel plot of lower limb studies (SE: standard error; SMD: standard standard mean difference)

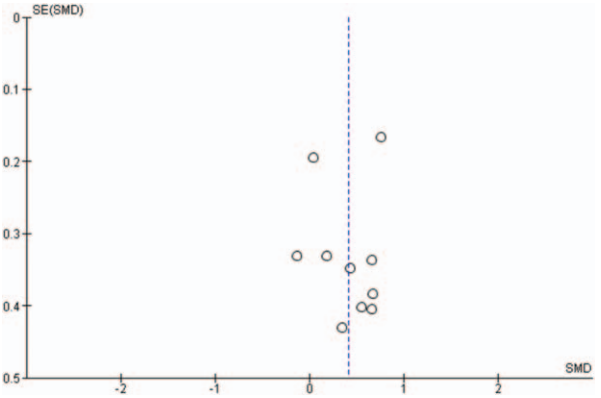

Figure 13: Funnel plot of lower limb studies (severe impairment) (SE: standard error; SMD: standard mean difference)

moderate/mild impairment patients, there were no significant differences between experimental and control groups (Acute/Sub-Acute: SMD 0.24, 95% CI −0.15 to 0.62, P = 0.23; Chronic: SMD −0.10, 95% CI −0.44 to 0.25, P = 0.59; Moderate/Mild: SMD −0.34, 95% CI −0.97 to 0.29, P = 0.29). However, for severe impairment patients, a statistically significant difference favoring the experimental group was found (Figure 12). The pooled SMD (random-effects model) was 0.41, 95% CI 0.19 to 0.63, $I^2 = 28\%$, P = 0.0003. No evidence for publication bias was found from the funnel plot (Figure 13).

Lower limb walking (TR = 0)

For the comparison of robotic therapy alone to conventional therapy alone (TR = 0), six studies with a total patient population of 207 were analyzed and the result showed no significant difference between experimental and control groups (Figure 14). The pooled SMD (random-effects model) was −0.08, 95% CI −0.74 to 0.58, $I^2 = 80\%$, P = 0.81. The funnel plot showed asymmetry indicative of publication bias (Figure 15).

Sub-group analyses for acute/sub-acute patients, chronic patients, severe impairment patients and moderate/mild impairment patients were conducted and these showed no significant differences between experimental and control groups (Acute/Sub-Acute: SMD −0.23, 95% CI −1.43 to 0.96, P = 0.70; Chronic: SMD 0.03, 95% CI −0.39 to 0.45, P = 0.88; Severe: SMD 0.40, 95% CI −0.13 to 0.93, P = 0.14; Moderate/Mild: SMD −0.31, 95% CI −1.13 to 0.51, P = 0.46).

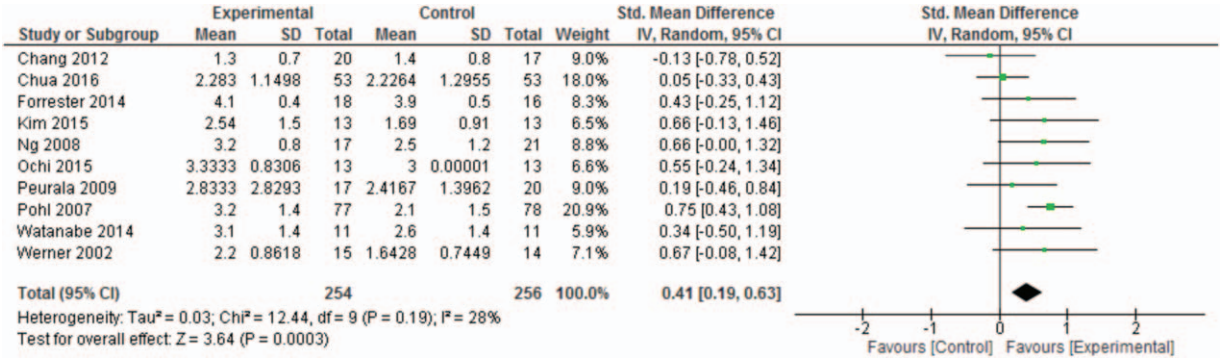

Figure 12: Effect of robotic therapy in experimental group compared with conventional therapy control group on lower limb walking (severe impairment) (SD: standard deviation; CI: confidence interval)

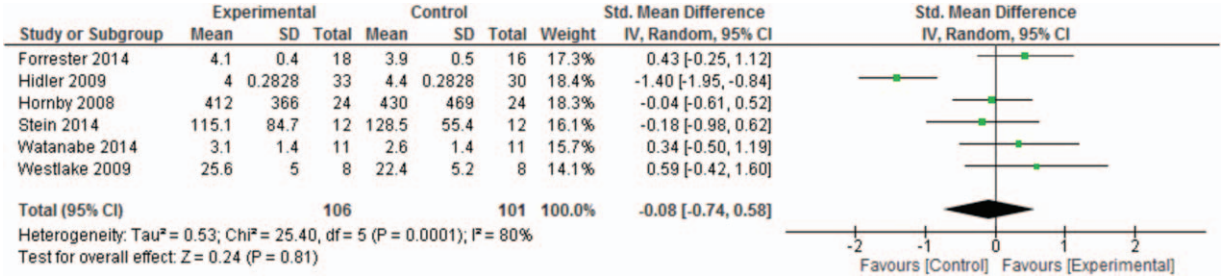

Figure 14: Effect of robotic therapy in experimental group compared with conventional therapy control group on lower limb walking (TR = 0) (SD: standard deviation; CI: confidence interval)

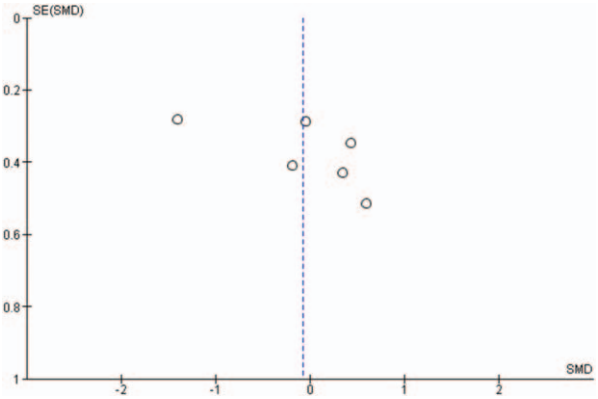

Figure 15: Funnel plot of lower limb studies (TR = 0) (SE: standard error; SMD: standard mean difference)

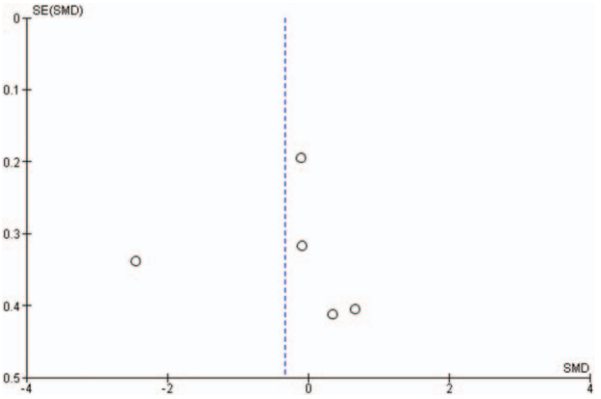

Figure 17: Funnel plot of lower limb studies with follow-up in less than or equal to 3 months (SE: standard error; SMD: standard mean difference)

Lower limb walking (sustainability)

Follow-up in less than or equal to three months

Five studies with a total patient population of 259 were analyzed. The forest plot showed no significant difference between experimental and control groups (Figure 16). The pooled SMD (random-effects model) was −0.33, 95% CI −1.31 to 0.65, $I^2 = 92\%$, P = 0.51. A potential for publication bias was found from the funnel plot (Figure 17).

Follow-up in more than three months

Six studies with a total patient population of 408 were analyzed. The forest plot showed no significant difference between experimental and control groups (Figure 18). The pooled SMD (random-effects model) was 0.30, 95% CI −0.05 to 0.65, $I^2 = 63\%$, P = 0.10. No evidence of publication bias was found from the funnel plot. (Figure 19).

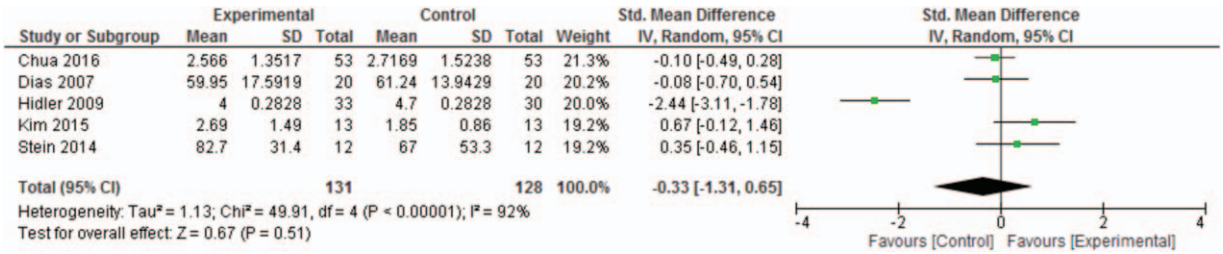

Figure 16: Effect of robotic therapy in experimental group compared with conventional therapy control group on lower limb walking (follow-up in less than or equal to 3 months) (SD: standard deviation; CI: confidence interval)

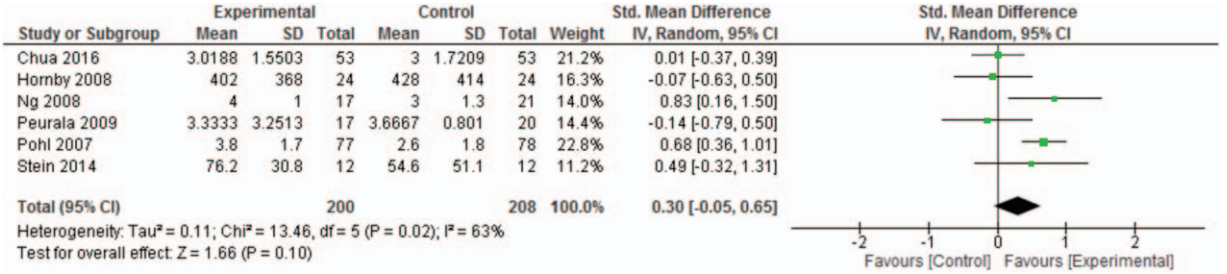

Figure 18: Effect of robotic therapy in experimental group compared with conventional therapy control group on lower limb walking (follow-up in more than 3 months) (SD: standard deviation; CI: confidence interval)

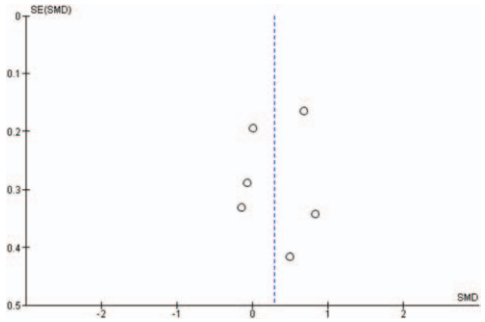

Figure 19: Funnel plot of lower limb studies with follow-up in more than 3 months (SE: standard error; SMD: standard mean difference)

Activities of daily living

Thirty-one studies with a total patient population of 1120 were analyzed. The forest plot showed no significant difference between experimental and control groups (Figure 20). The pooled SMD (random-effects model) was 0.11, 95% CI −0.11 to 0.33, $I^2 = 66\%$, $P = 0.32$. No evidence of publication bias was found from the funnel plot (Figure 21).

Sub-group analyses for acute/sub-acute patients, chronic patients, severe impairment patients and moderate/mild impairment patients were conducted and these showed no significant differences between experimental and control groups (Acute/Sub-Acute:

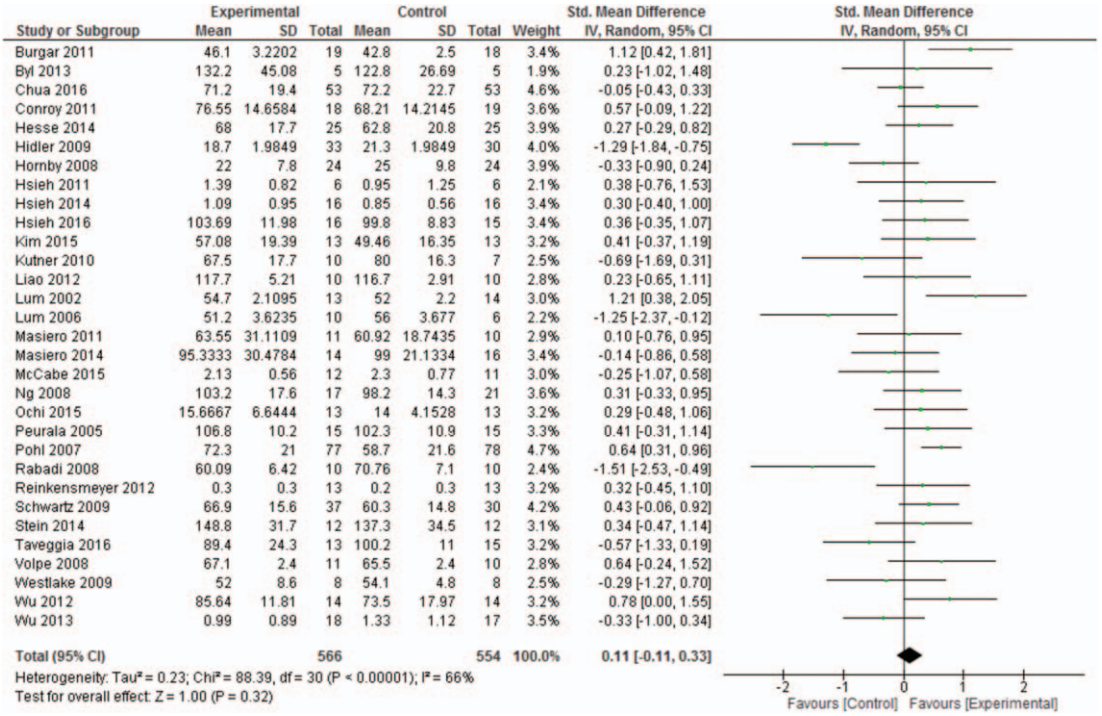

Figure 20: Effect of robotic therapy in experimental group compared with conventional therapy control group on activities of daily living (SD: standard deviation; CI: confidence interval)

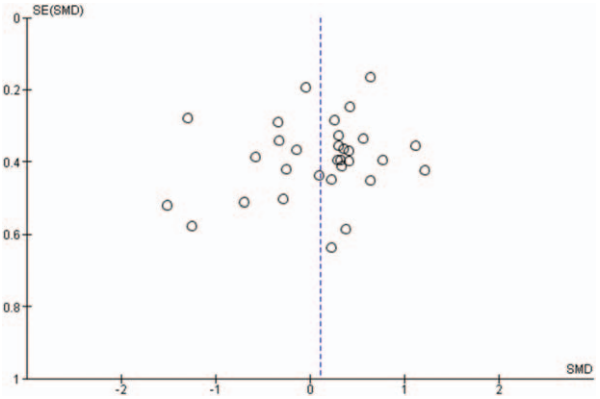

Figure 21: Funnel plot of activities of daily living studies (SE: standard error; SMD: standard mean difference)

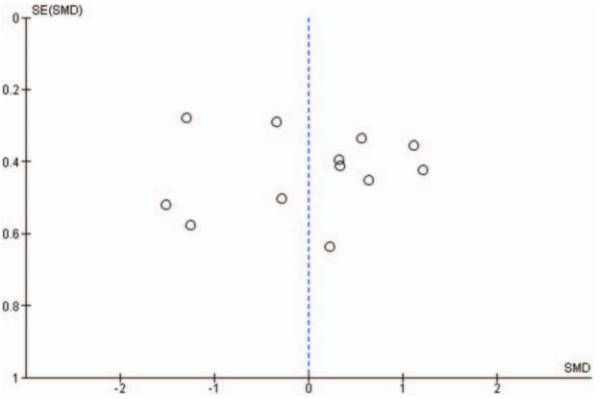

Figure 23: Funnel plot of activities of daily living studies (TR = 0) (SE: standard error; SMD: standard mean difference)

SMD −0.01, 95% CI −0.38 to 0.35, P = 0.95; Chronic: SMD 0.22, 95% CI −0.03 to 0.47, P = 0.08; Severe: SMD 0.20, 95% CI −0.10 to 0.49, P = 0.19; Moderate/Mild: SMD 0.06, 95% CI −0.24 to 0.36, P = 0.68).

Activities of daily living (TR = 0)

For the comparison of robotic therapy alone to conventional therapy alone (TR = 0), 12 studies with a total patient population of 345 were analyzed and the result showed no significant difference between experimental and control groups (Figure 22). The pooled SMD (random-effects model) was 0.00, 95% CI −0.54 to 0.53, $I^2 = 82\%$, P = 0.99. No evidence of publication bias was found from the funnel plot (Figure 23).

Sub-group analyses for acute/sub-acute patients, chronic patients, severe impairment patients and moderate/mild impairment patients were conducted and these showed no significant differences between experimental and control groups (Acute/Sub-Acute: SMD −0.71, 95% CI −1.95 to 0.54, P = 0.26; Chronic: SMD 0.33, 95% CI −0.05 to 0.70, P = 0.09; Severe: SMD −0.07, 95% CI −1.42 to 1.28, P = 0.92; Moderate/Mild: SMD 0.01, 95% CI −0.59 to 0.61, P = 0.98).

Activities of daily living (sustainability)

Follow-up in less than or equal to three months

Eleven studies with a total patient population of 428 were analyzed. The forest plot showed no significant difference between experimental and control groups (Figure 24). The pooled SMD (random-effects model) was −0.10, 95% CI −0.57 to 0.38, $I^2 = 81\%$, P = 0.68. A potential for publication bias was found from the funnel plot (Figure 25).

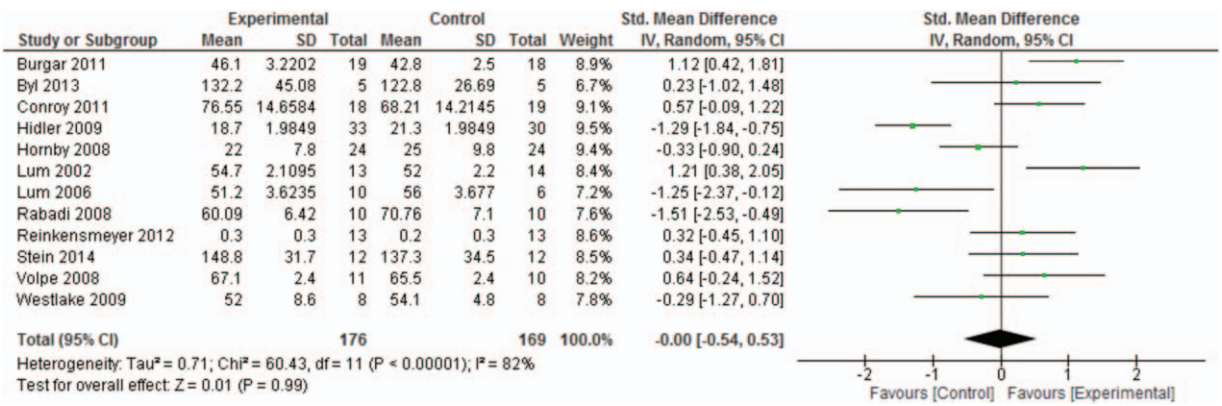

Figure 22: Effect of robotic therapy in experimental group compared with conventional therapy control group on activities of daily living (TR = 0) (SD: standard deviation; CI: confidence interval)

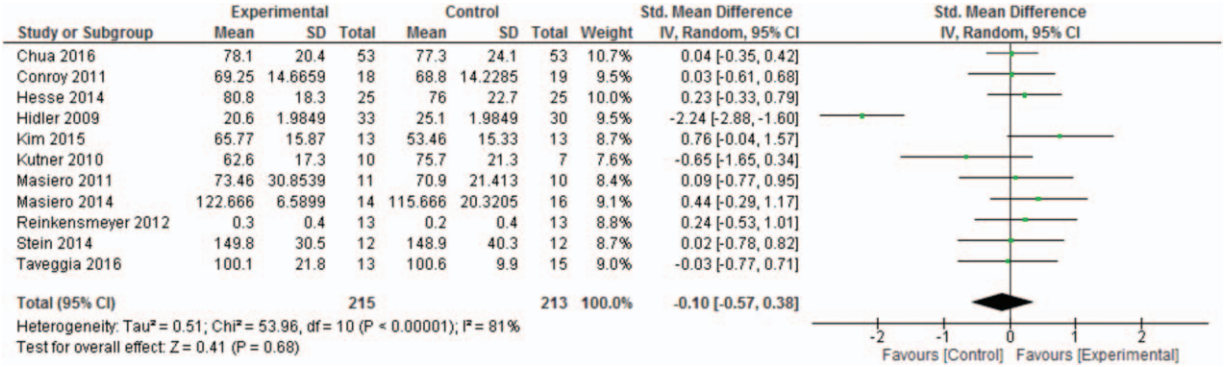

Figure 24: Effect of robotic therapy in experimental group compared with conventional therapy control group on activities of daily living (follow-up in less than or equal to 3 months) (SD: standard deviation; CI: confidence interval)

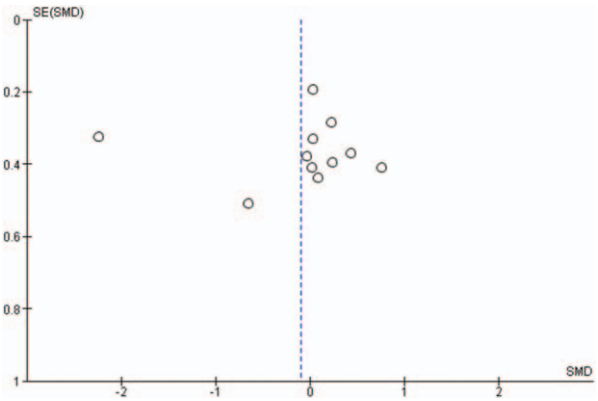

Figure 25: Funnel plot of activities of daily living studies with follow-up in less than or equal to 3 months (SE: standard error; SMD: standard mean difference)

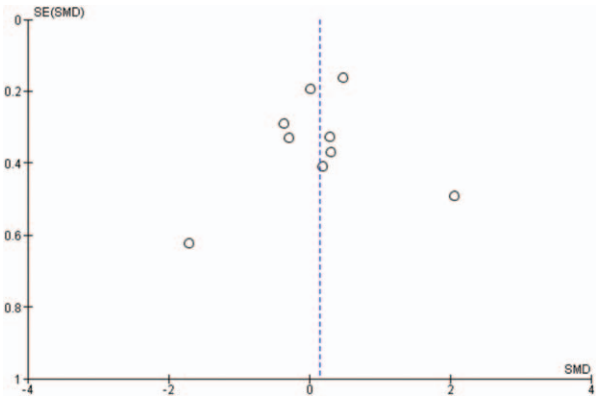

Figure 27: Funnel plot of activities of daily living studies with follow-up in more than 3 months (SE: standard error; SMD: standard mean difference)

Follow-up in more than three months

Nine studies with a total patient population of 481 were analyzed. The forest plot showed no significant difference between experimental and control groups (Figure 26). The pooled SMD (random-effects model) was 0.14, 95% CI −0.27 to 0.56, $I^2 = 76\%$, $P = 0.50$. No evidence of publication bias was found from the funnel plot. (Figure 27).

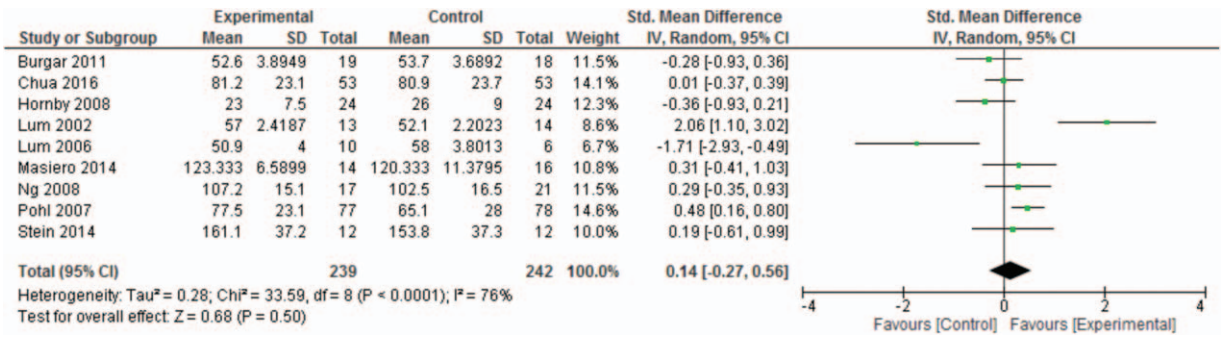

Figure 26: Effect of robotic therapy in experimental group compared with conventional therapy control group on activities of daily living (more than 3 months) (SD: standard deviation; CI: confidence interval)

Table 1: Results of narrative review of the three studies

	Husemann *et al.*[40]		Nunen *et al.*[41]		Tong *et al.*[39]	
	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group
Functional ambulation category (pre)	0 (1)	0 (0)	1.5 (1)	1 (1)	1 (0)	1 (1)
Functional ambulation category (post)	1 (3)	1 (3)	1.25 (0.58)†	1.29 (0.99)†	3 (1)*	2 (2)*
Functional ambulation category (follow-up)	NA	NA	2.60 (0.84)†	2.27 (1.42)†	NA	NA
Activities of daily living (pre)	35 (41.25)	35 (18)	34 (39)	38 (22)	56 (20)	66.5 (18)
Activities of daily living (post)	50 (25)	50 (10)	7 (21)†	12 (18)†	91 (17)	89.5 (26.5)
Activities of daily living (follow-up)	NA	NA	NA	NA	NA	NA

Values are median (Inter-Quartile Range); Unless otherwise indicated, comparison between groups was not statistically significant.
*significant differences between groups.
†values are gains from baseline.
NA, Not Applicable.

Narrative review

Three studies only reported median data that were not suitable for meta-analysis and the results of these studies are shown in Table 1.

Husemann *et al.*[40] found that there were no significant differences between experimental and control groups for outcome measures of Functional Ambulation Category and ADLs. The authors concluded that robotic training was comparable to conventional training. Nunen *et al.*[41] found no significant differences for between group comparisons and concluded that robotic therapy was as effective as conventional therapy. Tong *et al.*[39] found that for Functional Ambulation Category, the experimental group had significantly more improvement than the control group but for ADLs, no significant difference was found between the two groups. Tong *et al.* concluded that intervention patients had better mobility and improvement in functional ambulation than patients who underwent conventional gait training. In terms of sample sizes, the three studies had comparable samples of around 30 patients each and all involved acute/sub-acute patients with severe impairments. Although the three studies were dose-matched in terms of training durations for experimental and control groups, the significant improvement found by Tong *et al.* could be due to the number of repetitions received by patients: the robotic group had 10 times more repetitions compared to the conventional group.[39] No information on the quantity of training repetitions were provided in the other two studies.

Heterogeneity analysis

To identify causes of heterogeneity, sub-group analyses were conducted and the results are shown in Table 2. When sub-groups based on outcome scales were examined, there was a change in heterogeneity levels as compared to the main groups. For ADLs, the change was more pronounced: one outcome scale (Motor Activity Log - Quality of Movement) had an I^2 of 0%. We also divided the trial studies into two sub-groups: those whose intervention groups had no conventional therapy component (i.e. TR = 0) and those which had a combination of robotic and conventional therapies (i.e. TR>0). This analysis revealed that there was a clear difference in I^2 values. For upper limb, lower limb and ADLs studies, the same pattern of change was demonstrated: I^2 increased for sub-group TR = 0, while I^2 decreased for sub-group TR>0.

Table 2: Sub-groups analyzed for heterogeneity

Analysis by outcome scales			
Upper limb movement	**No. of studies**	**I^2 values**	**P-values (chi-squared test)**
Upper limb (all scales)	29	41%	0.01
Upper limb (only FM [UL])	25	36%	0.04
Lower limb walking			
Lower limb (all scales)	15	75%	<0.00001
Lower limb (only FAC measure)	10	82%	<0.00001
Activities of daily living (ADL)			
ADL (all scales)	31	66%	<0.00001
ADL (FIM [total])	4	71%	0.01
ADL (BI)	3	72%	0.03
ADL (MAL-QOM)	4	0%	0.48
Analysis by therapy ratio			
Upper limb movement	**No. of studies**	**I^2 values**	**P-values (chi-squared test)**
Upper limb (TR = 0)	16	48%	0.02
Upper limb (TR>0)	13	31%	0.13
Lower limb walking			
Lower Limb (TR = 0)	6	80%	0.0001
Lower Limb (TR>0)	9	56%	0.02
Activities of daily living (ADL)			
ADL (TR = 0)	12	82%	<0.00001
ADL (TR>0)	19	25%	0.15

BI, Barthel Index; FAC, Functional Ambulation Category; FIM (total), Functional Independence Measure (total); FM (UL), Fugl-Myer (upper limb); MAL-QOM, Motor Activity Log - Quality of Movement; TR, Therapy Ratio.

Sensitivity analysis for non-blinded assessment

Seven studies for meta-analysis of lower limb walking did not use blinded assessment. As there were 15 studies for this outcome, there could be a large effect for this analysis. A sensitivity analysis excluding studies with non-blinded assessment was done and the result indicated no significant difference between experimental and control groups (SMD 0.26, 95% CI −0.07 to 0.6, $I^2 = 63\%$, $P = 0.13$). For the severe impairment sub-group, a sensitivity analysis was also conducted and the result indicated that robotic therapy was more effective than conventional therapy (SMD 0.42, 95% CI 0.08 to 0.75, $I^2 = 57\%$, $P = 0.02$).

Discussion

The review found no significant differences between robotic therapy experimental and conventional therapy control groups for the outcomes of upper limb motor movement, lower limb walking and activities of daily living. This indicated that robotic training had equivalent treatment effect as conventional training. However, for severely impaired lower limb patients, a statistically significant difference favoring the experimental group was found.

Compared to the findings of other systematic reviews conducted, our findings were different. In the systematic review of lower limb by Mehrholz *et al.*,[52] the authors found that robotic-assisted gait

training increased the odds of participants becoming independent in walking. The difference in finding could be due to the method of data analysis. The authors pooled together data from robotic intervention arms that included other therapies, such as functional electrical stimulation applied to the legs during gait training. In our review, the intervention arm containing only robotic training (or combination of robotic and conventional training) was compared to the conventional training control arm. However, for the sub-group of severely impaired patients, both our findings indicated that robotic treatment was more effective.

For systematic reviews of upper limb by Mehrholz *et al.*[53] and Prange *et al.*,[54] Mehrholz *et al.* found that robot-assisted arm training improved arm motor movement and activities of daily living scores, while Prange *et al.* found that robot-assisted arm training improved arm motor movement. For the review by Prange *et al.*, only two studies (sample size of 70 patients) were included and this could have led to an under-powering of the review. Compared to the review by Mehrholz *et al.*, our finding could be different due, again, to the way data was pooled for analysis. The authors pooled together data from different intervention arms (containing robotic training and robotic training that is combined with other interventions such as electroencephalography-based brain computer interface or functional electrical stimulation) and compared it with the conventional training control arm.

Despite our findings being different to previous systematic reviews, we are judiciously confident of our findings, as a sufficient number of studies had been included and these studies had reasonably good quality of evidence.

Upper limb movement

Across the various sub-groups analyzed, we found that the robotic experimental group was just as effective as the conventional control group. It was possible that the proportion of conventional training of the experimental group could affect the outcome. For example, if an experimental group had majority conventional training, it could lead to outcomes similar to that of the control groups. To remove this potential confounding factor, an analysis was made for studies whereby there was only robotic training and no conventional training (i.e. TR = 0). Again, the results showed that there was no significant difference. A GRADE assessment was done for these two sub-groups and the included studies were rated as high quality.

The reason that there were no significant differences between experimental and control groups could be due to the number of training repetitions. It was possible that in conventional arm training, the amount of training repetitions that patients received was of the same intensity as robotic group. Given that upper limbs are physically lighter and easier to access, therapists could maneuver the limbs more and achieve the same intensity of training as robotic devices.

In terms of the treatment sustainability, we looked at follow-up measurements (<=3 months and >3 months) post intervention. From the forest plots, no significant difference between the experimental and control groups was found. This could indicate that the treatment effects of robotic training post intervention were the same as conventional training. However, in view of the low-quality GRADE evidence found for these two sub-groups, this result should be interpreted with caution.

Lower limb walking

No significant difference was found between the experimental and control groups. From the sub-groups analyzed, we found that the robotic experimental group was just as effective as the conventional control group, except for the sub-group of severe impairment patients. For this sub-group, we found a significant difference showing that the robotic training was more effective than conventional training. In five out of the 10 included studies for the severe sub-group, the experimental groups had post intervention FAC outcomes that scored 3 or higher, which indicated a reasonable degree of clinical improvement. An FAC score of 3 indicates walking without physical assistance but requiring verbal supervision, while an FAC score of less than 3 indicates dependency, whereby physical assistance must be given in walking.[34]

We also analyzed studies where there was only robotic training and no conventional training (i.e. TR = 0). Again, the results showed that there was no significant difference. A high-quality of GRADE evidence rating was found for sub-groups ''Lower Limb'' and ''Lower Limb - Severe'' but for ''Lower Limb - Therapy Ratio = 0'', the evidence was of low quality.

For patients with severe impairment, it could be that the amount of repetitions that patients performed during conventional training were of lower intensity than robotic group. As these patients had severe impairments, more effort was required from therapists to exercise the lower limbs, which are physically heavier and more difficult to access. As a result, therapists might not be able to maneuver the lower limbs as conveniently as upper limbs and so not achieve the same intensity of training as robotic devices. This could explain a preference for robotic training in patients with severe impairments, where higher repetitions could be achieved with minimal physical effort from therapists.

In terms of treatment sustainability, follow-up measurements (<=3 months and >3 months) post intervention were examined and from the forest plots, no significant differences between the experimental and control groups were found. A low-quality GRADE evidence was assessed for ''Lower limb - follow-up (<=3 months)'' but a high-quality GRADE score was assessed for ''Lower limb - follow-up (>3 months)''. This may indicate that the longer-term treatment effects of robotic training post intervention were the same as conventional training but, in view of the conflicting GRADE evidence found for these two sub-groups, the result should be interpreted with caution.

Activities of daily living

The review found that there was no significant difference between the experimental and control groups. From the various sub-groups analyzed, we found that the robotic experimental group was just as effective as the conventional control group. Similarly, an analysis was made for studies whereby there was only robotic training and no conventional training (i.e. TR = 0). Again, the results showed that there was no significant difference. A GRADE assessment was done for these two sub-groups and a high-quality of evidence was found for ''Activities of daily living (ADL)'' and moderate-quality for ''ADL - Therapy Ratio = 0''.

In terms of the treatment sustainability, we looked at follow-up measurements (<=3 months and >3 months) post intervention. From the forest plots, no significant differences between the experimental and control groups were found. The sub-group <= 3 months had a moderate-quality of GRADE evidence, while the sub-group >3 months had a high-quality of evidence.

In view of the reasonable quality of GRADE evidence found for all the four ADL sub-groups, the results could show that robotic training was as effective as conventional training.

Limitations

Differences in outcome scales

For the meta-analysis, we encountered various scales and included those scales which were more specific to measuring the motor movement of the patients. Scales that measured speeds of movements, walking distances or muscle strengths were excluded.

In upper limb studies, the Fugl-Myer (Upper Limb) was the most common scale but some of the studies measured sub-components of the scale, for example, the Fugl-Myer scale could be sub-divided into proximal and distal components. If the total Fugl-Myer (Upper Limb) score was not provided, these sub-components would then be added to obtain the total upper limb score. However, one study[55] had Fugl-Myer (Hand) data, as the study only involved training for the hand. Overall, for upper limb studies, scales used were: Fugl-Myer (Upper Limb), Fugl-Myer (Hand), Motricity Index (Upper Limb), Chedoke McMaster[56] and Wolf Motor Function Test.[57]

For lower limb studies, scales included were: Functional Ambulation Category, Fugl-Myer (Lower Limb), Motricity Index (Lower Limb), Functional Independence Measure (Walking), Emory Functional Ambulation Profile[58] and modified Emory Functional Ambulation Profile.[59]

For ADL studies, the scales involved were more varied and the most common scale encountered was Functional Independence Measure (FIM). For FIM, some authors reported data for sub-components of this scale, e.g. motor, self-care and transfer, and mobility. Where authors reported the total FIM, this data was used, otherwise the sub-components were included. One study[60] provided data only for components of the FIM relating to upper limb, as the study looked at upper limb therapy. Overall, scales used were: FIM, FIM (Upper Limb), FIM (Self Care and Transfer), FIM (Motor), FIM (Mobility), Stroke Impact Scale (SIS),[61] SIS – Activities of Daily Living/Instrumental Activities of Daily Living,[61] California Functional Evaluation 40 (CAFÉ 40),[62] Barthel Index, Frenchay Activities Index,[63] Motor Activity

Log – Quality of Movement,[64] Korea Modified Barthel Index,[65] Arm Motor Ability Test - Function[66] and Late Life Function and Disability Instrument – Function.[67]

In the meta-analyses, related scales were pooled together for sub-group analysis and the presence of different scales in the pooled sub-group could add bias to the findings. To minimize the risk of bias, standardized mean difference was applied. Details of the study outcomes included can be found under characteristics of included studies (Appendix III).

Heterogeneity of studies

Another potential limitation of our analysis is the heterogeneity of studies. For the three main sub-groups of upper limb, activities of daily living and lower limb, the level of heterogeneity (I^2) ranged from 41%, 66% to 75%, respectively, which was moderate to substantial levels of heterogeneity.[32] The heterogeneity could be due to the clinical and methodological diversities of the studies,[45] as the studies exhibited differences in outcome scales, intervention devices, intervention dosages, participant characteristics and study designs (2-arm, 3-arm and cross-over designs). For studies with follow-up data, heterogeneity could also be due to the outcomes being measured at various time points post intervention, ranging from one month to ten months after the intervention period.

When sub-group analysis based on outcome scales were examined, the change in I^2 heterogeneity level was more pronounced for ADLs. For ADLs, the wide range of measurement scales that had been used in the studies was a likely cause of heterogeneity. The included studies were further divided into two sub-groups: $TR = 0$ and $TR > 0$. This analysis revealed that there was a clear difference in I^2 values between the two sub-groups. It is probable that for studies with $TR > 0$, the presence of conventional training, as part of the robotic intervention, "masked" the effects of robotic training and gave these studies less clinical diversity. For those studies which had no conventional training as part of the robotic intervention, the different designs and types of robotic devices used could have caused a wider range of treatment effects, leading to higher I^2 values.

Despite using the random effects model, which pulls estimates towards smaller studies,[68] our results were in concordance with the outcomes of the largest trials included.[69] For upper limb, our results showed no significant difference between experimental and control groups, which was the same conclusion reached by Lo *et al.*[17] (sample size: 93 patients). For lower limb and ADLs, our results were also in agreement with Chua *et al.*[44] (sample size: 106 patients). Taken altogether, we believe that heterogeneity, although present, should not distract us from the treatment effect observed.

Non-blinded assessment

A potential source of bias is that some studies did not use blinded assessment. Eleven out of the 51 studies were of this nature and they had a sample size of 354 patients, which is around 20% of the total sample size. Two studies were for upper limbs and nine were for lower limbs. Out of the nine studies, one (Nunen *et al.*[41]) was for narrative review and one (Peurala *et al.*[70]) only had data for the ADL outcome. The remaining seven were for meta-analysis of lower limb walking. As there were 15 studies for this outcome, there could be a large effect for this analysis. Sensitivity analysis excluding studies with non-blinded assessment indicated no significant difference between experimental and control groups. For the severe impairment sub-group, the sensitivity analysis also indicated that robotic therapy was more effective than conventional therapy.

English language studies

For this review, only studies in English-language were included and the inclusion of non-English-language studies might have provided different outcome results. This language bias could have led us to overestimate the effect sizes, as it was possible that papers with positive results were more likely to be published in English-language journals, while papers with negative results might have been more likely to be published in non-English-language journals,[71] which catered more to local readers. However, in view that a number of papers from non-English speaking countries (e.g. Finland, Germany, Israel, Italy, Japan, Mexico, the Netherlands, Portugal, South Korea, Switzerland, Taiwan) had been included for review, the risk of language bias is not considered significant. There is also evidence to suggest that excluding non-English-language studies may not lead to bias. In a systematic review of risk of bias due to limiting studies to English-language, the authors found that that there were no major differences between treatment effects in English-language

restricted meta-analyses and non-English-language inclusive meta-analyses.[71]

Conclusion

We found that robotic training was just as effective as conventional training for upper limb motor movement, lower limb walking mobility and ADL. For patients with severe impairment of lower limbs, the analysis showed that robotic training produces better outcomes than conventional training. The sufficient quantity of studies included and the reasonable quality of GRADE evidence for the various intervention analysis lends confidence to our findings.

In terms of treatment sustainability, we also found that robotic training was just as effective as conventional training. However, the low-quality of GRADE evidence for upper and lower limb studies with follow-up data, and the relatively lower number of studies included require caution in interpreting this finding. For treatment sustainability of ADL, the better quality of GRADE evidence and the larger number of studies analyzed give us stronger reasons to believe that robotic training is just as effective as conventional training.

Recommendations for practice

For patients with severely impaired lower limbs, after their medical conditions stabilize, they may be treated using robotic gait training devices. With the higher repetitions that robotic devices can offer, patients can practice more and this will stimulate neural plasticity during the early stages of their recovery. When patients are more able to walk, they can then transition to conventional over-ground walking to further practice walking over different terrains, improve balance and correct any abnormal gait patterns. (Grade B: JBI Grades of Recommendation[31])

That robotic assisted training is just as effective as conventional physiotherapy may be utilized by physiotherapists to use robotic devices as a multiplier tool that enables them to provide training to more adult stroke patients. Instead of one-to-one conventional practice, therapists can simultaneously engage more patients using robotic devices. This can free up valuable therapist time either to give more severe patients personalized training or to practice more functional related tasks that require the integration of different motor skills. By channeling their time to these higher-value training activities and letting robotic devices do the routine ''heavy-lifting'' tasks, therapists can offer appropriate levels of personalized treatment for patients and increase their efficiency. (Grade B: JBI Grades of Recommendation[31])

Recommendations for research

The current review has observed that robotic and conventional training are equally effective and, as such, the considerations of introducing robotic devices into stroke rehabilitation units may need to turn to other factors such as economic cost, treatment efficiency and productivity. For example, by using robotic devices, what is the resulting cost of treating each patient and how many more patients can be treated? Also, how many devices should a stroke unit have and how can the workflow of robotic devices and therapists be optimized in order to maximize treatment efficiency? Research that addresses these questions will provide insights and assist in identifying optimal approaches into how robotic devices can be deployed into stroke rehabilitation units and be integrated into the work scope of therapists.

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References

1. Mackay J, Mensah G. The Atlas of Heart Disease and Stroke: Part 3 - The Burden: Global burden of stroke: World Health Organization; 2004 [cited 2016 18 April]. Available from: http://www.who.int/cardiovascular_diseases/resources/atlas/en/.
2. National Stroke Association, USA. Hemiparesis; [Internet]. [cited 2016 February 16]. Available from: http://www.stroke.org/we-can-help/survivors/stroke-recovery/post-stroke-conditions/physical/hemiparesis.
3. Intercollegiate Stroke Working Party. National Clinical Guideline for Stroke. 4th ed. London: Royal College of Physicians; 2012.
4. Gresham GE, Alexander D, Bishop DS, Giuliani C, Goldberg G, Holland A, *et al*. Rehabilitation. Stroke 1997;28(7):1522–6.
5. Van Peppen R, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? Clin Rehabil 2004;18(8):833–62.
6. French B, Thomas LH, Leathley MJ, Sutton CJ, McAdam J, Forster A, *et al*. Repetitive task training for improving functional ability after stroke. Cochrane Database Syst Rev (4)2007.

7. Whitall J. Stroke Rehabilitation Research: Time to Answer More Specific Questions? Neurorehabil Neural Repair 2004;18(1):3–11.
8. Takeuchi N, Izumi S. Rehabilitation with poststroke motor recovery: a review with a focus on neural plasticity. Stroke Res Treat 2013;2013:13.
9. Yakub F, Md Khudzari AZ, Mori Y. Recent trends for practical rehabilitation robotics, current challenges and the future. Int J Rehabil Res 2014;37(1):9–21.
10. Masiero S, Poli P, Rosati G, Zanotto D, Iosa M, Paolucci S, *et al*. The value of robotic systems in stroke rehabilitation. Expert Rev Med Devices 2014;11(2):187–98.
11. Hesse S, Schmidt H, Werner C, Bardeleben A. Upper and lower extremity robotic devices for rehabilitation and for studying motor control. Curr Opin Neurol 2003;16(6): 705–10.
12. Hidler J, Nichols D, Pelliccio M, Brady K, Campbell DD, Kahn JH, *et al*. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair 2009;23(1):5–13.
13. Werner C, Von Frankenberg S, Treig T, Konrad M, Hesse S. Treadmill training with partial body weight support and an electromechanical gait trainer for restoration of gait in subacute stroke patients: A randomized crossover study. Stroke 2002;33(12):2895–901.
14. Fazekas G. Robotics in rehabilitation: successes and expectations. Int J Rehabil Res 2013;36(2):95–6.
15. Chang WH, Kim MS, Huh JP, Lee PK, Kim YH. Effects of robot-assisted gait training on cardiopulmonary fitness in subacute stroke patients: a randomized controlled study. Neurorehabil Neural Repair 2012;26(4):318–24.
16. McCabe J, Monkiewicz M, Holcomb J, Pundik S, Daly JJ. Comparison of robotics, functional electrical stimulation, and motor learning methods for treatment of persistent upper extremity dysfunction after stroke: a randomized controlled trial. Arch Phys Med Rehabil 2015;96(6):981–90.
17. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, *et al*. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med 2010;362(19):1772–83.
18. Ang KK, Guan C, Phua KS, Wang C, Zhou L, Tang KY, *et al*. Brain-computer interface-based robotic end effector system for wrist and hand rehabilitation: results of a three-armed randomized controlled trial for chronic stroke. Front Neuroeng 2014;7(30):30.
19. Geroin C, Picelli A, Munari D, Waldner A, Tomelleri C, Smania N. Combined transcranial direct current stimulation and robot-assisted gait training in patients with chronic stroke: a preliminary comparison. Clin Rehabil 2011;25(6):537–48.
20. Hsieh YW, Lin KC, Horng YS, Wu CY, Wu TC, Ku FL. Sequential combination of robot-assisted therapy and constraint-induced therapy in stroke rehabilitation: a randomized controlled trial. J Neurol 2014;261(5):1037–45.
21. Tanaka N, Saitou H, Takao T, Iizuka N, Okuno J, Yano H, *et al*. Effects of gait rehabilitation with a footpad-type locomotion interface in patients with chronic post-stroke hemiparesis: a pilot study. Clin Rehabil 2012;26(8):686–95.
22. Brokaw EB, Nichols D, Holley RJ, Lum PS. Robotic therapy provides a stimulus for upper limb motor recovery after stroke that is complementary to and distinct from conventional therapy. Neurorehabil Neural Repair 2014;28(4): 367–76.
23. Geroin C, Mazzoleni S, Smania N, Gandolfi M, Bonaiuti D, Gasperini G, *et al*. Systematic review of outcome measures of walking training using electromechanical and robotic devices in patients with stroke. J Rehabil Med 2013;45(10): 987–96.
24. Feise RJ. Do multiple outcome measures require P-value adjustment? BMC Med Res Methodol 2002;2(1):8.
25. Lo K, Stephensen M, Lockwood C. Effectiveness of Robotic Assisted Rehabilitation for Mobility and Functional Ability in Adult Stroke Patients: a systematic review protocol. JBI Database System Rev Implement Rep 2017;15(1): 39–48.
26. Canadian Partnership for Stroke Recovery. Fugl-Meyer Assessment of Sensorimotor Recovery After Stroke (FMA); [Internet]. [cited 2016 April 18]. Available from: http://www.strokengine.ca/indepth/fma_indepth/.
27. Collin C, Wade D. Assessing motor impairment after stroke: a pilot reliability study. J Neurol Neurosurg Psychiatry 1990;53(7):576–9.
28. Canadian Partnership for Stroke Recovery. Functional Ambulation Categories (FAC); [Internet]. [cited 2016 April 18]. Available from: http://www.strokengine.ca/indepth/fac_indepth/.
29. Canadian Partnership for Stroke Recovery. Barthel Index (BI); [Internet]. [cited 2016 April 18]. Available from: http://www.strokengine.ca/indepth/bi_indepth/.
30. Canadian Partnership for Stroke Recovery. Functional Independence Measure (FIM); [Internet]. [cited 2016 April 18]. Available from: http://www.strokengine.ca/indepth/fim_indepth/.
31. The Joanna Briggs Institute. The University of Adelaide. Joanna Briggs Institute Reviewers' Manual: 2014 edition. Joanna Briggs Institute; 2014.
32. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE Handbook 2013 [cited 2017 31 March]. Available from: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html#h.svwngs6pm0f2.
33. Velozo CA, Woodbury ML. Translating measurement findings into rehabilitation practice: An example using Fugl-Meyer Assessment-Upper Extremity with patients following stroke. J Rehabil Res Dev 2011;48(10):1211.
34. Schwartz I, Sajin A, Fisher I, Neeb M, Shochina M, Katz-Leurer M, *et al*. The effectiveness of locomotor therapy using robotic-assisted gait training in subacute stroke patients: A randomized controlled trial. PM & R: the journal of injury, function, and rehabilitation 2009;1(6):516–23.

35. Peurala SH, Airaksinen O, Huuskonen P, Jakala P, Juhakoski M, Sandell K, *et al*. Effects of intensive therapy using gait trainer or floor walking exercises early after stroke. J Rehabil Med 2009;41(3):166–73.
36. Ochi M, Wada F, Saeki S, Hachisuka K. Gait training in subacute non-ambulatory stroke patients using a full weight-bearing gait-assistance robot: A prospective, randomized, open, blinded-endpoint trial. J Neurol Sci 2015;353(1–2):130–6.
37. Masiero S, Armani M, Ferlini G, Rosati G, Rossi A. Randomized Trial of a Robotic Assistive Device for the Upper Extremity During Early Inpatient Stroke Rehabilitation. Neurorehabil Neural Repair 2014;28(4):377–86.
38. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14(135):135.
39. Tong RK, Ng MF, Li LS. Effectiveness of gait training using an electromechanical gait trainer, with and without functional electric stimulation, in subacute stroke: A randomized controlled trial. Arch Phys Med Rehabil 2006;87(10): 1298–304.
40. Husemann B, Muller F, Krewer C, Heller S, Koenig E. Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke 2007;38(2):349–54.
41. Nunen MP, Gerrits KH, Konijnenbelt M, Janssen TW, Haan A. Recovery of walking ability using a robotic device in subacute stroke patients: a randomized controlled study. Disability and rehabilitation Assistive technology 2015;10(2): 141–8.
42. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
43. Pohl M, Werner C, Holzgraefe M, Kroczek G, Mehrholz J, Wingendorf I, *et al*. Repetitive locomotor training and physiotherapy improve walking and basic activities of daily living after stroke: a single-blind, randomized multicentre trial (DEutsche GAngtrainerStudie, DEGAS). Clin Rehabil 2007;21(1):17–27.
44. Chua J, Culpan J, Menon E. Efficacy of an Electromechanical Gait Trainer Poststroke in Singapore: A Randomized Controlled Trial. Arch Phys Med Rehabil 2016;97(5):683–90.
45. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011.
46. Jüni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. BMJ 2001;323(7303):42–6.
47. Klamroth-Marganska V, Blanco J, Campen K, Curt A, Dietz V, Ettlin T, *et al*. Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. Lancet Neurol 2014;13(2):159–66.
48. Krishna R, Maithreyi R, Suprapaneni KM. Research bias: a review for medical students. J Clin Diagn Res 2010;4(2): 2320–4.
49. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343: d5928.
50. Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. Lancet 2002;359(9307):696–700.
51. Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA 1999;282(11):1054–60.
52. Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke (Review). Cochrane Database Syst Rev (7):2013:CD006185.
53. Mehrholz J, Pohl M, Platz T, Kugler J, Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. Cochrane Database Syst Rev (11):2015:CD006876.
54. Prange GB, Jannink MJA, Groothuis-Oudshoorn CGM, Hermens HJ, Ijzerman MJ. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. J Rehabil Res Dev 2006;43(2):171–84.
55. Orihuela-Espina F, Roldan GF, Sanchez-Villavicencio I, Palafox L, Leder R, Sucar LE, *et al*. Robot training for hand motor recovery in subacute stroke patients: A randomized controlled trial. J Hand Ther 2016;29(1):51–7.
56. Canadian Partnership for Stroke Recovery. Chedoke-McMaster Stroke Assessment [Internet]. [cited 2016 October 16]. Available from: http://www.strokengine.ca/assess/cmmsa/.
57. Canadian Partnership for Stroke Recovery. Wolf Motor Function Test [Internet]. [cited 2016 October 16]. Available from: http://www.strokengine.ca/assess/wmft/.
58. Rehabilitation Measures Database. Rehab Measures: Emory Ambulation Profile; Modified Functional Ambulation Profile [Internet]. [cited 2016 October 23]. Available from: http://www.rehabmeasures.org/Lists/RehabMeasures/DispForm.aspx?ID=1100.
59. Baer HR, Wolf SL. Modified Emory Functional Ambulation Profile. Stroke 2001;2001(32):973–9.
60. Burgar CG, Lum PS, Scremin AM, Garber SL, Van der Loos HF, Kenney D, *et al*. Robot-assisted upper-limb therapy in acute rehabilitation setting following stroke: Department of Veterans Affairs multisite clinical trial. J Rehabil Res Dev 2011;48(4):445–58.
61. Canadian Partnership for Stroke Recovery. Stroke Impact Scale (SIS) [Internet]. [cited 2016 October 16]. Available from: http://www.strokengine.ca/assess/sis/.
62. Fung S, Byl N, Melnick M, Callahan P, Selinger A, Ishii K, *et al*. Functional outcomes: The development of a new instrument to monitor the effectiveness of physical therapy. Eur J Phys Rehab Med 1997;7(2):31–41.
63. Canadian Partnership for Stroke Recovery. Frenchay Activities Index [Internet]. [cited 2016 October 23]. Available from: http://www.strokengine.ca/assess/fai/.

64. Rehabilitation Measures Database. Rehab Measures: Motor Activity Log [Internet]. [cited 2016 August 2]. Available from: http://www.rehabmeasures.org/Lists/RehabMeasures/DispForm.aspx?ID=1215.
65. Jung HY, Park BK, Shin HS, Kang YK, Pyun SB, Paik NJ, *et al*. Development of the Korean Version of Modified Barthel Index (K-MBI): Multi-center Study for Subjects with Stroke. J Korean Acad Rehabil Med 2007;31(3): 283–97.
66. Rehabilitation Measures Database. Rehab Measures: Arm Motor Ability Test [Internet]. [cited 2016 August 15]. Available from: http://www.rehabmeasures.org/Lists/RehabMeasures/DispForm.aspx?ID=1188.
67. School of Public Health, Boston University. Late-Life Function & Disability Instrument™ [Internet]. 2002 [cited 2016 July 9]. Available from: http://www.bu.edu/sph/about/school-wide-centers/health-and-disability-research-institute/outcome-measures/llfdi/.
68. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, *et al*. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.
69. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629–34.
70. Peurala SH, Tarkka IM, Pitkanen K, Sivenius J. The effectiveness of body weight-supported gait training and floor walking in patients with chronic stroke. Arch Phys Med Rehabil 2005;86(8):1557–64.
71. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, *et al*. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care 2012;28(2):138–44.
72. Byl NN, Abrams GM, Pitsch E, Fedulow I, Kim H, Simkins M, *et al*. Chronic stroke survivors achieve comparable outcomes following virtual task specific repetitive training guided by a wearable robotic orthosis (UL-EXO7) and actual task specific repetitive training guided by a physical therapist. J Hand Ther 2013;26(4): 343–52.
73. Conroy SS, Whitall J, Dipietro L, Jones-Lush LM, Zhan M, Finley MA, *et al*. Effect of gravity on robot-assisted motor training after chronic stroke: a randomized trial. Arch Phys Med Rehabil 2011;92(11): 1754–61.
74. Dias D, Lains J, Pereira A, Nunes R, Caldas J, Amaral C, *et al*. Can we improve gait skills in chronic hemiplegics? A randomised control trial with gait trainer. Eura Medicophys 2007;43(4):499–504.
75. Forrester LW, Roy A, Krywonis A, Kehs G, Krebs HI, Macko RF. Modular ankle robotics training in early subacute stroke: a randomized controlled pilot study. Neurorehabil Neural Repair 2014;28(7):678–87.
76. Hesse S, Hess A, Werner CC, Kabbert N, Buschfort R. Effect on arm function and cost of robot-assisted group therapy in subacute patients with stroke and a moderately to severely affected arm: a randomized controlled trial. Clin Rehabil 2014;28:637–47.
77. Hornby TG, Campbell DD, Kahn JH, Demott T, Moore JL, Roth HR. Enhanced gait-related improvements after therapist- versus robotic-assisted locomotor training in subjects with chronic stroke: a randomized controlled study. Stroke 2008;39(6):1786–92.
78. Hsieh YW, Wu CY, Wang WE, Lin KC, Chang KC, Chen CC, *et al*. Bilateral robotic priming before task-oriented approach in subacute stroke rehabilitation: A pilot randomized controlled trial. Clin Rehabil 2017;31(2):225–33.
79. Hsieh YW, Wu CY, Lin KC, Yao G, Wu KY, Chang YJ. Dose-response relationship of robot-assisted stroke motor rehabilitation: The impact of initial motor status. Stroke 2012;43(10):2729–34.
80. Hsieh YW, Wu CY, Liao WW, Lin KC, Wu KY, Lee CY. Effects of treatment intensity in upper limb robot-assisted therapy for chronic stroke: A pilot randomized controlled trial. Neurorehabil Neural Repair 2011;25(6):503–11.
81. Hsieh YW, Lin KC, Horng YS, Wu CY, Wu TC, Ku FL. Sequential combination of robot-assisted therapy and constraint-induced therapy in stroke rehabilitation: A randomized controlled trial. J Neurol 2014;261(5):1037–45.
82. Kahn LE, Zygman ML, Rymer WZ, Reinkensmeyer DJ. Robot-assisted reaching exercise promotes arm movement recovery in chronic hemiparetic stroke: a randomized controlled pilot study. J Neuroeng Rehabil 2006;3:12.
83. Kim SY, Yang L, Park IJ, Kim EJ, JoshuaPark MS, You SH, *et al*. Effects of Innovative WALKBOT Robotic-Assisted Locomotor Training on Balance and Gait Recovery in Hemiparetic Stroke: A Prospective, Randomized, Experimenter Blinded Case Control Study With a Four-Week Follow-Up. IEEE Trans Neural Syst Rehabil Eng 2015;23(4):636–42.
84. Kutner NG, Zhang R, Butler AJ, Wolf SL, Alberts JL. Quality-of-life change associated with robotic-assisted therapy to improve hand motor function in patients with subacute stroke: a randomized clinical trial. Phys Ther 2010;90(4): 493–504.
85. Liao WW, Wu CY, Hsieh YW, Lin KC, Chang WY. Effects of robot-assisted upper limb rehabilitation on daily function and real-world arm activity in patients with chronic stroke: a randomized controlled trial. Clin Rehabil 2012;26(2):111–20.
86. Lum PS, Burgar CG, Van der Loos M, Shor PC, Majmundar M, Yap R. MIME robotic device for upper-limb neurorehabilitation in subacute stroke subjects: A follow-up study. J Rehabil Res Dev 2006;43(5):631–42.
87. Lum PS, Burgar CG, Shor PC, Majmundar M, Van der Loos M. Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. Arch Phys Med Rehabil 2002;83(7):952–9.

88. Masiero S, Armani M, Rosati G. Upper-limb robot-assisted therapy in rehabilitation of acute stroke patients: focused review and results of new randomized controlled trial. J Rehabil Res Dev 2011;48(4):355–66.
89. Ng MF, Tong RK, Li LS. A pilot study of randomized clinical controlled trial of gait training in subacute stroke patients with partial body-weight support electromechanical gait trainer and functional electrical stimulation: six-month follow-up. Stroke 2008;39(1):154–60.
90. Rabadi M, Galgano M, Lynch D, Akerman M, Lesser M, Volpe B. A pilot study of activity-based therapy in the arm motor recovery post stroke: a randomized controlled trial. Clin Rehabil 2008;22(12):1071–82.
91. Reinkensmeyer DJ, Wolbrecht ET, Chan V, Chou C, Cramer SC, Bobrow JE. Comparison of three-dimensional, assist-as-needed robotic arm/hand movement training provided with Pneu-WREX to conventional tabletop therapy after chronic stroke. Am J Phys Med Rehabil 2012;91(11 Suppl 3): S232–41.
92. Sale P, Franceschini M, Mazzoleni S, Palma E, Agosti M, Posteraro F. Effects of upper limb robot-assisted therapy on motor recovery in subacute stroke patients. J Neuroeng Rehabil 2014;11(1):104.
93. Sale P, Mazzoleni S, Lombardi V, Galafate D, Massimiani MP, Posteraro F, *et al*. Recovery of hand function with robot-assisted therapy in acute stroke patients: a randomized-controlled trial. Int J Rehabil Res 2013;37(3):236–42.
94. Stein J, Bishop L, Stein DJ, Wong CK. Gait training with a robotic leg brace after stroke: a randomized controlled pilot study. Am J Phys Med Rehabil 2014;93(11):987–94.
95. Susanto EA, Tong RK, Ockenfeld C, Ho NS. Efficacy of robot-assisted fingers training in chronic stroke survivors: a pilot randomized-controlled trial. J Neuroeng Rehabil 2015;12(1):42.
96. Taveggia G, Borboni A, Mule C, Villafane JH, Negrini S. Conflicting results of robot-assisted versus usual gait training during postacute rehabilitation of stroke patients: a randomized clinical trial. Int J Rehabil Res 2016;39(1): 29–35.
97. Vanoglio F, Bernocchi P, Mule C, Garofali F, Mora C, Taveggia G, *et al*. Feasibility and efficacy of a robotic device for hand rehabilitation in hemiplegic stroke patients: A randomized pilot controlled study. Clin Rehabil 2016;31(3):351–60.
98. Volpe BT, Lynch D, Rykman-Berland A, Ferraro M, Galgano M, Hogan N, *et al*. Intensive sensorimotor arm training mediated by therapist or robot improves hemiparesis in patients with chronic stroke. Neurorehabil Neural Repair 2008;22(3):305–10.
99. Watanabe H, Tanaka N, Inuta T, Saitou H, Yanagi H. Locomotion improvement using a hybrid assistive limb in recovery phase stroke patients: A randomized controlled pilot study. Arch Phys Med Rehabil 2014;95(11):2006–12.
100. Westlake KP, Patten C. Pilot study of Lokomat versus manual-assisted treadmill training for locomotor recovery post-stroke. J Neuroeng Rehabil 2009;6(1):18.
101. Wu CY, Yang CL, Chuang LL, Lin KC, Chen HC, Chen MD, *et al*. Effect of therapist-based versus robot-assisted bilateral arm training on motor control, functional performance, and quality of life after chronic stroke: a clinical trial. Phys Ther 2012;92(8):1006–16.
102. Wu CY, Yang CL, Chen MD, Lin KC, Wu LL. Unilateral versus bilateral robot-assisted rehabilitation on arm-trunk control and functions post stroke: a randomized controlled trial. J Neuroeng Rehabil 2013;10(1):35.

Appendix I: Search strategy

Database	Search terms	Returns
PubMed	Robotics[mh] OR Robot*[tw] OR Exoskeleton Device[mh] OR Exoskeleton*[tw] OR Gait Trainer[tw] OR Lokomat[tw] AND Rehabilitation[mh] OR Rehabilitation[tw] OR Habilitation[tw] AND Stroke[mh] OR Stroke*[tw] OR "Cerebrovascular Accident" OR Cerebral[tw] OR "Cerebral Stroke" OR "Cerebrovascular Stroke" OR "Acute Stroke" OR "Sub-acute Stroke" OR "Subacute Stroke"	1067
Embase	Robotics/exp OR Robotics/syn OR Robot*:ti,ab OR 'robotic exoskeleton'/exp OR 'robotic exoskeleton'/syn OR 'exoskeleton (rehabilitation)'/exp OR 'exoskeleton (rehabilitation)'/syn OR Exoskeleton*:ti,ab OR "Gait Trainer":ti,ab OR Lokomat:ti,ab AND Rehabilitation/exp OR Rehabilitation/syn OR Rehabilitation:ti,ab OR Habilitation:ti,ab AND Stroke/exp OR Stroke/syn OR Stroke*:ti,ab OR "Cerebrovascular Accident"/exp OR "Cerebrovascular Accident"/syn OR "Cerebrovascular Accident":ti,ab OR Cerebral:ti,ab OR "Cerebral Stroke":ti,ab OR "Cerebrovascular Stroke":ti,ab OR "Acute Stroke":ti,ab OR "Sub-acute Stroke":ti,ab OR "Subacute Stroke":ti,ab	1117
CINAHL	MH Robotics+ OR TI Robot* OR AB Robot* OR MH Assistive Technology Devices+ OR TI "Assistive Technology Devices" OR AB "Assistive Technology Devices" OR TI Exoskeleton* OR AB Exoskeleton* OR TI "Gait Trainer" OR AB "Gait Trainer" OR TI Lokomat OR AB Lokomat AND MH Rehabilitation+ OR TI Rehabilitation OR AB Rehabilitation OR TI Habilitation OR AB Habilitation AND MH Stroke+ OR TI Stroke* OR AB Stroke* OR TI "Cerebrovascular Accident" OR AB "Cerebrovascular Accident" OR TI Cerebral OR AB Cerebral OR TI "Cerebral Stroke" OR AB "Cerebral Stroke" OR TI "Cerebrovascular Stroke" OR AB "Cerebrovascular Stroke" OR TI "Acute Stroke" OR AB "Acute Stroke" OR TI "Sub-acute Stroke" OR AB "Sub-acute Stroke" OR TI "Subacute Stroke" OR AB "Subacute Stroke"	614
Cochrane	robot* and rehabilitation and stroke	189
PEDro	robot* rehabilitation stroke	61
MedNar	robot* and rehabilitation and stroke	438
ProQuest Dissertations and Theses	robot* and rehabilitation and stroke	22
ClinicalTrials.gov	robot* and rehabilitation and stroke	12
Google Scholar	robot rehabilitation stroke	209

Appendix II: Excluded studies

Study	Reason for exclusion
Abdollahi F, *et al.* Arm control recovery enhanced by error augmentation. IEEE Int Conf Rehabil Robot, 2011. 2011: 5975504.	No robotic intervention.
Amirabdollahian F, *et al.* Multivariate analysis of the Fugl-Meyer outcome measures assessing the effectiveness of GENTLE/S robot-mediated stroke therapy. J Neuroeng Rehabil, 2007. 4: 4.	Not the outcome of interest.
Bang DH, Shin WS. Effects of robot-assisted gait training on spatiotemporal gait parameters and balance in patients with chronic stroke: A randomized controlled pilot trial. NeuroRehabilitation, 2016.	Not the outcome of interest.
Bragoni M, *et al.* Influence of psychologic features on rehabilitation outcomes in patients with subacute stroke trained with robotic-aided walking therapy. Am J Phys Med Rehabil, 2013. 92(10 Suppl 2): e16–25.	Not the outcome of interest.
Brauer SG, *et al.* The efficacy of SMART Arm training early after stroke for stroke survivors with severe upper limb disability: a protocol for a randomised controlled trial. BMC Neurol, 2013. 13: 71.	No robotic intervention.
Brincks J. The order of gait training, including Lokomat® and physiotherapy, do not influence gait symmetry in subacute ambulatory persons with stroke. Physiotherapy (United Kingdom), 2011. 97: eS154.	Not the outcome of interest.
Buesing C, *et al.* Effects of a wearable exoskeleton stride management assist system (SMA®) on spatiotemporal gait characteristics in individuals after stroke: a randomized controlled trial. J Neuroeng Rehabil, 2015. 12: 69.	Not the outcome of interest.
Calabro RS, *et al.* Robotic neurorehabilitation in patients with chronic stroke: psychological well-being beyond motor improvement. Int J Rehabil Res, 2015. 38(3): 219–25.	Not a randomized controlled trial.
Chanubol R, *et al.* Gait rehabilitation in subacute hemiparetic stroke: Robot-assisted gait training versus conventional physical therapy. Journal of the Neurological Sciences, 2013. 333: e574.	Article is an abstract.
Chen C, Stein J, Bishop L. Robot-assisted hand training compared with conventional hand therapy in chronic ischemic stroke patients: A pilot study. Archives of Physical Medicine and Rehabilitation, 2012. 93(10): E37.	Article is an abstract.
Chen K, *et al.* Effects of wearable robotic training of ankle and mobility rehabilitation in acute stroke. Stroke, 2015. 46.	Article is an abstract.
Chen WS. Effect on shoulder training using rehabilitation robot for stroke patients. 2010.	This is a listing under ClinicalTrials.govand the recruitment status of this study is unknown.
Chisari C, *et al.* Training and assessment of upper limb motor function with a robotic exoskeleton in chronic stroke patients. Gait and Posture, 2014. 40: S27-S28.	Article is an abstract.
Cho DY, *et al.* Effects of robot-assisted gait training on the balance and gait of chronic stroke patients: focus on dependent ambulators. Journal of Physical Therapy Science, 2015. 27(10): 3053–57.	This is a duplicate of Cho, D.Y. *et al.*, 2015 (see study below).

(*Continued*)

Study	Reason for exclusion
Cho DY, *et al.* Effects of robot-assisted gait training on the balance and gait of chronic stroke patients: focus on dependent ambulators. Journal of physical therapy science, 2015. 27(10): 3053–7.	Not dose matched.
Cioara F, *et al.* Effectiveness of locomotor therapy using robotic-assisted gait training in patients with stroke. Osteoporosis International, 2015. 26(1): S347.	Not a randomized controlled trial.
Conroy S, *et al.* Comparison of robotic upper-extremity reaching to traditional arm exercise in patients with chronic hemiparesis. Archives of Physical Medicine and Rehabilitation, 2010. 91(10): e45.	This is an abstract of the study, Conroy SS, *et al.* Effect of gravity on robot-assisted motor training after chronic stroke: a randomized trial, 2011; which has been included for analysis.
Coote S, *et al.* The effect of the GENTLE/s robot-mediated therapy system on arm function after stroke. Clin Rehabil, 2008. 22(5): 395–405.	Not the outcome of interest.
de Araujo RC, *et al.* Effects of intensive arm training with an electromechanical orthosis in chronic stroke patients: a preliminary study. Arch Phys Med Rehabil, 2011. 92(11): 1746–53.	No robotic intervention.
Dragin AS, *et al.* Gait training of poststroke patients assisted by the Walkaround (body postural support). Int J Rehabil Res, 2014. 37(1): 22–8.	No robotic intervention.
Duff A, *et al.* Rehabilitation Gaming System (RGS): The impact of virtual reality based training on upper limb recovery in the acute and chronic phase of stroke. Cerebrovascular Diseases, 2011. 31: 190.	No robotic intervention.
Fasoli SE, *et al.* Effects of robotic therapy on motor impairment and recovery in chronic stroke. Arch Phys Med Rehabil, 2003. 84(4): 477–82.	No conventional control group.
Fazekas G, *et al.* Robot-mediated upper limb physiotherapy for patients with spastic hemiparesis: a preliminary study. J Rehabil Med, 2007. 39(7): 580–82.	Trial included non-stroke patients.
Fisher S, Lucas L, Thrasher TA. Robot-Assisted Gait Training for Patients with Hemiparesis Due to Stroke. Top Stroke Rehabil, 2011. 18(3): 269–76.	Not the outcome of interest.
Fluet GG, *et al.* Does training with traditionally presented and virtually simulated tasks elicit differing changes in object interaction kinematics in persons with upper extremity hemiparesis? Top Stroke Rehabil, 2015. 22(3): 176–84.	Not a randomized controlled trial.
Forrester L, *et al.* Feasibility for using ankle robotics in the acute phase of stroke: A controlled pilot study. Archives of Physical Medicine and Rehabilitation, 2012. 93(10): E40.	Article is an abstract.

(*Continued*)

Study	Reason for exclusion
Franceschini M, *et al*. Walking after stroke: what does treadmill training with body weight support add to overground gait training in patients early after stroke?: a single-blind, randomized, controlled trial. Stroke, 2009. 40(9): 3079–85.	No robotic intervention.
Freivogel S, Schmalohr D, Mehrholz J. Improved walking ability and reduced therapeutic stress with an electromechanical gait device. J Rehabil Med, 2009. 41(9): 734–39.	Trial included non-stroke patients.
Gassert R. Neurocognitive Robot-assisted Rehabilitation of Hand Function After Stroke. 2014.	This is a listing under ClinicalTrials.govand the trial is still on-going.
Gilliaux M, Stoquart G, Detrembleur C. Efficacy Study of an Interactive Robot for the Rehabilitation of the Upper Limb in Acute Stroke Patients. 2014.	This is a listing under ClinicalTrials.gov and the trial is still on-going.
Helbok R. Robot-assisted hand training (AMADEO) compared with conventional physiotherapy techniques in chronic ischemic stroke patients: A pilot study. Neurologie und Rehabilitation, 2010. 16(6): 281.	Article is an abstract.
Hesse S, *et al*. Robot-assisted practice of gait and stair climbing in nonambulatory stroke patients. J Rehabil Res Dev, 2012. 49(4): 613–22.	Not a randomized controlled trial.
Hesse S, Schmidt H, Werner C. Machines to support motor rehabilitation after stroke: 10 years of experience in Berlin. J Rehabil Res Dev, 2006. 43(5): 671–78.	Article was a general technology overview.
Housman SJ, Scott KM, Reinkensmeyer DJ. A randomized controlled trial of gravity-supported, computer-enhanced arm exercise for individuals with severe hemiparesis. Neurorehabil Neural Repair, 2009. 23(5): 505–14.	Robotic device with no assistive feature.
Ingemanson ML, *et al*. Robotic retraining of finger movements after stroke. Stroke, 2016. 47.	Article is an abstract.
Kahn JH, *et al*. Alterations in locomotor performance in individuals with hemiplegia post-stroke following robotic- or therapist-assisted locomotor training. Journal of Neurologic Physical Therapy, 2006. 30(4): 212.	Article is an abstract.
Kelley CP, *et al*. Over-ground and robotic-assisted locomotor training in adults with chronic stroke: a blinded randomized clinical trial. Disabil Rehabil Assist Technol, 2013. 8(2): 161.	Not the outcome of interest.
Kim H, *et al*. Kinematic data analysis for post-stroke patients following bilateral versus unilateral rehabilitation with an upper limb wearable robotic system. IEEE Trans Neural Syst Rehabil Eng, 2013. 21(2): 153–64.	Article is duplicate of Byl *et al*. 2013, whereby this paper compared only the kinematic data of bilateral vs unilateral robotic training.
Kim JH, *et al*. Effects of robot-assisted therapy on lower limb in geriatric patients with subacute stroke. European Geriatric Medicine, 2014. 5: S174.	Article is an abstract.

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Study	Reason for exclusion
Kim M-Y, *et al.* Effects of virtual reality-based rehabilitation on distal upper extremity function and health-related quality of life: a single-blinded, randomized controlled trial. Journal of NeuroEngineering and Rehabilitation, 2016. 13.	Virtual reality system with no robotic assistive feature.
Kim SM, *et al.* Clinical application of circuit training for subacute stroke patients: a preliminary study. Journal of Physical Therapy Science, 2016. 28(1): 169–74.	No robotic intervention.
Kiper P, *et al.* Reinforced feedback in virtual environment for rehabilitation of upper extremity dysfunction after stroke: Preliminary data from a randomized controlled trial. BioMed Research International, 2014. 2014.	Virtual reality system with no robotic assistive feature.
Kovrazhkina EA, *et al.* Rehabilitation of walking in patients with an acute stroke with assistance of a robotic device gait Trainer. Cerebrovascular Diseases, 2009. 27: 210.	Article is an abstract.
Krebs HI, *et al.* Increasing productivity and quality of care: robot-aided neuro-rehabilitation. J Rehabil Res Dev, 2000. 37(6): 639–52.	Not a randomized controlled trial.
Krebs HI, *et al.* Robot-aided neurorehabilitation: A robot for wrist rehabilitation. IEEE Trans Neural Syst Rehabil Eng, 2007. 15(3): 327–35.	Not a randomized controlled trial.
Lee Y, *et al.* Robot-guided ankle and knee therapeutic training improves motor functions in stroke. Stroke, 2016. 47.	Article is an abstract.
Lemmens R, *et al.* Transfer of motor learning in (robotic) task-oriented arm-hand training after stroke. Neurorehabilitation and Neural Repair, 2012. 26(6): 747.	Article is an abstract.
Lemmens RJ, *et al.* Accelerometry measuring the outcome of robot-supported upper limb training in chronic stroke: a randomized controlled trial. PLoS One, 2014. 9(5): e96414.	Not the outcome of interest.
Lewek M, *et al.* Alterations in joint kinesmatics following locomotor training in individuals with chronic stroke...Platforms, thematic posters, and posters for CSM 2007. Journal of Neurologic Physical Therapy, 2006. 30(4): 196.	Article is an abstract.
Lewek MD, *et al.* Allowing intralimb kinematic variability during locomotor training poststroke improves kinematic consistency: a subgroup analysis from a randomized clinical trial. Phys Ther, 2009. 89(8): 829–39.	Not the outcome of interest.
Lewis GN, Perreault EJ. An assessment of robot-assisted bimanual movements on upper limb motor coordination following stroke. IEEE Trans Neural Syst Rehabil Eng, 2009. 17(6): 595–604.	Not a randomized controlled trial.
Lin KC, Horng YS. Comparative Efficacy Research of Robot-Assisted Therapy With and Without Constraint-Induced Therapy in Stroke Rehabilitation. 2013.	This is a listing under ClinicalTrials.gov and the trial is still on-going.
Lin KC, Lee CY, Lee MW. Effects of Robot-Assisted Combined Therapy in Upper Limb Rehabilitation in Stroke Patients. 2014.	This is a listing under ClinicalTrials.gov and the trial is still on-going.

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Study	**Reason for exclusion**
Linder SM, *et al.* The home stroke rehabilitation and monitoring system trial: a randomized controlled trial. Int J Stroke, 2013. 8(1): 46–53.	Protocol of a trial that compared home-based robotic training vs home-based conventional training.
Liu Z, *et al.* Effects of robot-assisted therapy on upper-limb function of acute stroke patients. Chinese Journal of Tissue Engineering Research, 2011. 15(52): 9803–7.	Not a randomized controlled trial.
Lo AC, *et al.* Multicenter randomized trial of robot-assisted rehabilitation for chronic stroke: methods and entry characteristics for VA ROBOTICS. Neurorehabil Neural Repair, 2009. 23(8): 775–83.	This is an abstract of study, Lo AC, *et al.* Robot-assisted therapy for long-term upper-limb impairment after stroke; 2010, which has been included for analysis.
Lum PS, VAOo Research, and Development. Extension of the MIME Robotic System for Stroke Rehabilitation. 2012.	Article is an abstract.
Masiero S, *et al.* A novel robot device in rehabilitation of post-stroke hemiplegic upper limbs. Aging Clin Exp Res, 2006. 18(6): 531–35.	Not dose matched.
Masiero S, *et al.* A novel robot-assisted upper-limb rehabilitation program In acute management of post-stroke patients: A randomized controlled trial. Neurorehabilitation and Neural Repair, 2012. 26(4): 401.	Article is an abstract.
Masiero S, *et al.* Post-stroke robotic training of the upper limb: A randomised trial study. PM and R, 2010. 2(9): S2-S3.	Article is an abstract.
Masiero S, *et al.* Robotic-assisted rehabilitation of the upper limb after acute stroke. Arch Phys Med Rehabil, 2007. 88(2): 142–49.	Not dose matched.
Mayr A, *et al.* Prospective, blinded, randomized crossover study of gait rehabilitation in stroke patients using the Lokomat gait orthosis. Neurorehabil Neural Repair, 2007. 21(4): 307–14.	Not dose matched.
Mizukami M, *et al.* Effect of gait training with an exoskeleton robotic device on hemiplegic patients in the recovery stage. Physiotherapy (United Kingdom), 2015. 101: eS1017.	Article is an abstract.
Mizukami M, *et al.* Gait training of subacute stroke patients using a hybrid assistive limb: a pilot study. Disabil Rehabil Assist Technol, 2016: 1–8.	Not a randomized controlled trial.
Morone G, *et al.* Who may benefit from robotic-assisted gait training? A randomized clinical trial in patients with subacute stroke. Neurorehabil Neural Repair, 2011. 25(7): 636–44.	Not a randomized controlled trial.

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Study	Reason for exclusion
Morone G, *et al.* Who may have durable benefit from robotic gait training?: A 2-year follow-up randomized controlled trial in patients with subacute stroke. Stroke, 2012. 43(4): 1140–42.	This is an extension of Morone *et al.* 2011 (see item above) with follow-up data measured at 2 years after intervention. (Note: original study is not a randomized controlled trial).
Ohata K, *et al.* Gait training using new robotics device for patients with hemiplegia after stroke: A randomized cross-over trial. Physiotherapy (United Kingdom), 2015. 101: eS1123–4.	Article is an abstract.
Page S, Hill V, White S. Portable upper extremity robotics is as efficacious as upper extremity rehabilitative therapy. Archives of Physical Medicine and Rehabilitation, 2012. 93(10): E21.	Robotic device is activated by electromyographic signals.
Page SJ, Hill V, White S. Portable upper extremity robotics is as efficacious as upper extremity rehabilitative therapy: a randomized controlled pilot trial. Clin Rehabil, 2013. 27(6): 494–503.	This is a duplicate of the study above (Page *et al.* 2012).
Peurala SH, *et al.* Gait characteristics after gait-oriented rehabilitation in chronic stroke. Restor Neurol Neurosci, 2005. 23(2): 57–65.	Not a randomized controlled trial and not dose matched.
Prange GB, *et al.* The effect of arm support combined with rehabilitation games on upper-extremity function in subacute stroke: a randomized controlled trial. Neurorehabil Neural Repair, 2015. 29(2): 174–82.	Device has no robotic assistive feature.
Reinkensmeyer DJ, *et al.* Do robotic and non-robotic arm movement training drive motor recovery after stroke by a common neural mechanism? Experimental evidence and a computational model. Conf Proc IEEE Eng Med Biol Soc, 2009. 2009: 2439–41.	Not the outcome of interest. Aim of the trial was to determine a computational model for neural recovery.
Research, VAOo, Development, Bever C. Evaluation of Robotic Arm Rehabilitation in Stroke Patients. 2010.	This is a ClinicalTrials.gov listing of the study, Conroy *et al.* Effect of gravity on robot-assisted motor training after chronic stroke: a randomized trial, 2011, which has been included for analysis.
Rosati G, Gallina P, Masiero S. Design, implementation and clinical tests of a wire-based robot for neurorehabilitation. IEEE Trans Neural Syst Rehabil Eng, 2007. 15(4): 560–9.	Not dose matched.
Rumiantseva NA, *et al.* Robotic-assisted mechanotherapy as a part of complex ontogenesis based rehabilitation program aimed to restore gait function in acute stroke patients. Cerebrovascular Diseases, 2010. 29: 248.	Not dose matched

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Study	Reason for exclusion
Rumyantseva NA, *et al.* The complex assessment of the pathological walking pattern and the efficacy of rehabilitation in acute stroke patients. Cerebrovascular Diseases, 2011. 31: 192.	Not dose matched.
Russo A, *et al.* Utilization of a robotic exoskeleton to provide increased mass practice for gait training and its impact on discharge destination for individuals with acute stroke. Stroke, 2016. 47.	Article is an abstract.
Sale P. Robot walking rehabilitation in stroke patients. 2012.	This is a listing under ClinicalTrials.gov and the trial is still on-going.
Samsygina OM, Ivanova GE, Kovrazhkina EA. Upper limb targeted complex rehabilitation with mechanotherapy in acute stroke patients. Cerebrovascular Diseases, 2010. 29: 251.	Not dose matched
Shahine EM, Shafshak TS. Central neuroplasticity and lower limbs functional outcome following repetitive locomotor training in chronic stroke patients. European Journal of Neurology, 2012. 19(P2332): 569.	Article is an abstract.
Simkins M, *et al.* Robotic unilateral and bilateral upper-limb movement training for stroke survivors afflicted by chronic hemiparesis. IEEE Int Conf Rehabil Robot, 2013. 2013: 6650506.	Trial is duplicate of Byl *et al.* 2013.
Sklyannaya K, Bronnikov V. Possibilities of the robot-assisted kinesitherapy in complex rehabilitation of post-stroke patients. European Journal of Neurology, 2015. 22: 673.	Not dose matched.
Skvortsova VI, *et al.* Current approaches to restoring walking in patients during the acute phase of cerebral stroke. Neuroscience and Behavioral Physiology, 2011. 41(5): 536–41.	Not dose matched.
Takebayashi T, *et al.* Which stroke patients benefit from robotic therapy for the upper extremities? Cerebrovascular Diseases, 2013. 35: 145.	Article is an abstract.
Tanaka N, *et al.* Effects of gait rehabilitation with a footpad-type locomotion interface in patients with chronic post-stroke hemiparesis: a pilot study. Clinical Rehabilitation, 2012. 26(8): 686–95.	Not the outcome of interest.
Thielman G, Bonsall P. Rehabilitation of the Upper Extremity after Stroke: A Case Series Evaluating REO Therapy and an Auditory Sensor Feedback for Trunk Control. Stroke Res Treat, 2012. 2012: 348631.	Case study with 3 patients.
Timmermans A, *et al.* Effectiveness of haptic master supported task-oriented arm training in chronic stroke patients. Neurorehabilitation and Neural Repair, 2012. 26(6): 751–52.	Article is an abstract.
Timmermans AA, *et al.* Effects of task-oriented robot training on arm function, activity, and quality of life in chronic stroke patients: a randomized controlled trial. J Neuroeng Rehabil, 2014. 11: 45.	Control group had no conventional physiotherapy. Patients received video instructions with no therapist assistance.
Uçar DE, Paker N, Buğdayci D. Lokomat: A therapeutic chance for patients with chronic hemiplegia. NeuroRehabilitation, 2014. 34(3): 447–53.	Conventional therapy was conducted at home.

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Study	Reason for exclusion
Van Nunen M, *et al.* RCT evaluating the effectiveness of robot-assisted treadmill training in restoring walking ability of stroke patients. Neurorehabilitation and Neural Repair, 2012. 26(6): 766.	This is an abstract duplicate of Van Nunen *et al.* 2011 (see below: "Robot-assisted treadmill training during rehabilitation of stroke patients")
Van Nunen M, *et al.* Robot-assisted treadmill training during rehabilitation of stroke patients. Archives of Physical Medicine and Rehabilitation, 2011. 92(10): 1716.	Article is an abstract.
van Nunen MP, *et al.* Recovery of walking ability using a robotic device in subacute stroke patients: a randomized controlled study. Disabil Rehabil Assist Technol, 2015. 10(2): 141–8.	This is a duplicate of Nunen *et al.* 2015, which has been included for analysis.
Volpe BT, *et al.* A novel approach to stroke rehabilitation: robot-aided sensorimotor stimulation. Neurology, 2000. 54(10): 1938–44.	Not a randomized controlled trial and not dose matched.
Wadiwala MF, Kamal AK. Are robots any better in stroke rehabilitation? J Pak Med Assoc, 2012. 62(10): 1104–5.	Article is an abstract.
Waldman G, *et al.* Effects of robot-guided passive stretching and active movement training of ankle and mobility impairments in stroke. NeuroRehabilitation, 2013. 32(3): 625–34.	Control group was home based rehabilitation.
Watanabe H, *et al.* Recovery of walking ability using a hybrid assistive limb in persons with subacute stroke: A randomized controlled pilot study. Physiotherapy (United Kingdom), 2015. 101: eS1607-eS1608.	Article is an abstract.
Werner C, *et al.* A new gait machine G-EO for stair climbing and descending in non-ambulatory neurological patients. Annals of Physical and Rehabilitation Medicine, 2011. 54: e235.	Article is an abstract.
Winstein CJ, *et al.* Effect of a Task-Oriented Rehabilitation Program on Upper Extremity Recovery Following Motor Stroke. JAMA, 2016. 315(6): 571–81.	No robotic intervention.
Wu X, *et al.* Long-term Effectiveness of Intensive Therapy in Chronic Stroke. Neurorehabil Neural Repair, 2015.	This is a duplicate of Lo *et al.* 2010, which has been included for analysis.
Xu G, *et al.* Adaptive hierarchical control for the muscle strength training of stroke survivors in robot-aided upper-limb rehabilitation. International Journal of Advanced Robotic Systems, 2012. 9.	Not the outcome of interest. Trial was to study control software of robotic device.
Yoo DH, Kim SY. Effects of upper limb robot-assisted therapy in the rehabilitation of stroke patients. J Phys Ther Sci, 2015. 27(3): 677–79.	Not a randomized controlled trial.

(*Continued*)	
Study	**Reason for exclusion**
Yoo DH, *et al.* Effect of Three-Dimensional Robot-Assisted Therapy on Upper Limb Function of Patients with Stroke. Journal of Physical Therapy Science, 2013. 25, 407–9.	Not dose matched.
Yoon Y, *et al.* Gait training with the newly developed active-assistive system for gait is feasible for hemiplegic patients after stroke. PM and R, 2015. 7(9): S115-S116.	Article is an abstract.
Yoshimoto T, *et al.* Feasibility and efficacy of high-speed gait training with a voluntary driven exoskeleton robot for gait and balance dysfunction in patients with chronic stroke: nonrandomized pilot study with concurrent control. International journal of rehabilitation research. Internationale Zeitschrift für Rehabilitationsforschung. Revue internationale de recherches de réadaptation, 2015. 38(4): 338–43.	Not a randomized controlled trial and not dose matched.
Yoshimoto T, *et al.* Gait training with a new exoskeleton robot hybrid assistive limb improves gait and balance performances in chronic stroke subjects. Physiotherapy (United Kingdom), 2015. 101: eS1703.	Article is an abstract.
Zhao Y, Hao Z, Li J. Auditory P300 as an Indicator in Effectiveness of Robot-Assisted Lower Limb Rehabilitation Training among Hemiplegic Patients after Ischemic Stroke. Open Journal of Therapy and Rehabilitation, 2014. 2(02): 76.	Not dose matched.
Zhao Y-n, Hao Z-w, Li J.m. Effect of Lokomat Lower Gait Training Rehabilitation Robot on Joint Motion of Post-acute Stroke Patients. Chinese General Practice, 2013. 7: 36.	Article is an abstract.

Appendix III: Characteristics of included studies

Study	Location	Age (mean ± SD)	Male (n)	Ischemic stroke (n)	Hemorrhagic stroke (n)	Acute/sub-acute	Chronic	Severe	Moderate/mild	Upper limb	Lower limb	Total training hours	Therapy ratio	EG (n)	CG (n)	Outcome measure of interest
Ang *et al.*, 2014[18]	Singapore	EG: 51.1 ± 6.3 CG: 58.0 ± 19.3	10	9	6		x		x	x		27	0.5	8	7	> FM (UL) > No ADL measure
Brokaw *et al.*, 2014[22]	USA	57 ± 11.7 (Total)	9	NR	NR		x		x	x		12	0	7	5	> FM (UL) > No ADL measure
Burgar *et al.*, 2011[60]	USA	EG: 62.5 ± 2.0 CG: 68.1 ± 3.3	NR	NR	NR	x			x	x		9	0	19	18	> FM (UL) > ADL measure: FIM (UL)
Byl *et al.*, 2013[72]	USA	EG: 54.2 ± 20.5 CG: 59.3 ± 6.8	8	NR	NR		x		x	x		18	0	5	5	> FM (UL) > ADL measure: SIS & CAFE 40
Chang *et al.*, 2012[15]	South Korea	EG: 55.5 ± 12.0 CG: 59.7 ± 12.1	23	23	14	x		x			x	16.67	1.5	20	17	> FAC > No ADL measure
Chua *et al.*, 2016[44]	Singapore	EG: 62.1 ± 10.3 CG: 60.7 ± 10.7	75	NR	NR	x		x			x	36	1.25	53	53	> FAC > ADL measure: BI
Conroy *et al.*, 2011[73]	USA	EG: 60 ± 13 CG: 56 ± 6.3	20	35	2		x	x		x		18	0	18	19	> FM (UL) > ADL measure: SIS (ADL)
Dias *et al.*, 2007[74]	Portugal	EG: 70.35 ± 7.36 CG: 68.00 ± 10.69	30	NR	NR		x		x		x	16.67	1	20	20	> MI (LL) > No ADL measure
Forrester *et al.*, 2014[75]	USA	EG: 63.3 ± 2.3 CG: 60.0 ± 3.1	NR	NR	NR	x		x			x	10	0	18	16	> FIM (Walking Item) > No ADL measure
Hesse *et al.*, 2014[76]	Germany	EG: 71.4 ± 15.5 CG: 69.7 ± 16.6	28	41	9	x		x		x		20	1	25	25	> FM (UL) > ADL measure: BI
Hidler *et al.*,2009[12]	USA	EG: 59.9 ± 11.3 CG: 54.6 ± 9.4	39	47	16	x			x		x	18	0	33	30	> FAC > ADL measure: FAI
Hornby *et al.*, 2008[77]	USA	EG: 57 ± 10 CG: 57 ± 11	30	22	26		x		x		x	6	0	24	24	> mEFAP > ADL measure: FAI
Hsieh *et al.*, 2016[78]	Taiwan	EG: 49.28 ± 10.90 CG: 52.87 ± 10.40	18	16	15	x			x	x		30	1	16	15	> FM (UL) > ADL measure: FIM (Total)
Hsieh *et al.*, 2012[79]	Taiwan	EG: 56.51 ± 10.03 CG: 54.83 ± 9.84	23	21	15		x		x	x		30	0.29	18	18	> FM (UL) > ADL measure: MAL-QOM
Hsieh *et al.*, 2011[80]	Taiwan	EG: 56.04 ± 13.74 CG: 54.00 ± 8.05	9	9	3		x		x	x		30	0.29	6	6	> FM (UL) > ADL measure: MAL-QOM
Hsieh *et al.*, 2014[81]	Taiwan	EG: 52.34 ± 13.20 CG: 54.12 ± 9.98	23	20	12		x		x	x		30	0.2	16	16	> FM (UL) > ADL measure: MAL-QOM
Husemann *et al.*, 2007[40]	Germany	EG: 60 ± 13 CG: 57 ± 11	21	22	8	x		x			x	20.00	1	16	14	> FAC > ADL measure: BI
Kahn *et al.*, 2006[82]	USA	EG: 55.6 ± 12.2 CG: 55.9 ± 12.3	11	NR	NR		x	x		x		18	0	10	9	> Chedoke McMaster > No ADL measure
Kim *et al.*, 2015[83]	South Korea	EG: 54.1 ± 12.6 CG: 50 ± 16.2	19	13	13	x		x			x	26.67	1	13	13	> FAC > ADL measure: KMBI

(*Continued*)

Study	Location	Age (mean ± SD)	Male (n)	Ischemic stroke (n)	Hemorrhagic stroke (n)	Acute/subacute	Chronic	Severe	Moderate/mild	Upper limb	Lower limb	Total training hours	Therapy ratio	EG (n)	CG (n)	Outcome measure of interest
Klamroth-Marganska *et al.*, 2014[47]	Switzerland	EG: 55 ± 13 CG: 58 ± 14	46	NR	NR		x		x	x		18	0	38	35	> FM (UL) > No ADL measure
Kutner *et al.*,2010[84]	USA	57.4 ± 13.4 (Total)	10	12	5		x		x	x		60	1	10	7	> No movement measure > ADL measure: SIS ADL/IADL
Liao *et al.*, 2012[85]	Taiwan	EG: 55.51 ± 11.17 CG: 54.56 ± 8.20	13	NR	NR		x		x	x		30	0.2	10	10	> FM (UL) > FIM (Total)
Lo *et al.*, 2010[17]	USA	EG: 66 ± 11 CG: 64 ± 11	89	80	13		x	x		x		36	0	47	46	> FM (UL) > No ADL measure
Lum *et al.*, 2006[86]	USA	EG: 62.3 ± 2.8 CG: 59.9 ± 5.5	13	NR	NR	x			x	x		12.5	0	10	6	> FM(UL) > ADL measure: FIM (Self Care & Transfer)
Lum *et al.*, 2002[87]	USA	EG: 63.2 ± 3.6 CG: 65.9 ± 2.4	20	NR	NR		x		x	x		24	0	13	14	> FM(UL) > ADL measure: FIM (Self Care & Transfer)
Masiero *et al.*, 2014[37]	Italy	EG: 65.60 ± 9.2 CG: 66.83 ± 7.9	20	26	4	x			x	x		50	2	14	16	> FM (UL) > ADL measure: FIM (Motor)
Masiero *et al.*, 2011[88]	Italy	EG: 72.4 ± 7.1 CG: 75.5 ± 4.8	16	18	3	x			x	x		50	2	11	10	> FM (UL) > ADL measure: FIM (Motor)
McCabe *et al.*, 2015[16]	USA	EG: 2 (Age group: 21–49); 10 (Age group: 50–81) CG: 2 (Age group: 21–49); 9 (Age group:50–81)	16	NR	NR		x		x	x		300	2.33	12	11	> FM (UL) > ADL measure: AMAT-F
Ng *et al.*, 2008[89]	Hong Kong	EG: 66.6 ± 11.3 CG: 73.4 ± 11.5	24	31	7	x		x			x	10	0.5	17	21	> FAC > ADL measure: FIM (Total)
Nunen *et al.*, 2015[41]	the Netherlands	EG: 50.0 ± 9.6 CG: 56.0 ± 8.7	15	19	11	x		x			x	35	0.75	16	14	> FAC > ADL measure: SIS-ADL
Ochi *et al.*, 2015[36]	Japan	EG: 61.8 ± 7.5 CG: 65.5 ± 12.1	20	10	16	x		x			x	46.67	6	13	13	> FAC > ADL measure: FIM (Mobility)
Orihuela-Espina *et al.*, 2016[55]	Mexico	EG: 56.22 ± 13.72 CG: 55.00 ± 25.78	11	17	0	x		x		x		40	0	9	8	> FM (Hand) > No ADL measure
Peurala *et al.*, 2009[35]	Finland	EG: 65.7 ± 9.2 CG: 65.3 ± 9.9	19	27	10	x		x			x	18.75	2.75	17	20	> FAC > No ADL measure
Peurala *et al.*, 2005[70]	Finland	EG: 51.2 ± 7.9 CG: 52.3 ± 6.8	24	15	15		x		x		x	18.75	2.75	15	15	> No movement measure > ADL measure: FIM (Total)
Pohl *et al.*, 2007[43]	Germany	EG: 62.3 ± 12.0 CG: 64.0 ± 11.6	104	124	31	x		x			x	15.00	1.25	77	78	> FAC > ADL measure: BI

(*Continued*)

Study	Location	Age (mean ± SD)	Male (n)	Ischemic stroke (n)	Hemorrhagic stroke (n)	Acute/subacute	Chronic	Severe	Moderate/mild	Upper limb	Lower limb	Total training hours	Therapy ratio	EG (n)	CG (n)	Outcome measure of interest
Rabadi *et al.*, 2008[90]	USA	EG: 79.50 ± 6.17 CG: 67.80 ± 12.66	10	20	0	x		x		x		8	0	10	10	> FM (UL) > ADL measure: FIM (Total)
Reinkensmeyer *et al.*, 2012[91]	USA	EG: 60 ± 10 CG: 61 ± 13	17	13	8 (5 unknown)		x		x	x		24	0	13	13	> FM (UL) > ADL measure: MAL-QOM
Sale *et al.*, 2014[92]	Italy	EG: 67.7 ± 14.2 CG: 67.7 ± 14.2	31	46	7	x			x	x		22.5	0	26	27	> FM (UL) > No ADL measure
Sale *et al.*, 2013[93]	Italy	EG: 67.0 ± 12.4 CG: 72.56 ± 8.98	14	15	5	x			x	x		13.33	0.33	11	9	> FM (UL) > No ADL measure
Schwartz *et al.*, 2009[34]	Israel	EG: 62 ± 8.5 CG: 65 ± 7.5	40	49	18	x		x			x	24	1	37	30	> No movement measure > ADL measure: FIM (Motor)
Stein *et al.*, 2014[94]	USA	EG: 57.6 ± 10.7 CG: 56.6 ± 15.1	17	NR	NR		x		x		x	18	0	12	12	> EFAP > ADL measure: CAFÉ 40
Susanto *et al.*, 2015[95]	Hong Kong	EG: 50.7 ± 9.0 CG: 55.1 ± 10.6	14	11	8		x		x	x		20	0	9	10	> FM (UL) > No ADL measure
Taveggia *et al.*, 2016[96]	Italy	EG: 71 ± 5 CG: 73 ± 7	17	NR	NR	x		x			x	37.5	2	13	15	> No movement measure > ADL measure: FIM (Total)
Tong *et al.*, 2006[39]	Hong Kong	EG: 66.1 ± 9.9 CG: 71.4 ± 14.0	21	28	7	x		x			x	10	0.5	15	20	> FAC > ADL measure: FIM (Total)
Vanoglio *et al.*, 2016[97]	Italy	EG: 72 ± 11 CG: 73 ± 14	14	17	10	x		x		x		20	0	14	13	> MI (UL) > No ADL measure
Volpe *et al.*, 2008[98]	USA	EG: 62 ± 3 CG: 60 ± 3	15	20	1		x	x		x		18	0	11	10	> FM (UL) > ADL measure: SIS
Watanabe *et al.*, 2014[99]	Japan	EG: 67.0 ± 16.8 CG: 75.6 ± 13.9	11	12	10	x		x			x	4	0	11	11	> FAC > No ADL measure
Werner *et al.*, 2002[13]	Germany	EG: 60.3 ± 8.6 CG: 59.7 ± 10.2	13	NR	NR	x		x			x	10.83	2.25	15	14	> FAC > No ADL measure
Westlake *et al.*, 2009[100]	USA	EG: 58.6 ± 16.9 CG: 55.1 ± 13.6	13	8	8		x		x		x	6	0	8	8	> FM (LL) > ADL measure: LLFDI-Function
Wu *et al.*, 2012[101]	Taiwan	EG: 55.13 ± 12.72 CG: 51.30 ± 6.23	20	NR	NR		x		x	x		30	0.2	14	14	> FM (UL) > ADL measure: SIS ADL/IADL
Wu *et al.*, 2013[102]	Taiwan	EG: 52.21 ± 12.20 CG: 54.22 ± 9.78	25	NR	NR		x		x	x		30	0.2	18	17	> WMFT-FAS > ADL measure: MAL-QOM

ADL, Activities of Daily Living; AMAT-Function, Arm Motor Ability Test - Function; BI, Barthel Index, CAFÉ 40, California Functional Evaluation 40; CG, Control Group; EFAP, Emory Functional Ambulation Profile; EG, Experimental Group; FAC, Functional Ambulation Category; FAI, Frenchay Activities Index; FIM (Mobility), Functional Independence Measure (Mobility); FIM (Motor), Functional Independence Measure (Motor); FIM (Self Care & Transfer), Functional Independence Measure (Self Care & Transfer); FIM (Total), Functional Independence Measure (Total); FIM (UL), Functional Independence Measure (Upper Limb); FM (LL), Fugl-Myer (Lower Limb); FM (UL), Fugl-Myer (Upper Limb); KMBI, Korea Modified Barthel Index; LLFDI-Function, Late Life Function and Disability Instrument - Function; MAL-QOM, Motor Activity Log - Quality of Movement, mEFAP, modified Emory Functional Ambulation Profile; MI (LL), Motricity Index (Lower Limb); n, Sample Size; NR, Not Recorded; SD, Standard Deviation; SIS, Stroke Impact Scale; SIS-ADL/IADL, Stroke Impact Scale - Activities of Daily Living/Instrumental Activities of Daily Living; WMFT-FAS, Wolf Motor Function Test - Functional Ability Score.

Appendix IV: Methodological quality of included studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13
Ang *et al.*, 2014[18]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Brokaw *et al.*, 2014[22]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Burgar *et al.*, 2011[60]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Byl *et al.*, 2013[72]	Yes	No	Yes	NA	NA	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Chang *et al.*, 2012[15]	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Chua *et al.*, 2016[44]	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conroy *et al.*, 2011[73]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Dias *et al.*, 2007[74]	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Forrester *et al.*, 2014[75]	Yes	No	Yes	NA	NA	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Hesse *et al.*, 2014[76]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hidler *et al.*,2009[12]	Yes	No	No	NA	NA	No	Yes	Yes	No	Yes	Yes	No	Yes
Hornby *et al.*, 2008[77]	Yes	Yes	Yes	NA	NA	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Hsieh *et al.*, 2016[78]	Yes	Yes	Yes	NA	NA	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hsieh *et al.*, 2012[79]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hsieh *et al.*, 2011[80]	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hsieh *et al.*, 2014[81]	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Husemann *et al.*, 2007[40]	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Kahn *et al.*, 2006[82]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kim *et al.*, 2015[83]	Yes	No	Yes	NA	NA	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Klamroth-Marganska *et al.*, 2014[47]	Yes	Yes	Unclear	NA	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Kutner *et al.*,2010[84]	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Liao *et al.*, 2012[85]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lo *et al.*, 2010[17]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Lum *et al.*, 2006[86]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lum *et al.*, 2002[87]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Masiero *et al.*, 2014[37]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Masiero *et al.*, 2011[88]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
McCabe *et al.*, 2015[16]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Ng *et al.*, 2008[89]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nunen *et al.*, 2015[41]	Yes	No	Yes	NA	NA	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Ochi *et al.*, 2015[36]	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Orihuela-Espina *et al.*, 2016[55]	Yes	No	Yes	NA	NA	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Peurala *et al.*, 2009[35]	Yes	No	Yes	NA	NA	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Peurala *et al.*, 2005[70]	Yes	Yes	Yes	NA	NA	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pohl *et al.*, 2007[43]	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rabadi *et al.*, 2008[90]	Yes	Yes	No	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reinkensmeyer *et al.*, 2012[91]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

(*Continued*)

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13
Sale *et al.*, 2014[92]	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sale *et al.*, 2013[93]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Schwartz *et al.*, 2009[34]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stein *et al.*, 2014[94]	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Susanto *et al.*, 2015[95]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Taveggia *et al.*, 2016[96]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tong *et al.*, 2006[39]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vanoglio *et al.*, 2016[97]	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Volpe *et al.*, 2008[98]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Watanabe *et al.*, 2014[99]	Yes	No	No	NA	NA	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Werner *et al.*, 2002[13]	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Westlake *et al.*, 2009[100]	Yes	Yes	Yes	NA	NA	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wu *et al.*, 2012[101]	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wu *et al.*, 2013[102]	Yes	No	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

NA: Not Applicable.

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Principal Author

Name of Principal Author (Candidate)	Kenneth Lo		
Contribution to the Paper	I was responsible for the overall creation of this paper. As the primary author I developed the protocol, conducted the literature searches, retrieved papers, and assessed each paper for their eligibility. I subsequently undertook critical appraisal, data extraction and data analysis. I was also responsible for responses to reviewers and revisions to the paper. The review was conducted using tools provided by the Joanna Briggs Institute.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	October 2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr. Matthew Stephenson		
Contribution to the Paper	Supervisor: provided conceptualization and methodological guidance to the manuscript. Contributed to the writing and revision of the paper, including responding to peer review comments, and reviewing the findings and conclusion.		
Signature		Date	October 2019

Name of Co-Author	Assoc. Prof. Craig Lockwood		
Contribution to the Paper	Supervisor: provided conceptualization and methodological guidance to the manuscript. Contributed to the writing and revision of the paper, including responding to peer review comments, and reviewing the findings and conclusion.		
Signature		Date	October 2019

Please cut and paste additional co-author panels here as required.

Effectiveness of robotic assisted rehabilitation for mobility and functional ability in adult stroke patients: a systematic review protocol

Kenneth Lo • Matthew Stephenson • Craig Lockwood

Joanna Briggs Institute, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, Australia

Review question/objective: The objective of this review is to synthesize the best available evidence on the effectiveness of robotic assistive devices in the rehabilitation of adult stroke patients for recovery of impairments in the upper and lower limbs. The secondary objective is to investigate the sustainability of treatment effects associated with use of robotic devices.
The specific review question to be addressed is: can robotic assistive devices help adult stroke patients regain motor movement of their upper and lower limbs?

Keywords Rehabilitation; robot; robotic; robotic assisted rehabilitation; stroke

JBI Database System Rev Implement Rep 2017; 15(1):39–48.

Background

Stroke is a leading cause of long-term disability and is the third most common cause of mortality in developed countries with 15 million people suffering a stroke yearly.[1] Different parts of the brain control different bodily functions. If a person survives a stroke, the effects can vary, depending on the location of brain damage, severity and duration of the stroke. Broadly, the effects of stroke can be physical, cognitive or emotional in nature. In terms of the physical effects of stroke, the loss of motor abilities of the limbs presents significant challenges for patients, as their mobility and activities of daily living (ADLs) are affected. The upper or lower limbs can experience weakness (paresis) or paralysis (plegia), with the most common type of limb impairment being hemiparesis, which affects eight out of 10 stroke survivors.[2] Other physical effects of stroke are loss of visual fields, vision perception, difficulty swallowing (dysphagia), apraxia of speech, incontinence, joint pain or neuropathic pain (caused by inability of the brain to correctly interpret sensory signals in response to stimuli on the affected limbs). Cognitive effects of stroke are aphasia, memory loss and vascular dementia. Stroke patients can lose the ability to understand speech or the capacity to read, think or reason, and normal mental tasks can present big challenges, affecting their quality of life. The drastic changes in physical and cognitive abilities caused by stroke also lead to emotional effects for stroke patients. Stroke survivors can experience depression when they encounter problems in doing tasks that they can easily do pre-stroke. Along with depression, they can experience a lack of motivation and mental fatigue.

For stroke patients, rehabilitation is the pathway to regaining or managing their impaired functions. There is no definite end to recovery but the most rapid improvement is within the first six months post stroke.[3] Before a patient undergoes rehabilitation, an assessment is first done to determine if a patient is medically stable and fit for a rehabilitation program. If the patient is assessed to be suitable, then depending on the level of rehabilitative supervision required, the patient could undergo rehabilitation in various settings – as an in-patient/outpatient (at either a hospital or nursing facility) or at home.[3,4] Rehabilitation should be administered by a multi-disciplinary team of physiotherapists, occupational therapist, speech therapist and neuropsychologists, who work together to offer an integrated, holistic rehabilitation therapy.[4] Depending on the type of impairment, rehabilitation specialists will assess the appropriate therapies needed and set realistic goals for patients to achieve. Generally, stroke patients should be given a minimum of 45 min for each therapy session over at least five days per

Correspondence: Kenneth Lo, kenneth.lo@adelaide.edu.au
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week, as long as the patient can tolerate the rehabilitation regimen.[3]

One of the main goals in stroke rehabilitation is the restoration of motor skills, and this involves patients undergoing repetitive, high-intensity, task-specific exercises that enable them to regain their motor and functional abilities.[5,6] It is theorized that the brain is plastic in nature and that repetitive exercises over long periods can enable the brain to adapt and regain the motor functionality that has been repeatedly stimulated.[7] This involves the formation of new neuronal interconnections that enable the re-transmission of motor signals.[8]

Over the years, a number of robotic assistive devices have been used to rehabilitate patients based on high repetitions of task-specific exercises.[9] These robotic assistive devices provide consistent and repetitive cycles over long periods and help train the limbs of patients to keep receiving and sending signals from and back to the brain and thereby regain their motor abilities. Such devices are also complex in nature involving interactive automation, sensors and dynamic control logic and are able to function without much intervention from physiotherapists. Several devices have been used for rehabilitation of both upper limb (e.g. ARMin, MIT-MANUS, NeReBot and T-Wrex) and lower limb (e.g. Lokomat, Gait Trainer, G-EO System and Hybrid Assistive Leg).[10,11] As an example, for patients who are unable to walk, there are gait-training devices such as the Lokomat that help patients to recover their walking ability. Initially, the physiotherapist will set the patient up with the device and start a software program that cycles through the various stages of walking. The patient's lower limbs will be moved by the device and the physiotherapist is able to set the pace of the simulated walking and the amount of guidance force to assist movement of the legs and extent of body weight support.

In comparison, for conventional rehabilitation of the lower limbs without assistive devices, it would require at least two physiotherapists to train a patient to walk, and the pace and pattern of walking may not be consistent. It is also physically strenuous for the physiotherapists to sustain the exercise over long periods, thus affecting the rehabilitation progress of the patient. The labor-intensive nature of conventional physiotherapy places great strain on physiotherapists. Coupled with the requirements of stroke patients for medical care and intensive rehabilitation exercises (which frequently entail one-to-one manual interaction with therapists), therapist time and organizational budgets, it is not always possible to provide an optimal rehabilitation program for patients.[10] Therefore, it is hoped that with robotic assistive devices, better rehabilitation progress can be achieved for patients together with alleviation of time and physical demands on physiotherapists. With the assistance of robots, physiotherapists will be able to concentrate more on functional rehabilitation during individual training sessions and supervision of multiple patients simultaneously during robot-assisted therapy sessions. This approach would maximize the expertise and time of physiotherapists, thus improving the effectiveness of the rehabilitation program.[10]

There have been clinical studies to determine the effectiveness of robotic assistive devices in the rehabilitation of stroke patients.[12] However, these studies presented a mixed picture of the effectiveness of robotic devices. One study on lower limbs reported an improvement in a motor movement scale (Fugl-Meyer Assessment lower extremity score) but not for another motor scale (leg score of Motricity Index) and also stated no improvement on a walking scale (Functional Ambulation Category).[13] Others reported that there was no statistically significant difference between robotic assisted therapy and conventional therapy,[14,15] while one study that investigated walking speeds and distance found that conventional therapy was more effective than robotic assisted therapy.[16] There were also various types of study designs. Some studies examined not just robot-assisted rehabilitation but combinations of robot-assisted rehabilitation and non-conventional physiotherapies (e.g. functional electrical simulation [FES], constraint induced therapy [CIT], transcranial direct current stimulation or motor imagery) versus conventional therapies in three-arm studies.[17-19] Other studies involved patients in a randomized controlled crossover trial with or without a washout period.[20,21]

Typically, in studies, authors used different scales for their primary and secondary outcomes. These scales were used to measure motor movement, motor strength/duration, walking speed or functional activities. With various outcome scales used, it will be a challenge to compare the results of clinical trials,[22] and the suitability of certain scales will also depend on the modality of the robotic therapy given.

As an example, for arm muscle strength outcome, it will be better if patients have less assistive guidance force provided (or conversely, more resistive guidance force provided) and minimal gravity support during therapy sessions.[23] Also, in a trial with multiple outcome measures, testing multiple simultaneous hypotheses at set *P* values could lead to increased risk of Type I errors.[24] To mitigate this, Feise[24] recommended that researchers facing multiple outcome measures select a primary outcome measure or use a global assessment measure. As robotic devices are primarily designed to enable movement of a particular limb,[10] a suitable measurement scale that reflects the design function of the device is necessary to accurately determine the effectiveness of these devices. In view of this, scales that measure movement abilities of the paretic limbs should be used, such as Fugl-Meyer Scale Assessment (upper extremity) for the upper limbs or Functional Ambulation Category for the lower limbs.

A preliminary search of PubMed, Embase, *JBI Database of Systematic Reviews and Implementation Reports* and Cochrane Library identified three systematic reviews that have been conducted in this topic area.[25-27]

These reviews included a variety of outcome measures for motor function, muscle strength, walking capacity and walking velocity. Mehrholz *et al.*[25,26] found that robot-assisted arm training improved ADLs, arm function and muscle strength of the paretic arm, and for the lower limbs walking was improved but not for walking velocity or walking capacity. Prange *et al.*[27] found that arm control improved but not functional ability. The proposed systematic review being undertaken has different aspects to the previous reviews. First is the selection of the outcome measure to examine primarily the motor movement of the paretic limbs in order to have a meaningful comparison across studies.[22] Second is the analysis approach toward multiple-arm studies. In the first two reviews,[25,26] the results of the arms of robotic intervention groups, some with additional forms of non-conventional treatment, were pooled together for comparison against the control group. In this review, only the arm of robotic intervention group (without other forms of non-conventional treatment, e.g. FES) will be compared to the control group to clarify the effects of the intervention. The current review also seeks to address the question of sustainability of the treatment effects; for example, is the improved motor movement ability measured at the end of intervention period maintained post intervention? If the outcome measure is maintained (or improved) during follow-up measurements after intervention, then the effect of rehabilitation can be considered as being sustainable. From analyzing the intervention sustainability, it is hoped that the optimal duration and frequency of rehabilitation that generate the best sustainability outcome can be identified. This could assist rehabilitation specialists to formulate a suitable proportion of robotic assisted therapy in their treatment protocols. Lastly, there have been new studies[28-33] published since these existing systematic reviews were conducted, and this review seeks to incorporate the most recent trial findings.

The diverse range of outcomes and study designs does not provide a clear determination of the effectiveness of robotic assisted rehabilitation, and it is the intent of this review to provide clarity to the discussion and offer useful recommendations for clinical practice. In this review, robotic assisted therapies for both upper and lower limbs will be evaluated to gain a detailed understanding of the effectiveness of robotic devices in these two areas to which a large proportion of rehabilitation efforts is devoted.

Inclusion criteria

Types of participants

The current review will consider studies that include adult stroke patients (18 years and older) of all genders, regardless if stroke is due to ischemic or hemorrhagic causes. Patients with pre-existing impairments that are not caused by stroke, such as disabilities due to spinal cord injuries, Parkinson's disease, multiple sclerosis and traumatic brain injuries (caused by accidents, falls, infections, tumors or chemical toxins), will be excluded. Study participants may be new stroke patients or repeat stroke patients at acute, sub-acute or chronic stages of their stroke, so long as they have been accepted into a formal rehabilitation program. Only trials where the rehabilitation setting is either in-patient or outpatient will be included. Home rehabilitation patients will be excluded due to potential confounding of treatment adherence. The rehabilitation program can be conducted at hospitals, nursing facilities or across multi-centers, and only physical impairments related to upper and lower limbs will be considered.

Types of intervention(s)

The current review will consider studies that evaluate rehabilitation of stroke patients using interactive, automated electromechanical equipment (i.e. assistive robotics). The types of robotic assistive devices can be varied (e.g. either robotic exoskeletons or end-effectors for gait training), as long as interventions involve electromechanical assistive devices with automation, sensors and dynamic control logic that help patients regain their motor abilities. Interventions involving the devices below are not considered as robotic rehabilitation devices as they do not exhibit assistive automation that robotic devices have:

- Non-interactive devices that deliver passive motion such as treadmills, static body-weight-assisted treadmills, bicycles, static walking aids, static orthoses (such as ankle-foot orthoses addressing foot drop) or pure mechanical trainers (e.g. Reha-Slide, Reha-Slide duo).
- Standalone video games controlled solely by patient without automated assistive feature, such as Nintendo Wii.
- Rehabilitation programs using non-conventional therapies such as acupuncture, FES, transcranial direct current stimulation, motor imagery, biofeedback and CIT.

The intervention group can have or not have an added conventional physiotherapy component. If the intervention group has an added conventional physiotherapy component, this can involve non-interactive static devices.

The intervention should not contain other types of non-conventional therapy (e.g. FES, transcranial direct current stimulation, motor imagery or CIT). For multiple-arm studies, only results of the intervention arm with robotic assisted rehabilitation will be compared to the control arm. The intervention arm with a combination of robotic assistive devices and non-conventional therapy will be excluded from analysis.

Comparator

As control groups, patients do not receive robotic assisted rehabilitation but receive only conventional physiotherapy or no physiotherapy treatment at all. The conventional physiotherapy treatment, however, may include non-interactive static devices (e.g. bicycles, treadmills and acupuncture).

The amount of therapy treatment in both intervention and control groups should be the same in terms of frequency and duration, that is, dose-matched. For example, if patients in the intervention group undergo 60 min of therapy using a robotic assistive device on top of a conventional physiotherapy component, then in the control group the patients should also undergo additional 60 min of conventional physiotherapy. Therefore, the total amount of therapy planned for patients (in terms of frequency per week, duration of a therapy session and overall rehabilitation period) should be the same for both groups. This does not apply if, in the control group, patients do not receive conventional physiotherapy.

For robotic assisted rehabilitation, the duration of therapy will consist of time for the patient to be set up with and be taken out of the robotic device, thus limiting the time for exercising the paretic limb (e.g. for Lokomat, a robotic exoskeleton device, actual exercise time can range from 35 to 40 min in a 60-min therapy session).[34] Although the actual exercise duration can be less than the allocated duration of therapy, it can still be considered as being equivalent to the duration of a conventional physiotherapy session, as during a conventional therapy session not the full duration will be used for exercising. There will also be time for patients to prepare or rest in between exercises. In addition, some trials do not provide a breakdown of actual exercise duration but only the duration of a therapy session.

Outcomes

The current review will consider studies that include the outcome measure of the amount of motor movement demonstrated by the paretic limbs. To have an accurate point of reference across studies, only studies that have used scales that measure motor movement will be considered for the review.

For outcome measure of upper limbs, the Fugl-Meyer Assessment[35] (upper extremity score) is the preferred scale. If a study does not use this scale, then an alternative measurement scale that quantifies upper limb motor movement (e.g. upper limb Motricity Index[36]) will be considered.

For outcome measure of lower limbs, the Functional Ambulation Category[37] is the preferred scale. If a study does not use this scale, then an alternative measurement scale that quantifies walking will be considered, for example Barthel Index[38] (ambulation item) or Functional Independence Measure[39] (walking item).

Another aspect that will be examined is the level of ADLs attained after the intervention. For outcome measure of ADLs, Functional Independence Measure is the preferred scale. If a study does not use this scale, then an alternative measurement scale that quantifies the level of ADLs will be considered, for example, the Barthel Index. As ADLs involve usage of both upper and lower limbs, a global ADL measurement combining both subgroups of upper and lower limbs will be considered.

In clinical trials, patient outcomes at different stages of the rehabilitation process are measured. Usually measures are taken at pre-, mid- and post-intervention stages but some studies will continue to take follow-up measurements in the months after the end of the intervention therapy. For this review, measurements taken at pre- and post-intervention therapy will be included for analysis. Follow-up measurements taken after the intervention has ended will also be compared to measurements taken at the end of the intervention to examine the sustainability of the treatment effect.

Types of studies

The current review will consider experimental study designs of randomized controlled trials. For studies with crossover design, only the first study period will be considered for inclusion, as it is not clear if carry-over effects will have diminished sufficiently during the washout period. Also, given the context of rehabilitation where it is likely and desired for patients to retain the effects of rehabilitative training, the two different phases will have a dependence on each other.[16] Thus, it will be confounding if both the first and second study periods of crossover trials are used to assess the effectiveness of robotic assistive devices.

Search strategy

The search strategy aims to find published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of PubMed will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Third, the reference list of all identified reports and articles will be searched for additional studies. Studies published in English will be considered for inclusion in this review and a date limit starting from 2000 will be set, as automated robotic devices have been increasingly used since 2000, together with an associated increase in the number of studies undertaken.

The databases to be searched include:
PubMed, Embase, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL) and PEDro (Physiotherapy Evidence Database).

The search for unpublished studies will include:
Mednar, ProQuest Dissertations & Theses, Clinical-Trials.gov, Google Scholar

Initial search terms to be used will be:
Robotics[mh] OR Robot*[tw] OR Exoskeleton Device[mh] OR Exoskeleton*[tw] OR Gait Trainer[tw] OR Lokomat[tw] AND Rehabilitation[mh] OR Rehabilitation[tw] OR Habilitation[tw] AND Stroke[mh] OR Stroke*[tw] OR "Cerebrovascular Accident" OR Cerebral[tw] OR "Cerebral Stroke" OR "Cerebrovascular Stroke" OR "Acute Stroke" OR "Sub-acute Stroke" OR "Subacute Stroke"

Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer.

Data extraction

Data will be extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. In the event of specific data of interest being absent from published articles, corresponding authors will be contacted to request access to the relevant data.

Data synthesis

Quantitative data will, where possible, be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as odds ratio (for categorical data)

and weighted/standardized mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using I^2 and the standard chi-square. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate. Sub-groups that may be considered for analysis include upper limb interventions, lower limb interventions, acute patients (i.e. less than three months post stroke), sub-acute/chronic patients, duration and frequency of intervention.

Acknowledgements

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References

1. Tong RK, Ng MF, Li LS. Effectiveness of gait training using an electromechanical gait trainer, with and without functional electric stimulation, in subacute stroke: a randomized controlled trial. Arch Phys Med Rehabil 2006;87(10):1298–304.
2. National Stroke Association, USA. Hemiparesis; [Internet]. [cited February 16, 2016]. Available from: http://www.stroke.org/we-can-help/survivors/stroke-recovery/post-stroke-conditions/physical/hemiparesis.
3. Intercollegiate Stroke Working Party. National clinical guideline for stroke. 4th ed. Royal College of Physicians; 2012
4. Gresham GE, Alexander D, Bishop DS, Giuliani C, Goldberg G, Holland A, *et al*. Rehabilitation. Stroke 1997;28(7):1522–6.
5. Van Peppen R, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? Clin Rehabil 2004;18(8):833–62.
6. French B, Thomas LH, Leathley MJ, Sutton CJ, McAdam J, Forster A, *et al*. Repetitive task training for improving functional ability after stroke. Cochrane Database Syst Rev 2007;(4):CD006073.
7. Whitall J. Stroke rehabilitation research: time to answer more specific questions? Neurorehabil Neural Repair 2004;18(1):3–11.
8. Takeuchi N, Izumi S. Rehabilitation with poststroke motor recovery: a review with a focus on neural plasticity. Stroke Res Treat 2013;2013:128641.
9. Yakub F, Md Khudzari AZ, Mori Y. Recent trends for practical rehabilitation robotics, current challenges and the future. Int J Rehabil Res 2014;37(1):9–21.
10. Masiero S, Poli P, Rosati G, Zanotto D, Iosa M, Paolucci S, *et al*. The value of robotic systems in stroke rehabilitation. Expert Rev Med Devices 2014;11(2):187–98.
11. Hesse S, Schmidt H, Werner C, Bardeleben A. Upper and lower extremity robotic devices for rehabilitation and for studying motor control. Curr Opin Neurol 2003;16(6):705–10.
12. Fazekas G. Robotics in rehabilitation: successes and expectations. Int J Rehabil Res 2013;36(2):95–6.
13. Chang WH, Kim MS, Huh JP, Lee PK, Kim YH. Effects of robot-assisted gait training on cardiopulmonary fitness in subacute stroke patients: a randomized controlled study. Neurorehabil Neural Repair 2012;26(4):318–24.
14. McCabe J, Monkiewicz M, Holcomb J, Pundik S, Daly JJ. Comparison of robotics, functional electrical stimulation, and motor learning methods for treatment of persistent upper extremity dysfunction after stroke: a randomized controlled trial. Arch Phys Med Rehabil 2015;96(6):981–90.
15. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, *et al*. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med 2010;2010(362):1772–83.
16. Hidler J, Nichols D, Pelliccio M, Brady K, Campbell DD, Kahn JH, *et al*. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair 2009;23(1):5.
17. Hsieh YW, Lin KC, Horng YS, Wu CY, Wu TC, Ku FL. Sequential combination of robot-assisted therapy and constraint-induced therapy in stroke rehabilitation: a randomized controlled trial. J Neurol 2014;261(5):1037–45.
18. Geroin C, Picelli A, Munari D, Waldner A, Tomelleri C, Smania N. Combined transcranial direct current stimulation and robot-assisted gait training in patients with chronic stroke: a preliminary comparison. Clin Rehabil 2011;25(6):537–48.
19. Ang KK, Guan C, Phua KS, Wang C, Zhou L, Tang KY, *et al*. Brain-computer interface-based robotic end effector system for wrist and hand rehabilitation: results of a three-armed randomized controlled trial for chronic stroke. Front Neuroeng 2014;7:30.
20. Brokaw EB, Nichols D, Holley RJ, Lum PS. Robotic therapy provides a stimulus for upper limb motor recovery after stroke that is complementary to and distinct from conventional therapy. Neurorehabil Neural Repair 2014;28(4):367–76.
21. Tanaka N, Saitou H, Takao T, Iizuka N, Okuno J, Yano H, *et al*. Effects of gait rehabilitation with a footpad-type locomotion interface in patients with chronic post-stroke hemiparesis: a pilot study. Clin Rehabil 2012;26(8):686–95.
22. Geroin C, Mazzoleni S, Smania N, Gandolfi M, Bonaiuti D, Gasperini G, *et al*. Systematic review of outcome measures of walking training using electromechanical and robotic devices in patients with stroke. J Rehabil Med 2013;45(10):987–96.
23. Klamroth-Marganska V, Blanco J, Campen K, Curt A, Dietz V, Ettlin T, *et al*. Three-dimensional, task-specific robot therapy of the arm after stroke: a multicentre, parallel-group randomised trial. Lancet Neurol 2014;13(2):159–66.
24. Feise RJ. Do multiple outcome measures require *P*-value adjustment? BMC Med Res Methodol 2002;2(1):8.

25. Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke (Review). Cochrane Database Syst Rev 2013;(7):CD006185.
26. Mehrholz J, Pohl M, Platz T, Kugler J, Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke (Review). Cochrane Database Syst Rev (11)2015.
27. Prange GB, Jannink MJA, Groothuis-Oudshoorn CGM, Hermens HJ, Ijzerman MJ. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. J Rehabil Res Dev 2006;43(2):171–84.
28. Chua J, Culpan J, Menon E. Efficacy of an electromechanical gait trainer poststroke in Singapore: a randomized controlled trial. Arch Phys Med Rehabil 2016;97(5):683–90.
29. Hsieh YW, Wu CY, Wang WE, Lin KC, Chang KC, Chen CC, *et al*. Bilateral robotic priming before task-oriented approach in subacute stroke rehabilitation: a pilot randomized controlled trial. Clin Rehabil 2016. [Epub ahead of print].
30. Orihuela-Espina F, Roldan GF, Sanchez-Villavicencio I, Palafox L, Leder R, Sucar LE, *et al*. Robot training for hand motor recovery in subacute stroke patients: a randomized controlled trial. J Hand Ther 2016;29(1):51–7.
31. Taveggia G, Borboni A, Mule C, Villafane JH, Negrini S. Conflicting results of robot-assisted versus usual gait training during postacute rehabilitation of stroke patients: a randomized clinical trial. Int J Rehabil Res 2016;39(1):29–35.
32. Vanoglio F, Bernocchi P, Mule C, Garofali F, Mora C, Taveggia G, *et al*. Feasibility and efficacy of a robotic device for hand rehabilitation in hemiplegic stroke patients: a randomized pilot controlled study. Clin Rehabil 2016. [Epub ahead of print].
33. Mizukami M, Yoshikawa K, Kawamoto H, Sano A, Koseki K, Asakwa Y, *et al*. Gait training of subacute stroke patients using a hybrid assistive limb: a pilot study. Disabil Rehabil Assist Technol 2016:1–8; [Epub ahead of print].
34. Dundar U, Toktas H, Solak O, Ulasli AM, Eroglu S. A comparative study of conventional physiotherapy versus robotic training combined with physiotherapy in patients with stroke. Top Stroke Rehabil 2014;21(6):453–61.
35. Canadian Partnership for Stroke Recovery. Fugl-Meyer assessment of sensorimotor recovery after stroke (FMA); [Internet]. [cited April 18, 2016]. Available from: http://www.strokengine.ca/indepth/fma_indepth/.
36. Collin C, Wade D. Assessing motor impairment after stroke: a pilot reliability study. J Neurol Neurosurg Psychiatry 1990;53(7):576–9.
37. Canadian Partnership for Stroke Recovery. Functional ambulation categories (FAC); [Internet]. [cited April 18, 2016]. Available from: http://www.strokengine.ca/indepth/fac_indepth/.
38. Canadian Partnership for Stroke Recovery. Barthel index (BI); [Internet]. [cited April 18, 2016]. Available from: http://www.strokengine.ca/indepth/bi_indepth/.
39. Canadian Partnership for Stroke Recovery. Functional independence measure (FIM); [Internet]. [cited April 18, 2016]. Available from: http://www.strokengine.ca/indepth/fim_indepth/.

Appendix I: Appraisal instruments

MAStARI appraisal instrument

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix II: Data extraction instruments

MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting

Population

Sample size

Group A _____ Group B _____

Interventions

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Chapter Three: Meta-regression Analysis (Paper Three - Published)

Paper 3: Lo K, Stephenson M, Lockwood C. Analysis of heterogeneity in a systematic review using meta-regression technique. International journal of evidence-based healthcare. 2019.

Statement of Contribution

Kenneth Lo (Candidate)

I was responsible for the overall creation of this paper. As the primary author, I developed the analysis concept, drafted the content, and structured the paper for journal submission. I was also responsible for responses to reviewers and revisions to the paper.

Statement of Authorship

Title of Paper	Analysis of heterogeneity in a systematic review using meta-regression technique.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Journal: International journal of evidence-based healthcare Citation: Lo K, Stephenson M, Lockwood C. Analysis of heterogeneity in a systematic review using meta-regression technique. International journal of evidence-based healthcare. 2019.

Principal Author

Name of Principal Author (Candidate)	Kenneth Lo		
Contribution to the Paper	I was responsible for the overall creation of this paper. As the primary author, I developed the analysis concept, drafted the content, and structured the paper for journal submission. I was also responsible for responses to reviewers and revisions to the paper.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	October 2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr. Matthew Stephenson		
Contribution to the Paper	Supervisor: provided conceptualization and methodological guidance to the manuscript. Contributed to the writing and revision of the paper, including responding to peer review comments, and reviewing the findings and conclusion.		
Signature		Date	October 2019

Name of Co-Author	Assoc. Prof. Craig Lockwood		
Contribution to the Paper	Supervisor: provided conceptualization and methodological guidance to the manuscript. Contributed to the writing and revision of the paper, including responding to peer review comments, and reviewing the findings and conclusion.		
Signature		Date	October 2019

Please cut and paste additional co-author panels here as required.

ORIGINAL RESEARCH

Analysis of heterogeneity in a systematic review using meta-regression technique

Kenneth Lo MEng, Matthew Stephenson PhD and Craig Lockwood PhD

The Joanna Briggs Institute, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia

ABSTRACT

Aim: Heterogeneity is an important consideration in systematic reviews, as high heterogeneity may imply that it is not suitable to perform meta-analysis. The degree of variation could be caused by clinical or methodological differences among the studies, or it could be due to the randomness of chance. Methods of assessing heterogeneity are calculating a statistical test for heterogeneity (the I^2 value), visual evaluations of forest plots, conducting subgroup analysis or meta-regression. We conducted meta-regression on data of our previous systematic review on the effectiveness of robotic rehabilitation, and in this article, we present the findings and discuss its implications.

Method: In our meta-regression plots, plotted on the *x*-axis was the trial covariate (duration of intervention group therapy), and plotted on the *y*-axis was the effect size measure (standardized mean differences), with positive effect sizes favouring robotic intervention. Analysis using random effects was applied, and each study symbol was sized in proportion to its precision (inverse-variance weighting).

Results: Differences were observed in the meta-regression plots between the subgroups of therapy ratio = 0 and therapy ratio more than 0 for upper limb movement, lower limb walking and activities of daily living. For upper limb movement, positive linear relationships were found for both subgroups. However, in terms of the strength of the relationship, a stronger relationship was found for therapy ratio = 0. For lower limb walking, opposing linear relationships were found in both subgroups: therapy ratio = 0 had a negative linear relationship, whereas therapy ratio more than 0 had a positive linear relationship. For activities of daily living, positive linear relationships were found for both subgroups, but a stronger linear relationship was found for therapy ratio = 0.

Conclusion: From the meta-regression analysis, we found that differing levels of linear relationships and the varying spread of effect sizes across positive and negative ranges were the likely sources of heterogeneity. This was especially so in the meta-regression of lower limb walking, which showed opposing directions of linear relationships. The wider spread of effect sizes for therapy ratio = 0 could indicate that some robotic devices were more effective than others. In addition, for therapy ratio more than 0, the effect sizes were mainly found in the positive region, which implied that adding conventional training to robotic training was generally positive for robotic devices.

Key words: Meta-analysis, meta-regression, robotic rehabilitation, stroke, systematic review

Int J Evid Based Healthc 2019; 17:000–000.

What is known about the topic?

- Meta-analysis is used in quantitative systematic reviews to statistically pool the results of outcome measures from across various studies to obtain an overall effect size.
- Heterogeneity is an important consideration as it affects the appropriateness of reporting a meta-analysis, and one method of assessing and exploring potential causes of heterogeneity is meta-regression.
- Meta-regression is a statistical technique for exploring the linear associations between trial covariates and the treatment effect. However, associations found in meta-regression cannot be regarded as being definitive proof of causality.

What does this article add?

- From the meta-regression analysis, we found that differing levels of linear relationships and the varying spread of effect sizes across positive and negative ranges were the likely sources of heterogeneity.
- The wider spread of effect sizes for therapy ratio = 0 could indicate that some robotic devices were more effective than others. This might highlight the need for research to identify what types of robotic devices were more effective.
- For therapy ratio more than 0, the effect sizes were mainly found in the positive region, which implied that adding conventional training to robotic training was generally positive for robotic devices, and it would be interesting to identify the optimal ratio of robotic training to conventional training, in terms of duration in a single therapy session.

Correspondence: Kenneth Lo, MEng, The Joanna Briggs Institute, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia. E-mail: kenneth.lo@adelaide.edu.au

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Background

Systematic reviews are used frequently in evidence-based healthcare to evaluate the effectiveness of interventions, and meta-analysis is used in quantitative systematic reviews to statistically pool the results of outcome measures from across various studies to obtain an overall effect size. During meta-analysis, the amount of variation in the characteristics between included studies is termed heterogeneity.[1] The amount of variation could be due to clinical or methodological differences among the studies, or it could be due to the randomness of chance.[2] Causes of clinical heterogeneity include differences in patient populations, intervention dosages, follow-up periods or outcome measures between the included studies.[2] Methodological heterogeneity is caused by including different types of study designs and quality issues in the included studies (such as presence of selection, performance, detection and attrition biases).[1,2]

Heterogeneity is an important consideration as it affects the appropriateness of reporting a meta-analysis. If included studies for review are clinically and methodologically heterogeneous, it may not be suitable to report a meta-analysis, or to limit reporting to the identification and exploration of the heterogeneity.[1,3] To estimate the level of heterogeneity in meta-analysis, a commonly applied statistical test for heterogeneity is I^2, whereby low, moderate and high levels of heterogeneity could be tentatively associated with calculated I^2 values of 25, 50 and 75%, respectively.[4] Other methods of assessing and exploring potential causes of heterogeneity include visual evaluations of forest plots and conducting subgroup analysis or meta-regression.[2,5]

Meta-regression is a statistical technique for exploring whether there is a linear association between trial covariates and the treatment effect, and also the direction of the association.[2] Associations found in meta-regression are useful for generating hypotheses of causes of heterogeneity but cannot be regarded as being definitive proof of causality.[2,6] In a meta-regression, one or more trial covariates are plotted against an outcome measure in a scatter plot to find the line of 'best fit' and show the direction of the association. In such a scatter plot, a circular symbol representing each study is plotted, in which the size of the circular symbol is proportional to the precision of the study, and a larger symbol is plotted for a study that has more precision (i.e. has less variance).[2,6]

In meta-regression, aggregate level data and not patient level data are used. Although both meta-regression and linear regression aim to explore linear associations between an independent variable and a dependant variable, in a meta-regression each study is a data point in the regression analysis, whereas in a typical clinical linear regression, each individual patient is a data point in the regression analysis.[2] When selecting the trial covariates, reviewers should also take note not to use too many covariates, as it may lead to a false positive conclusion when there are no true associations between covariates and the outcome measure.[2,6,7]

In our systematic review (the effectiveness of robotic rehabilitation on mobility and functional ability of adult stroke patients,[8] a random effects meta-analysis with 51 studies) moderate to high levels of heterogeneity were encountered. Consequently, we used meta-regression to explore the sources of heterogeneity. In this article, we present the results of our meta-regression analysis and discuss its implications to inform and contextualize the findings of our systematic review.

Meta-regression method

In our meta-regression plots, the duration (hours) of intervention group therapy was the trial covariate, which was plotted on the *x*-axis. This trial covariate was chosen because different therapy durations were applied in the studies, and this variability of durations facilitated the plotting of a meta-regression line. Another positive consideration was that the trials were dose-matched due to the inclusion criteria of the original systematic review (i.e. therapy duration was the same for both intervention and control groups), and this minimized the within-trial variation. The outcome measure used was standardized mean differences and these effect sizes were plotted on the *y*-axis, with positive effect sizes favouring the robotic intervention. The meta-regression line was plotted using a software package for meta-analysis (Comprehensive Meta Analysis Version 3 from Biostat, Inc., Frederick, Maryland, USA). Analysis using random effects was applied, and each study symbol was sized in proportion to its precision (inverse-variance weighting). The line started from the coordinate point (0,0), as there would be no effect sizes when duration of therapy was nil.

Results

During our systematic review conducted on the effectiveness of robotic rehabilitation,[8] we found moderate-to-high levels of heterogeneity for the outcomes of upper limb movement ($I^2 = 41\%$), lower limb walking ($I^2 = 75\%$) and activities of daily living (ADL) ($I^2 = 66\%$). As a first step, we undertook subgroup analysis to identify the sources of heterogeneity. One cause of heterogeneity was due to the range of outcome

Table 1. Subgroups analysed for heterogeneity

Analysis by outcome scales			
Upper limb movement	**No. of studies**	**I^2 values (%)**	**P values (Chi-squared test)**
Upper limb (all scales)	29	41	0.01
Upper limb [only FM (UL)]	25	36	0.04
Lower limb walking			
Lower limb (all scales)	15	75	<0.00001
Lower limb (only FAC measure)	10	82	<0.00001
ADL			
ADL (all scales)	31	66	<0.00001
ADL [FIM (total)]	4	71	0.01
ADL (BI)	3	72	0.03
ADL (MAL-QOM)	4	0	0.48
Analysis by therapy ratio			
Upper limb movement	**No. of studies**	**I^2 values (%)**	**P values (Chi-squared test)**
Upper limb (TR = 0)	16	48	0.02
Upper limb (TR > 0)	13	31	0.13
Lower limb walking			
Lower limb (TR = 0)	6	80	0.0001
Lower limb (TR > 0)	9	56	0.02
ADL			
ADL (TR = 0)	12	82	<0.00001
ADL (TR > 0)	19	25	0.15

ADL, activities of daily living; BI, Barthel index; FAC, functional ambulation category; FIM (total), functional independence measure (total); FM (UL), Fugl-Meyer (upper limb); MAL-QOM, motor activity log-quality of movement; TR, therapy ratio [TR = Duration of conventional training/Duration of robotic training. Intervention groups that had no conventional therapy component (i.e. TR = 0) and intervention groups that had a combination of both robotic and conventional therapies (i.e. TR > 0)].

scales used in the included studies to measure motor movement and ADL. Another cause was that, in the intervention group of some trials, the intervention therapy could be purely robotic training with no conventional component or mixed (i.e. a mix of robotic and conventional training). The results of the subgroup analysis performed in our previous systematic review are presented in Table 1.

We observed that for all the three outcomes examined (upper limb movement, lower limb walking and ADL), there was the same pattern of change in I^2, that is I^2 increased for subgroup therapy ratio = 0, whereas I^2 decreased for subgroup therapy ratio more than 0. In that review, we had hypothesized that for studies whereby therapy ratio was more than 0, the presence of conventional training, as part of the robotic intervention, 'masked' the effects of robotic training and gave these studies less clinical diversity. For those studies that had no conventional training as part of the robotic intervention, the different designs and types of robotic devices used could have caused a wider range of treatment effects, leading to higher I^2 values. Looking to further understand the sources of heterogeneity, we conducted meta-regression analysis. Presented here are the results of our meta-regression.

Upper limb movement (therapy ratio = 0)

Based on the line of 'best fit' (Fig. 1), the meta-regression analysis showed a positive linear relationship between duration of therapy and effect size, that is, as therapy duration increased, the effect sizes trend towards more positive values. Looking at the scatter plot, there was a spread of effects sizes with about equal numbers of studies that had negative and positive effect sizes.

Upper limb movement (therapy ratio >0)

Based on the line of 'best fit' (Fig. 2), the meta-regression analysis showed a positive linear relationship between duration of therapy and effect size. As therapy duration increased, the effect sizes trend towards more positive values. Looking at the scatter plot, the spread of effect sizes was more in the positive range, with more studies that had positive effect sizes.

One study (McCabe *et al.*[9]) was excluded as its intervention therapy duration was 300 h, which was an outlier and would have skewed the plot.

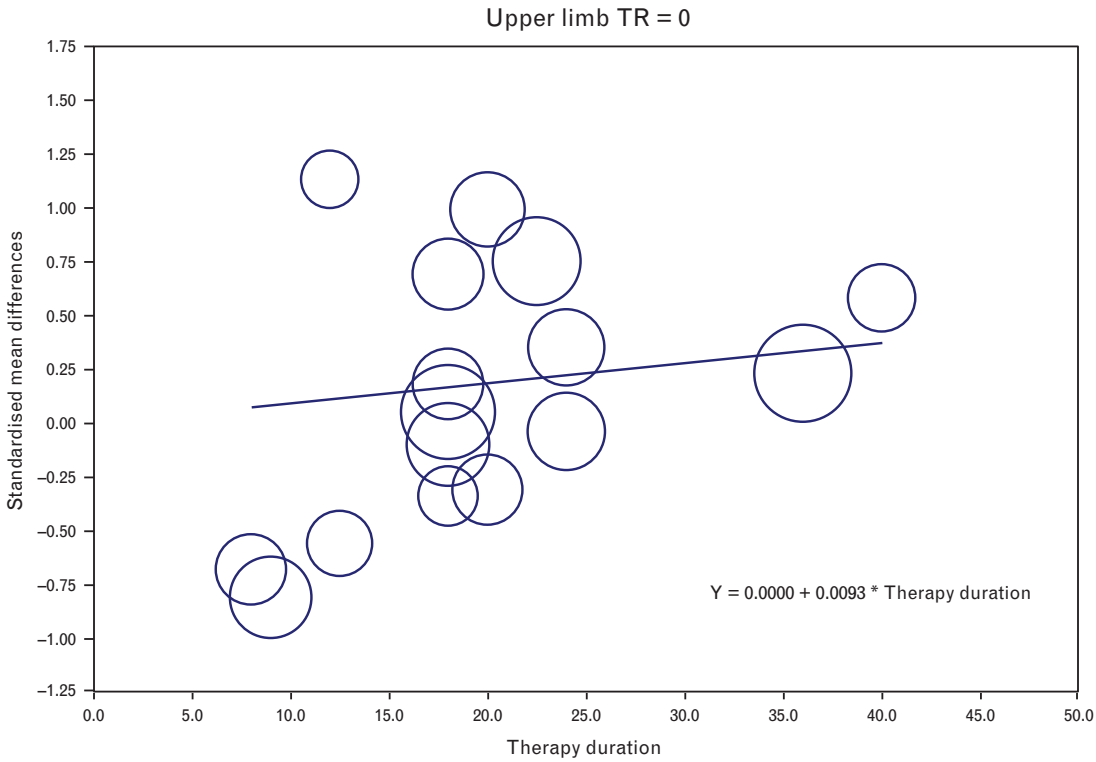

Figure 1. Meta-regression plot of upper limb (therapy ratio = 0).

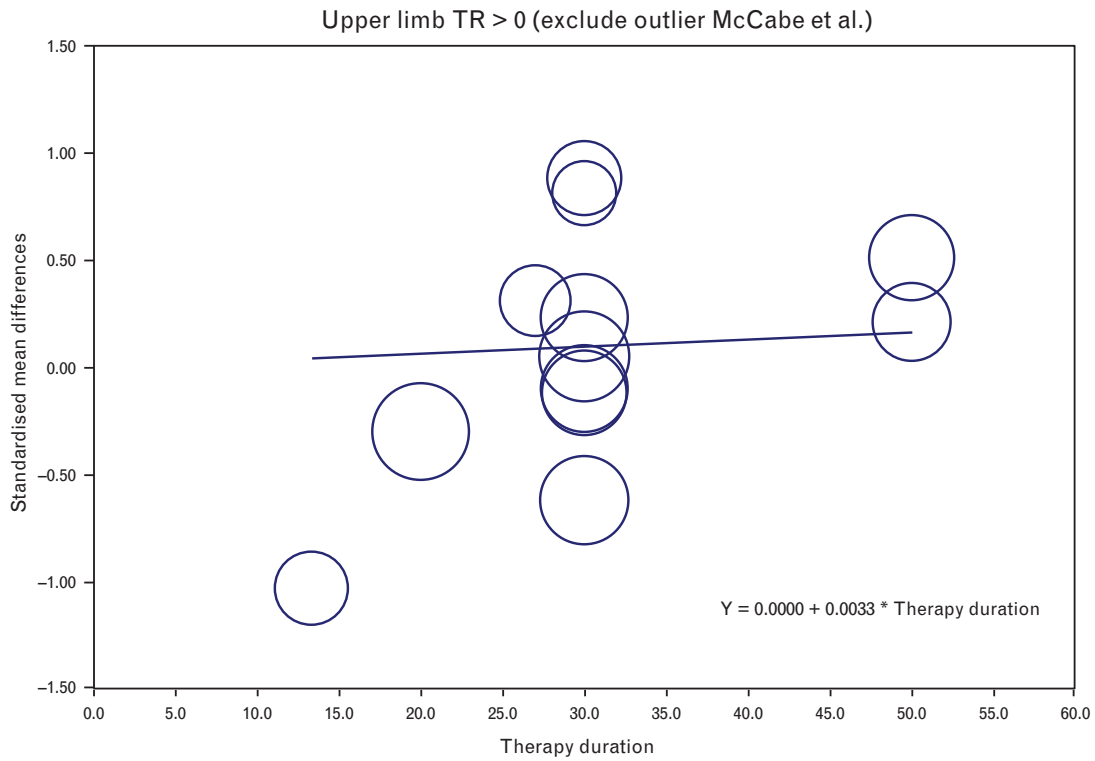

Figure 2. Meta-regression plot of upper limb (therapy ratio >0).

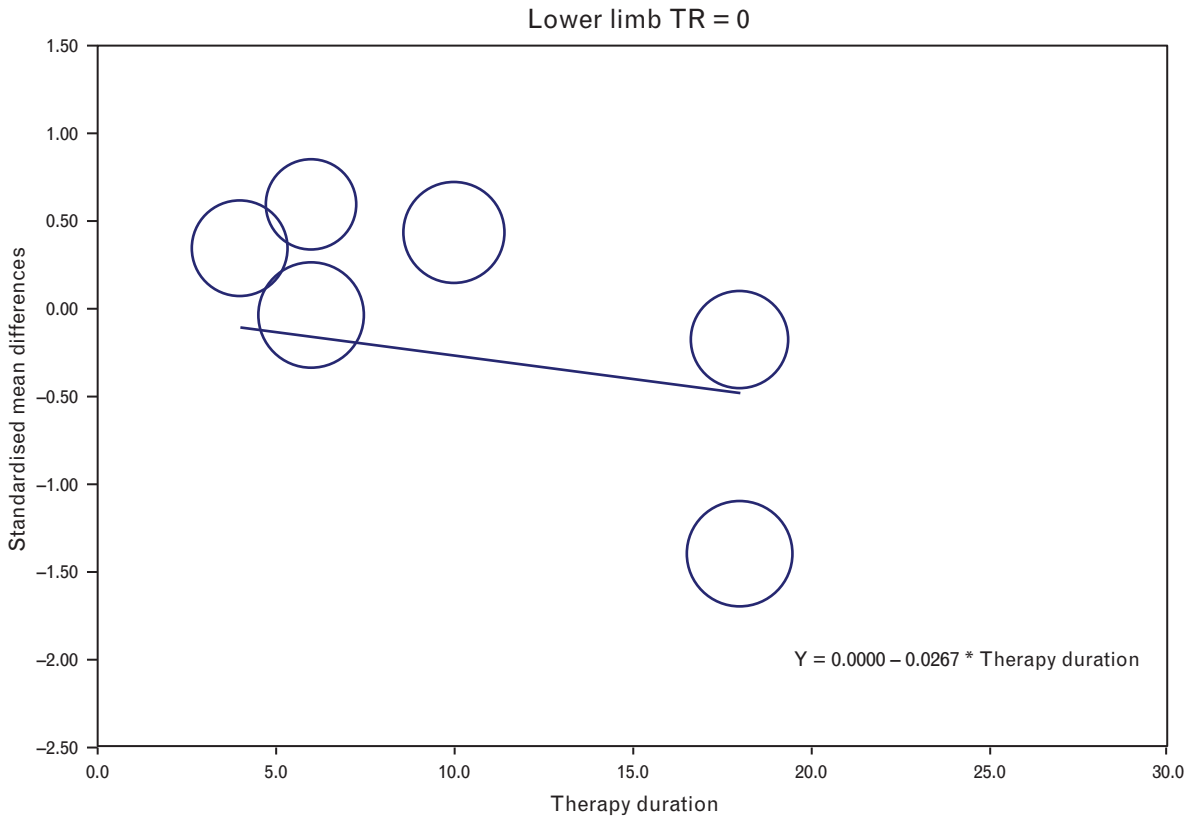

Figure 3. Meta-regression plot of lower limb (therapy ratio = 0).

Lower limb walking (therapy ratio = 0)

Based on the line of 'best fit' (Fig. 3), the meta-regression analysis showed a negative linear relationship between duration of therapy and effect size. As therapy duration increased, the effect sizes trend towards more negative values. Looking at the scatter plot, there was a spread of effects sizes with equal numbers of studies that had negative and positive effect sizes.

Lower limb walking (therapy ratio >0)

Based on the line of 'best fit' (Fig. 4), the meta-regression analysis showed a positive linear relationship between duration of therapy and effect size. As therapy duration increased, the effect sizes trend towards more positive values. Looking at the scatter plot, the spread of effect sizes was more in the positive range, with more studies that had positive effect sizes.

Activities of daily living (therapy ratio = 0)

Based on the line of 'best fit' (Fig. 5), the meta-regression analysis showed a positive linear relationship between duration of therapy and effect size. As therapy duration increased, the effect sizes trend towards more positive values. Looking at the scatter plot, there was a spread of effects sizes with about equal numbers of studies that had negative and positive effect sizes.

Activities of daily living (therapy ratio >0)

Based on the line of 'best fit' (Fig. 6), the meta-regression analysis showed a positive linear relationship between duration of therapy and effect size. As therapy duration increased, the effect sizes trend towards more positive values. Looking at the scatter plot, the spread of effect sizes was more in the positive range, with more studies that had positive effect sizes.

One study was excluded as its intervention therapy duration was 300 h, which was an outlier and would have skewed the plot.[9]

Sensitivity analysis

A sensitivity analysis was conducted for meta-regression plots by including the outlier study of McCabe *et al.*[9] For upper limb, a slight negative relationship was shown (Fig. 7), while for ADL, no relationship was shown (Fig. 8).

We also conducted a sensitivity analysis for meta-regression plots with an intercept. The meta-regression

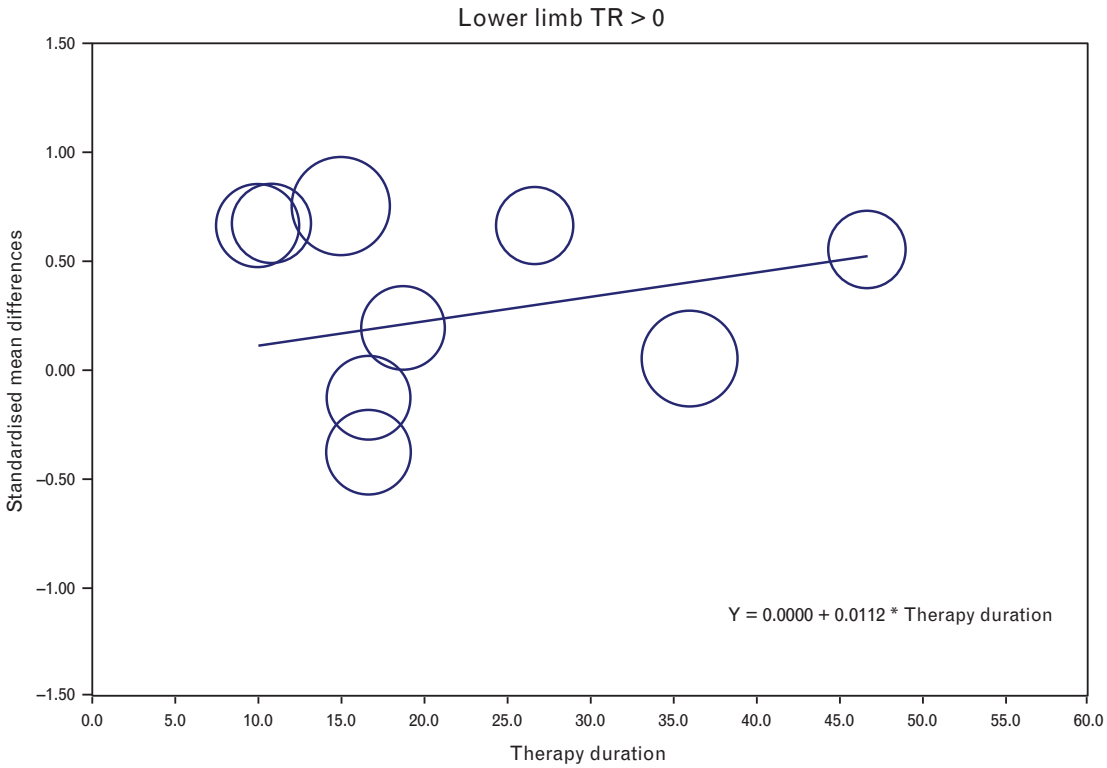

Figure 4. Meta-regression plot of lower limb (therapy ratio >0).

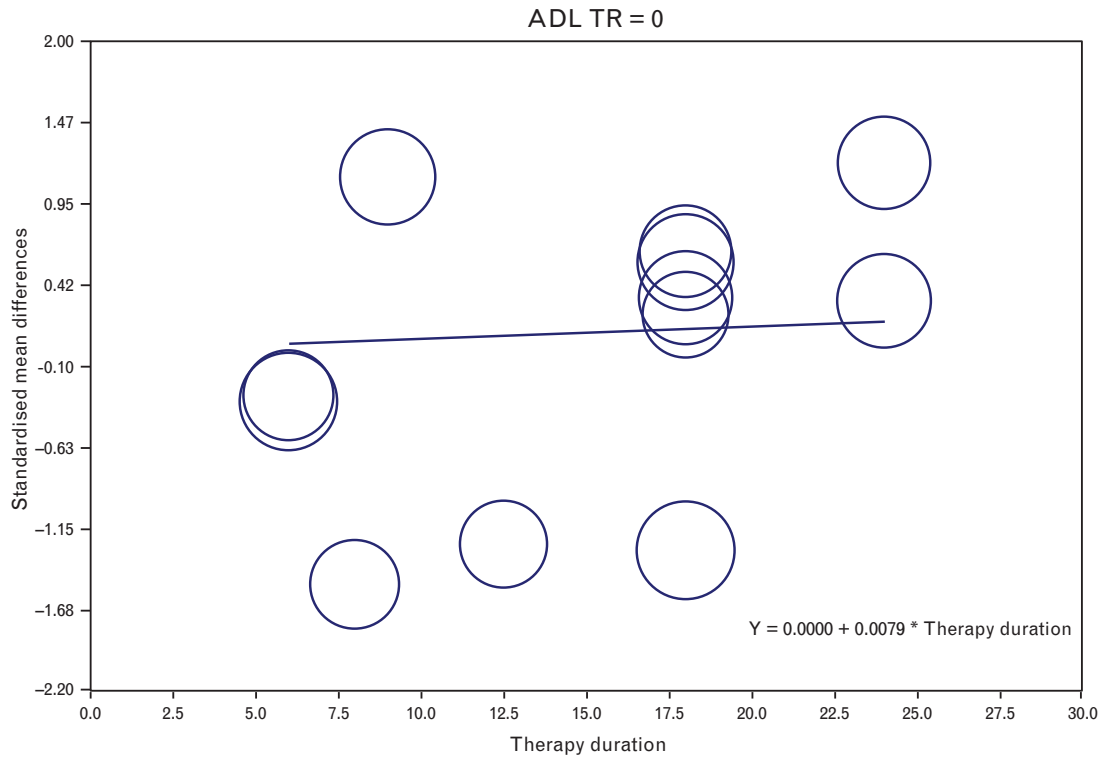

Figure 5. Meta-regression plot of activities of daily living (therapy ratio = 0).

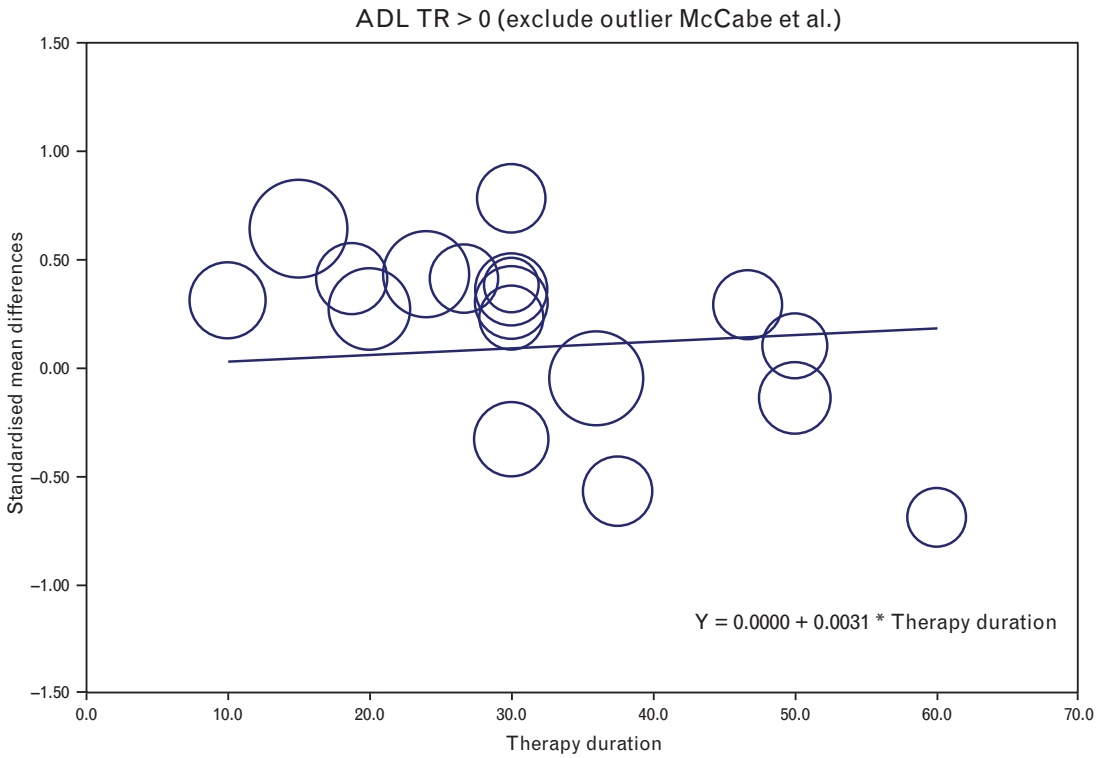

Figure 6. Meta-regression plot of activities of daily living (therapy ratio >0).

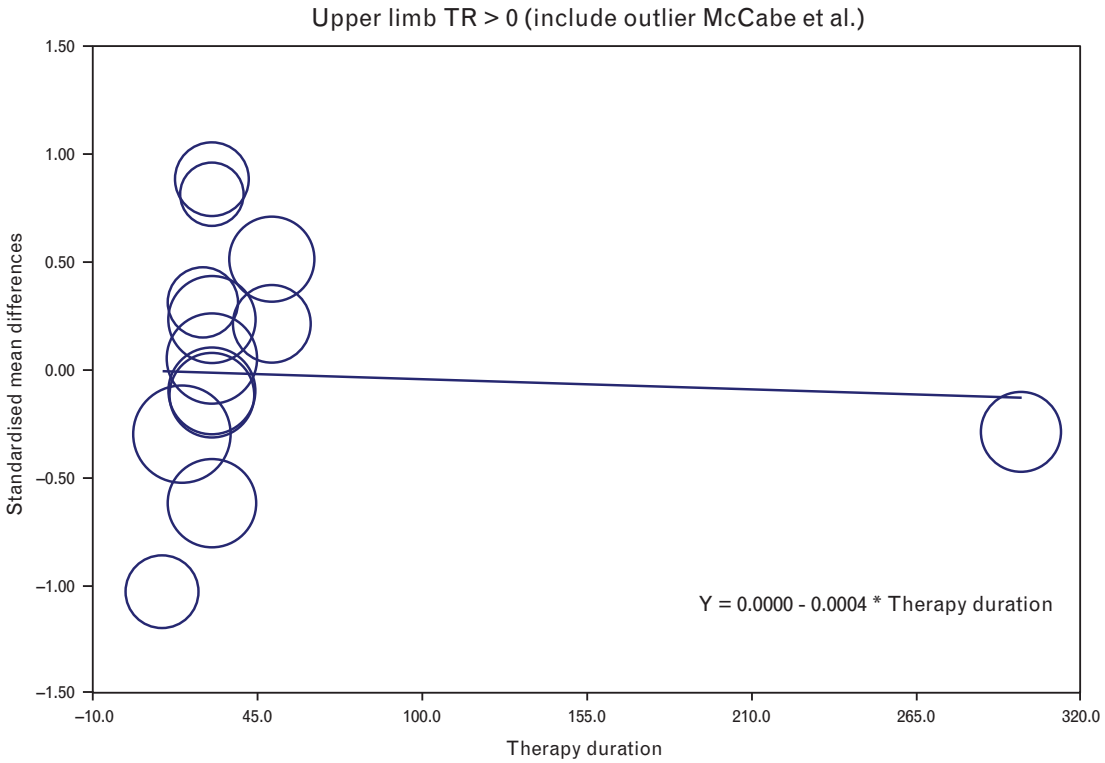

Figure 7. Plot of upper limb (therapy ratio >0) including outlier McCabe *et al.*[9]

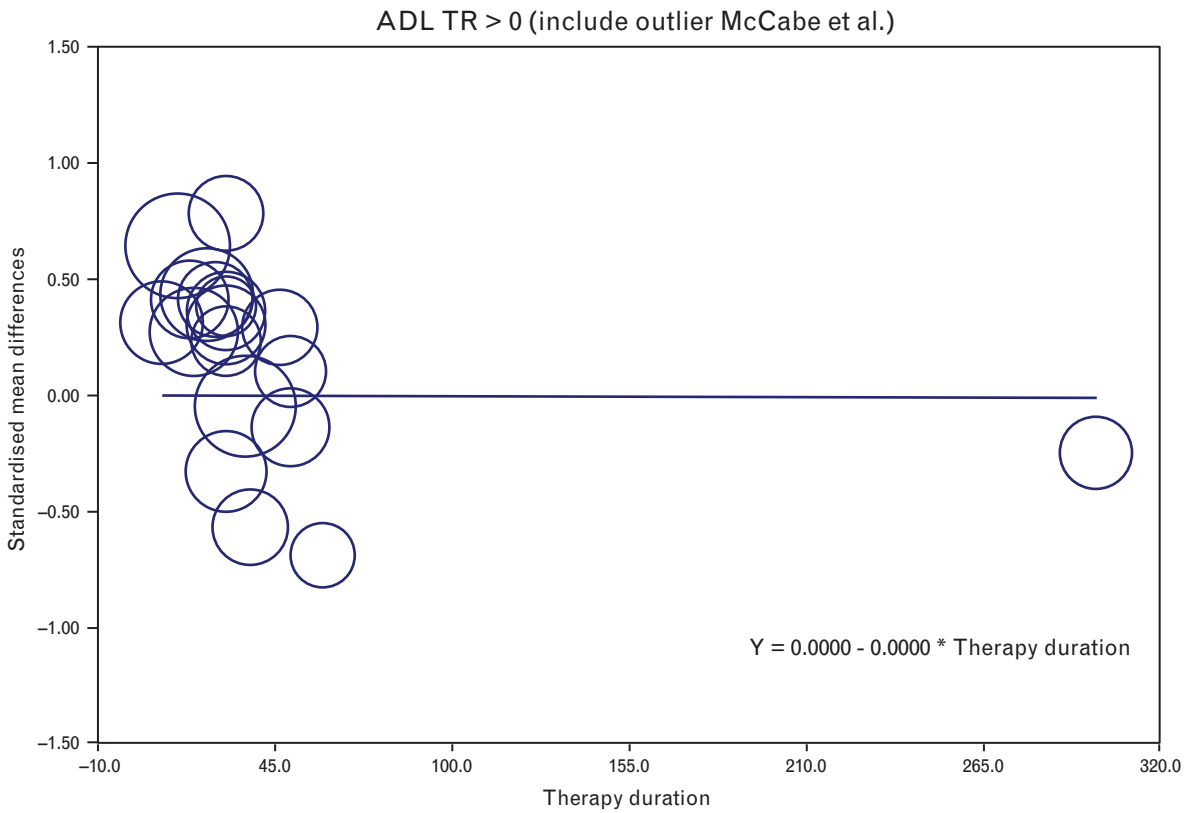

Figure 8. Plot of activities of daily living (therapy ratio >0) including outlier McCabe *et al.*[9]

scatter plots presented in Figures 1–8 did not include an intercept, as we had considered that when there was no therapy (i.e. when therapy duration was nil), there should not be any effect sizes.

Under the sensitivity analysis, for upper limb movement, a positive linear relationship was still observed for both therapy ratio = 0 and therapy ratio more than 0, whereby a stronger relationship was found for therapy ratio = 0. This was similar to the trends observed in the main analysis. For lower limb walking, a negative relationship was still observed for therapy ratio = 0, but for therapy ratio more than 0, a slight negative relationship was found. This was in contrast to the positive relationship found for therapy ratio more than 0 in the main analysis. For ADL, therapy ratio = 0 had a positive relationship but therapy ratio more than 0 had a negative relationship. This finding was different from the main analysis, which showed positive relationships for both subgroups.

When the outlier study, McCabe *et al.*, was included for upper limb therapy ratio more than 0, a slight negative relationship was observed, which was similar to the main analysis. For ADL, the inclusion of McCabe *et al.* showed a negative relationship, instead of no relationship that was observed under the main analysis. Table 2 shows the line equations of the meta-regression analysis with an intercept.

Discussion

We conducted meta-regression to investigate sources of heterogeneity and, from the analysis, we could see differences in the meta-regression plots between the subgroups of therapy ratio = 0 and therapy ratio more than 0 for upper limb movement, lower limb walking and ADL.

Upper limb movement

In terms of the linear relationship seen in subgroups of therapy ratio = 0 and therapy ratio more than 0, we found positive relationships for both subgroups. However, in terms of the strength of the relationship, a stronger relationship was found for therapy ratio = 0, as seen by the line equations. Looking at therapy duration of 50 h, the effect size was 0.465 for therapy ratio = 0, but for therapy ratio more than 0 the corresponding effect size was less at 0.165. Viewing the scatter

Table 2. Line equations of meta-regression with an intercept

	TR = 0	TR > 0
Upper limb movement	$Y = -0.4516 + 0.0281 \times$ therapy duration	$Y = -0.8287 + 0.0274 \times$ therapy duration
Lower limb walking	$Y = 0.8432 - 0.0894 \times$ therapy duration	$Y = 0.4130 - 0.0039 \times$ therapy duration
Activities of daily living	$Y = -0.8504 + 0.0563 \times$ therapy duration	$Y = 0.8186 - 0.0204 \times$ therapy duration
Lower limb walking (including McCabe *et al.*[9])	Not applicable	$Y = 0.0389 - 0.0007 \times$ therapy duration
Activities of daily living (including McCabe *et al.*[9])	Not applicable	$Y = 0.3033 - 0.0026 \times$ therapy duration

TR, therapy ratio.

plots of both subgroups, there was a wider spread of effect sizes in therapy ratio = 0, as compared with therapy ratio more than 0, which had mainly positive effect sizes. The moderately high heterogeneity of upper limb movement ($I^2 = 41\%$) was likely due to these differences found between the meta-regression plots of therapy ratio = 0 and therapy ratio more than 0.

It is also to note that in subgroup therapy ratio = 0, the stronger linear relationship could mean more pronounced shifts in effect sizes across studies and, coupled with a wider spread of effect sizes across both positive and negative ranges, implied that some trials (and its associated robotic devices) were more effective than others. Future research could potentially examine the effectiveness of robotic rehabilitation based on different types of robotic devices, for example the effectiveness of end-effector robotics compared with exoskeleton devices.

Lower limb walking

In terms of the linear relationship seen in subgroups of therapy ratio = 0 and therapy ratio more than 0, we found opposing relationships in both subgroups: therapy ratio = 0 had a negative linear relationship, whereas therapy ratio more than 0 had a positive linear relationship. Viewing the scatter plots of both subgroups, again there was a wider spread of effect sizes in therapy ratio = 0, whereas in therapy ratio more than 0, the effect sizes were mainly in the positive range. The opposite directions of linear relationships and the wider spread of effect sizes for therapy ratio = 0 very likely explained the high heterogeneity seen in lower limb walking, which had an I^2 value of 75%.

The contrasting relationships found between therapy ratio = 0 and therapy ratio more than 0 was unexpected, especially a negative relationship for therapy ratio = 0. One possibility was that there might not be a linear relationship but a quadratic relationship between therapy duration and effect sizes for therapy ratio = 0 (Fig. 9). It might be that, up to a certain therapy duration, robotic training was more effective than conventional training, and beyond this point, robotic training progressively became less effective than conventional training. It could be hypothesized that at the beginning, robotic devices could provide more training repetitions and improve the motor movement ability of a patient. However, as a patient gradually regained his motor movement skills over time, his walking speed might exceed that of the robotic device, which would then limit the training effectiveness. This limit on training progress was also discussed in a trial on lower limb robotic training,[10] in which the authors found that conventional training had better outcomes than robotic training, and one of the reasons discussed was due to the speed of robotic training. In the trial, the lower limb robotic device allowed a maximum walking speed up to 3 km/h and the authors postulated that this limited the training potential when patients were able to walk faster than 3 km/h. As conventional training allowed for overground walking without speed restriction, patients could train to walk up to higher self-selected walking speeds.

It might be insightful to conduct trials to examine the dose–response relationship for patients using lower limb robotic devices to determine the true relationship between intervention therapy duration and effect size. To avoid confounding due to impairment levels of patients, it might be suitable to measure the progress for severely impaired patients, who would have a lower base to start with. This would help to answer if there was a transition point beyond which stroke patients ought to progress from robotic to conventional training.

Activities of daily living

In terms of the linear relationship seen in subgroups of therapy ratio = 0 and therapy ratio more than 0, we found positive relationships for both subgroups. However, in terms of the strength of the relationship, a stronger relationship was found for therapy ratio = 0, as seen by the line equations. Looking at therapy duration of 25 h, the effect size was 0.1975 for therapy ratio = 0, but for therapy ratio more than 0 the corresponding effect size was less at 0.0775. Viewing the

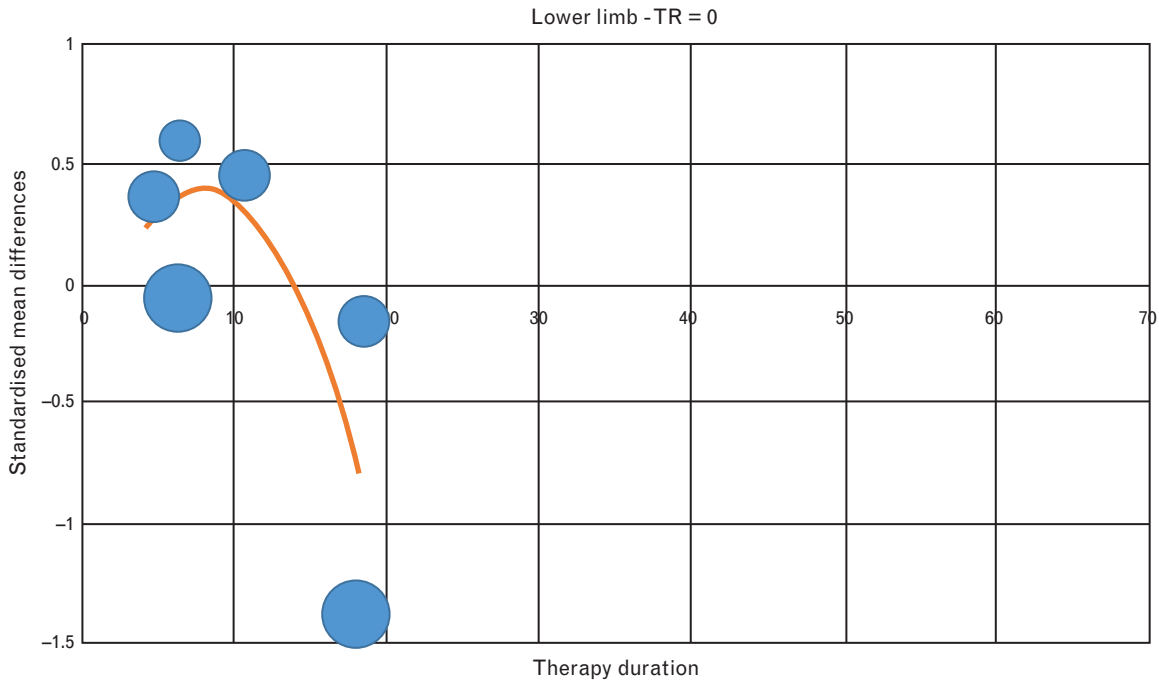

Figure 9. Hypothetical quadratic plot of lower limb (therapy ratio = 0).

scatter plots of both subgroups, there was a wider spread of effect sizes in therapy ratio = 0, as compared with therapy ratio more than 0, which had mainly positive effect sizes. These differences likely explained the moderately high heterogeneity for ADL, which had an I^2 of 66%.

In subgroup therapy ratio = 0, the stronger linear relationship could mean more pronounced shifts in effect sizes across studies and, coupled with a wider spread of effect sizes across both positive and negative ranges, similarly implied that some trials (and its associated robotic devices) were more effective than others. Again, future research could potentially examine the effectiveness of robotic rehabilitation based on different types of robotic devices.

Spread of effect sizes

In therapy ratio more than 0, the effect sizes were mainly found in the positive region, which favoured the intervention for robotic devices. This was in contrast to therapy ratio = 0, which showed a wider spread of effect sizes across positive and negative values. This probably implied that adding conventional training to robotic training was generally positive for robotic devices and it would be interesting to identify the optimum ratio of robotic training to conventional training in terms of duration in a single therapy session.

Limitations

One limitation was that aggregate level data were used. In our meta-regression, therapy duration was the trial covariate and this might not reflect the actual therapy duration of each patient, and could lead to aggregation bias.[6] It was likely that the duration of therapy varied according to patients, depending on their individual capacity to tolerate training and the amount of rest breaks needed. That the data for our meta-regression analysis came from aggregated data of the meta-analysis also limited the test of homoscedasticity assumptions, due to lack of individual patient data. In a linear regression with nonaggregated data, homo/heteroscedasticity could be explored. If the spread of values of the dependent variable is consistent across all values of an independent variable in a scatter plot of residuals, then a linear regression plot line would be representative of the data.[11] However, in meta-regression, aggregated data is used. Nevertheless, Higgins and Thompson[7] investigated the error rates of meta-regression in various situations in which the authors had considered sample sizes, number of covariates, and the extent of collinearity among the covariates; and found that 'all random effects meta-regression methods performed well on single covariates when the number of studies is large' (page 1679). In our meta-regression, we had a large number of studies (51 studies) and only one covariate (therapy

duration) was investigated. Hence, we would consider the use of random-effects meta-regression in our analysis to be appropriate.

Another limitation was that the use of the intervention therapy duration as trial covariate was not prespecified in our systematic review protocol.[6] Preferably, it should have been prespecified but at the time of drafting the protocol, we had only considered using subgroups for analysis of heterogeneity. Despite this, we believed the trial covariate chosen for our meta-regression analysis was appropriate, as a range of therapy durations were used across different studies. This allowed us to have variability of therapy durations across studies, which made it easier to interpret our results.[6]

Although the use of therapy duration as a trial covariate facilitated discussions of the dose–response relationship in the analysis of lower limb walking, we would hesitate to draw any firm understanding, as the plot was based on aggregated data and could be confounded by other within-trial or patient characteristics. Furthermore, none of the lower limb trials in the systematic review had examined the relationship between therapy dose and treatment effect, which would otherwise have offered some direct evidence.

Sensitivity analysis

Inclusion of outlier study

We had excluded the trial by McCabe *et al.*,[9] as its intervention therapy duration was 300 h, which, if included, would have 'bunched up' the other plots (Fig. 7) and render plotting the meta-regression line not so meaningful. Nevertheless, if McCabe *et al.*[9] were to be included for upper limb therapy ratio more than 0, its inclusion would have led to showing that there was a negative relationship between therapy duration and effect size. This would have been a starker contrast to the positive relationship seen for therapy ratio = 0 and would have reinforced our analysis of heterogeneity instead. This was also the case for the analysis of ADL therapy ratio more than 0 (Fig. 8). The inclusion of McCabe *et al.*[9] led to showing that there was no relationship between therapy duration and effect size, which was, again, a starker contrast to the positive relationship seen for therapy ratio = 0.

Meta-regression analysis with an intercept

The meta-regression scatter plots presented in the main analysis did not include an intercept, and to understand the differences, we conducted a parallel analysis assuming that there was an intercept. Under this parallel analysis, we found differences in the trends of relationships for the outcomes of lower limb walking and ADL.

For lower limb walking, therapy ratio = 0 showed a negative relationship, but for therapy ratio more than 0 a slight negative relationship was found. This was in contrast to the positive relationship found for therapy ratio more than 0 in the main analysis. Nevertheless, the difference in slope coefficients between therapy ratio = 0 and therapy ratio more than 0 of the parallel analysis still accounted for the heterogeneity. For ADL, therapy ratio = 0 had a positive relationship but therapy ratio more than 0 had a negative relationship. This finding was different from the main analysis, which showed positive relationships for both subgroups. However, that therapy ratio = 0 and therapy ratio more than 0 had opposite relationships still explained the heterogeneity.

When the outlier study, McCabe *et al.*,[9] was included under the parallel analysis, a slight negative relationship was observed for upper limb therapy ratio more than 0, which still contrasted to the more negative relationship of therapy ratio = 0. Similarly for ADL, the inclusion of McCabe *et al.*[9] showed a negative relationship, which still contrasted to the positive relationship for therapy ratio = 0.

Overall, the differences observed in the relationships between therapy ratio = 0 and therapy ratio more than 0 (within the meta-regression plots with an intercept) still served to explain the heterogeneity, although the trends of the relationships were somewhat different from the meta-regression plots without an intercept.

Conclusion

We used the technique of meta-regression to understand the moderate to high heterogeneity levels seen in outcomes of upper limb movement, lower limb walking and ADL. From the meta-regression analysis, we found that differing levels of linear relationships and the varying spread of effect sizes across positive and negative ranges were the likely sources of heterogeneity. This was especially so in the meta-regression of lower limb walking, which showed opposing directions of linear relationships.

The wider spread of effect sizes for therapy ratio = 0 could indicate that some robotic devices were more effective than others. This might highlight the need for research to identify what types of robotic devices were more effective. In addition, for therapy ratio more than 0, the effect sizes were mainly found in the positive region, which implied that adding conventional training to robotic training was generally positive for robotic devices and it would be interesting to identify the optimal ratio of robotic training to conventional training, in terms of duration in a single therapy session.

Acknowledgements

Conflicts of interest

The authors report no conflicts of interest.

References

1. The Joanna Briggs Institute; The University of Adelaide. The systematic review of evidence generated through quantitative research – study guide. Adelaide: Joanna Briggs Institute; 2013
2. Baker WL, White CM, Cappelleri JC, *et al*. Understanding heterogeneity in meta-analysis: the role of meta-regression. *Int J Clin Pract* 2009; 63: 1426–34.
3. Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. *Int J Evid Based Healthc* 2015; 13: 196–207.
4. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–60.
5. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *J Health Serv Res Policy* 2002; 7: 51–61.
6. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002; 21: 1559–73.
7. Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. *Stat Med* 2004; 23: 1663–82.
8. Lo K, Stephenson M, Lockwood C. Effectiveness of robotic assisted rehabilitation for mobility and functional ability in adult stroke patients: a systematic review. *JBI Database System Rev Implement Rep* 2017; 15: 3049–91.
9. McCabe J, Monkiewicz M, Holcomb J, *et al*. Comparison of robotics, functional electrical stimulation, and motor learning methods for treatment of persistent upper extremity dysfunction after stroke: a randomized controlled trial. *Arch Phys Med Rehabil* 2015; 96: 981–90.
10. Hidler J, Nichols D, Pelliccio M, *et al*. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. *Neurorehabil Neural Repair* 2009; 23: 5–13.
11. Rosopa PJ, Schaffer MM, Schroeder AN. Managing heteroscedasticity in general linear models. *Psychol Methods* 2013; 18: 335–51.

Chapter Four: Economic Systematic Review (Paper Four and Five – Published)

Paper 4: Lo K, Stephenson M, Lockwood C. The economic cost of robotic rehabilitation for adult stroke patients: a systematic review. JBI Database System Rev Implement Rep. 2019;17(4):520-47.

Paper 5: Lo K, Stephenson M, Lockwood C. The economic cost of robotic rehabilitation for adult stroke patients: a systematic review protocol. JBI Database System Rev Implement Rep. 2018;16(8):1593-8.

Statement of Contribution

Kenneth Lo (Candidate)

I was responsible for the overall creation of this paper. As the primary author I developed the protocol, conducted the literature searches, retrieved papers, and assessed each paper for their eligibility. I subsequently undertook critical appraisal, data extraction and data analysis. I was also responsible for responses to reviewers and revisions to the paper. The review was conducted using tools provided by the Joanna Briggs Institute.

Statement of Authorship

Title of Paper	The economic cost of robotic rehabilitation for adult stroke patients: a systematic review.
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Journal: JBI Database of Systematic Reviews and Implementation Reports Citation: Lo K, Stephenson M, Lockwood C. The economic cost of robotic rehabilitation for adult stroke patients: a systematic review. JBI Database System Rev Implement Rep. 2019;17(4):520-47.

Principal Author

Name of Principal Author (Candidate)	Kenneth Lo		
Contribution to the Paper	I was responsible for the overall creation of this paper. As the primary author I developed the protocol, conducted the literature searches, retrieved papers, and assessed each paper for their eligibility. I subsequently undertook critical appraisal, data extraction and data analysis. I was also responsible for responses to reviewers and revisions to the paper. The review was conducted using tools provided by the Joanna Briggs Institute.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	October 2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr. Matthew Stephenson		
Contribution to the Paper	Supervisor: provided conceptualization and methodological guidance to the manuscript. Contributed to the writing and revision of the paper, including responding to peer review comments, and reviewing the findings and conclusion.		
Signature		Date	October 2019

Name of Co-Author	Assoc. Prof. Craig Lockwood		
Contribution to the Paper	Supervisor: provided conceptualization and methodological guidance to the manuscript. Contributed to the writing and revision of the paper, including responding to peer review comments, and reviewing the findings and conclusion.		
Signature		Date	October 2019

Please cut and paste additional co-author panels here as required.

The economic cost of robotic rehabilitation for adult stroke patients: a systematic review

Kenneth Lo[1,2,3] • Matthew Stephenson[1] • Craig Lockwood[1]

[1]Joanna Briggs Institute, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, Australia, [2]College of Medicine and Public Health, Flinders University, Adelaide, Australia, and [3]Australian Institute of Health Innovation, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia

ABSTRACT

Objective: The objective of this review was to examine the economic cost of robotic therapy compared to conventional therapy for adult stroke patients, from the perspective of hospitals.

Introduction: It is important to identify appropriate treatment methods that not only reduce the disability experienced by stroke survivors but also do so cost effectively. While robotic devices enable a high-intensity training regime for patients, robotic training equipment involves a significant capital outlay for healthcare providers. Hence, the decision to introduce robotic devices into clinical settings and offer robotic stroke rehabilitation to patients has an important cost consideration for hospitals.

Inclusion criteria: This review included rehabilitation trials of adult stroke patients (18 years and older) involving robotic devices and comparing the economic outcomes to control groups that used conventional physiotherapy.

Methods: We searched major databases such as PubMed, Embase and CINAHL for trial studies conducted from year 2000 and published in English. Included studies were critically appraised, and data were extracted and synthesized using the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI).

Results: Five studies with 213 patients were included in this review. Four studies examined upper limb interventions, and one study evaluated both upper limb and lower limb interventions. Of the five studies, two included acute/sub-acute patients and three included chronic patients. The overall methodological quality of the studies was of a moderate level. The included studies compared the cost of providing robotic intervention against the cost of providing conventional therapy in dose-matched therapy sessions and computed the cost measures in terms of cost per patient session or cost per patient. We performed a cost comparison of the various studies and reviewed the data based on two approaches: the dominance ranking framework and the dominance ranking score. By comparing the cost outcome of each study, four of the five studies showed better cost benefits for the robotic intervention group. Under the dominance ranking framework and the dominance ranking score, the overall dominance levels for most sub-groups favored robotic intervention.

Conclusions: Our review indicated that robotic therapy had a better economic outcome than conventional therapy. For patients with severe disability from significant stroke, a moderate dominance favoring robotic therapy for health benefit was found, and a strong dominance for robotic therapy for cost benefit was found. However, the limited number of studies in the review required us to view the results with caution. Key sensitivity factors affecting robotic therapy were the number of patients who could be treated per robotic session and the time therapists spent with patients during a robotic session. Robotic therapy could be prescribed primarily for patients with severe impairment after stroke. To maximize the cost economics, hospital providers may wish to organize their robotic therapy programs based on cost-sensitivity factors. For further research, we suggest better collaboration in methods within this field to enable a more comparable cost computation across studies.

Keywords Cost; economic; robotic rehabilitation; stroke; systematic review

JBI Database System Rev Implement Rep 2019; 17(4):520–547.

Correspondence: Kenneth Lo, kenneth.lo@flinders.edu.au

There is no conflict of interest in this project.

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Introduction

Stroke is a leading cause of disability. Each year, 15 million people suffer a stroke.[1] It is important to identify appropriate treatment methods that not only reduce the disability of stroke survivors but also do so cost effectively. Systematic reviews conducted on robotic training devices for stroke rehabilitation have shown varying degrees of clinical effectiveness. One systematic review assessing lower limb outcomes found that robotic-assisted gait training increased the odds of participants walking independently.[2] For the sub-group of patients with severe impairment, the findings indicated that robotic treatment was more effective.[2] In terms of upper limb outcomes, two systematic reviews found that robot-assisted arm training improved arm motor movement[3,4] and activities of daily living scores.[3] A recent systematic review found that robotic training was as effective as conventional physiotherapy for upper limb motor movement, lower limb walking and activities of daily living, but for patients with severe lower limb impairment, robotic training was found to be more effective than conventional training.[5] Overall, these reviews showed that robotic devices, at a minimum, offered equivalent treatment outcomes as conventional physiotherapy.

Traditionally, stroke patients undergo rehabilitation post stroke. For physical impairments, patients usually receive conventional physiotherapy, which involves repetitive, high-intensity, task-specific exercises that enable them to regain their motor and functional abilities.[6,7] Neuroplasticity is the underlying principle of motor learning and is associated with a reorganization of the undamaged motor cortex to enable recovery of motor abilities of the affected limbs[8] via repetitive, high-intensity, task-specific exercises to the limbs.[9] To facilitate the high number of repetitions required, robotic devices have been used to assist therapists.[10] These devices provide intensive, consistent and repetitive cycles over long periods to train the impaired limbs of patients. There are two main types of robotic devices: exoskeletons and end-effectors. Exoskeletons are devices that wrap around limbs and are able to assist each limb joint to move. End-effectors are devices that assist only the extremities of a limb (either hands or feet).[11] Regardless of design mechanism, one key feature of robotic devices is the ability to automatically assist patients to move their limbs when they are unable to do so by themselves. This automated assistive feature enables a high number of repetitions to be achieved.

While robotic devices enable a high-intensity training regime that can be as effective as conventional therapy, the robotic training equipment can cost up to several hundred thousand dollars per device,[12] which is a significant capital outlay for healthcare providers. Hence, the decision to introduce robotic devices into clinical settings and offer robotic stroke rehabilitation to patients has an important cost consideration for hospitals. Despite the cost, robotic devices may increase the work efficiency of therapists, meaning that more patients can be treated, leading to an overall reduction in cost of treatment per patient.[13,14] There have been clinical studies to determine the economic cost of robotic devices in the rehabilitation of stroke patients.[15] However, these studies presented a mixed picture of the cost impact of robotic devices. One study that compared the cost-effectiveness of robotic rehabilitation with conventional rehabilitation had an uncertain finding,[16] while another study found that robotic devices were economically sustainable.[17] A third study compared the treatment costs and found that robotic training was less expensive than conventional training.[18] A preliminary search of PubMed, Embase, *JBI Database of Systematic Reviews and Implementation Reports*, Cochrane Library and PROSPERO was also carried out to identify systematic reviews that had been conducted on this topic, and no reviews were found.

The current literature does not provide a clear determination of the cost impact of using robotic devices for stroke rehabilitation, and it is the aim of this review to examine the economic cost of robotic therapy compared to conventional therapy for adult stroke patients. The methods of the review have been described in a previously published protocol.[19]

Review objective

The objective of this review was to identify the best available evidence on the economic cost of robotic rehabilitation for adult stroke patients to improve their motor movement abilities. More specifically, the objective was to identify the evidence on the economic cost of robotic training compared to conventional physiotherapy for adult stroke patients, from the perspective of healthcare organizations (such as hospitals).

Inclusion criteria

Participants

This review considered studies that included adult stroke patients (18 years and older) of all sexes, regardless if stroke was due to ischemic or hemorrhagic causes. Patients with pre-existing impairments that were not caused by stroke, such as disabilities due to spinal cord injuries, Parkinson's disease, multiple sclerosis and traumatic brain injuries, were excluded. Study participants were of different impairment levels and at various stages of recovery: acute, sub-acute or chronic.

Intervention

This review considered studies that evaluated the rehabilitation of stroke patients using robotic devices. The types of robotic devices varied (e.g. either robotic exoskeletons or end-effectors), but all devices had automated assistive feature that helped patients to move their limbs if they were unable to do so by themselves.

Comparator

This review considered studies that compared the intervention to control groups using conventional physiotherapy. In the control groups, patients did not receive robotic rehabilitation, only conventional physiotherapy. The amount of therapy treatment in both intervention and control groups were the same in terms of duration, i.e. dose-matched.

Context

The settings of selected studies included both inpatient and outpatient rehabilitation. Trials with home rehabilitation patients were excluded due to potential confounding of treatment adherence. The rehabilitation program was conducted either at a single hospital or across multi-centers, and only physical impairments related to upper and lower limbs were considered.

Outcomes

This review considered studies that had the following outcomes:

Cost minimization

Studies that aimed to compare the cost of providing robotic rehabilitation against the cost of providing conventional physiotherapy.

Cost effectiveness

Studies that aimed to compare the cost of providing robotic rehabilitation against the cost of providing conventional physiotherapy, whereby the outcome was to be presented as relative costs to achieve a unit of effect. The unit of effect was to reflect the motor movement ability of patients and involve the following measurement scales:

- For measurement scale of upper limbs, the Fugl-Meyer Assessment[20] (upper extremity score) was the preferred scale. If a study did not use this scale, then an alternative measurement scale that quantified upper limb motor movement (e.g. upper limb Motricity Index[21]) would be considered.
- For measurement scale of lower limbs, the Functional Ambulation Category[22] was the preferred scale. If a study did not use this scale, then an alternative measurement scale that quantified walking would be considered, e.g. Barthel Index[23] (ambulation item) or Functional Independence Measure[24] (walking item).

Cost utility

Studies that aimed to compare the cost of providing robotic rehabilitation against the cost of providing conventional physiotherapy, whereby the outcome was to be presented as relative costs to achieve a unit of utility, which was measured in quality-adjusted life-years (QALY).

Cost benefit

Studies that aimed to compare the cost of providing robotic rehabilitation against the cost of providing conventional physiotherapy, whereby the outcome was to be presented as relative costs to achieve a unit of benefit, which was measured in monetary units.

The cost perspective adopted in this review was from the viewpoint of healthcare organizations, as hospitals are usually the main decision makers for introducing robotic rehabilitation to stroke patients in a clinical setting. As such, only direct medical costs (e.g. therapist time, medical devices) were considered. Indirect costs, such as the cost of patients' caregivers or patients' travel expenses, were excluded. Direct non-medical costs (e.g. hospital administrative cost) were also excluded as this type of cost was common to all patients, regardless of robotic or conventional training. Cost components during the follow-up period were excluded, as it was the intent of the review to examine the costs

associated with providing the intervention during the treatment period.

Types of studies

Any study containing economic data was considered for inclusion. The economic component of the review only had cost minimization studies, which compared robotic rehabilitation to conventional physiotherapy in dose-matched therapy sessions.

Studies published in English were considered for inclusion in this review and a date limit starting from 2000 was set, as automated robotic devices had increasingly been used since 2000, together with an associated increase in the number of studies undertaken.

Methods

Search strategy

The search strategy aimed to find both published and unpublished studies. An initial limited search of PubMed was undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe articles. This then informed the development of a search strategy, which was tailored for each information source. Full search strategies for the various databases are detailed in Appendix I. The reference lists of studies selected for critical appraisal were also screened for additional studies. The overall search date range was from January 2000 to September 2017.

The databases that were searched included PubMed, Embase, CINAHL, Cochrane (CENTRAL), PEDro (Physiotherapy Evidence Database), NHS Economic Evaluation Database (NHS EED), Cost-Effectiveness Analysis (CEA) registry and Health Technology Assessment (HTA) database.

The search for unpublished studies included MedNar, ProQuest Dissertations and Theses and ClinicalTrials.gov.

Study selection

Following the search, all identified citations were collated and uploaded into the bibliographic software EndNote X7.8 (Clarivate Analytics, PA, USA), and duplicates were removed. Titles and abstracts were screened against the inclusion criteria for the review. Studies that potentially met the inclusion criteria were retrieved in full and assessed in detail against the inclusion criteria. Full-text studies that did not meet the inclusion criteria were excluded, and the reasons for exclusion were provided. Included studies then underwent a process of critical appraisal.

Assessment of methodological quality

Selected studies were critically appraised by two independent reviewers at the study level for methodological quality using the standardized critical appraisal instrument from the Joanna Briggs Institute for Economic Evaluation.[25] Disagreements that arose between the reviewers were resolved through discussion. As economic analysis of robotic devices was an emerging research area with limited numbers of studies available, all studies regardless of methodological quality underwent data extraction and synthesis to maximize data collection.

Data extraction

Data were extracted by two independent reviewers from papers included in the review using the standardized data extraction tool from JBI SUMARI. The data extracted included descriptive data about the interventions and comparators examined, study participants and context, study methods, results for the resource use and cost measures and authors' conclusions on the cost comparisons.

Data synthesis

Economic findings were synthesized and presented via a tabular summary and the dominance ranking framework.[26,27] The findings were also tabulated as a dominance ranking score to further facilitate data synthesis. The methodology of the dominance ranking score is explained as follows:

Methodology of dominance ranking score

The dominance ranking framework shows the distribution of studies in the three different bands, where a predominance of the number of studies in a certain band will indicate the likely implication of the intervention. However, if there are equal numbers of studies across two or three bands, no clear conclusion can be drawn.

Also, as the basis of the distribution is on the number of studies, this approach does not take into account sample sizes of the studies. To illustrate, if there are three studies and one is under the band that favors the intervention while the other two are under the band that rejects the intervention, under the current ranking framework, it will imply that the intervention is to be rejected. However, the two

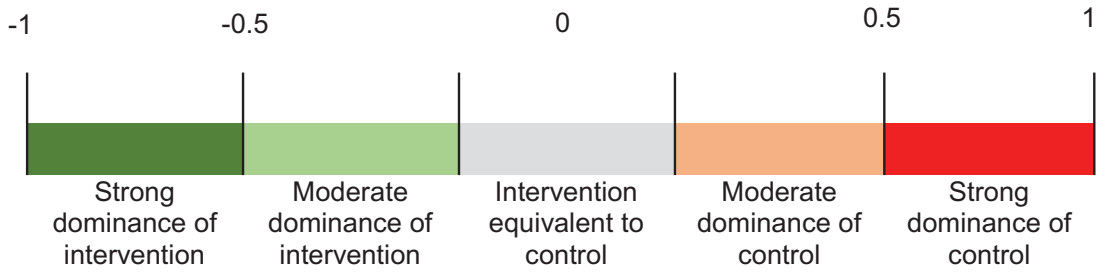

Figure 1: Dominance ranking score scale

studies that reject the intervention could be smaller while the study that favors the intervention may have a larger sample size. Rejecting the intervention in such a scenario may lead to an inaccurate conclusion. If we can extend the current framework to incorporate sample size data, it can help to provide more information for the analysis of dominance.

The sample size of a trial improves the precision of the trial and the larger the sample size, the smaller the confidence interval.[28] We also know that under the fixed effects model for meta-analysis, studies are weighted by their variance, with larger studies having more weight.[29] To give a similar weighting to larger studies, which should have more precision in their effects, we can modify the existing dominance ranking framework by adding a weighting to the cost and health benefits that is based on their sample sizes. The calculation schema are as follows:

$$\text{Weighted Benefit} = \frac{n}{N} \times \text{Benefit Value}$$

Where: n = sample size of a study; N = total sample size of studies in a sub-group analysis; Benefit Value = −1, 0 or +1

$$\text{Overall Dominance Ranking Score} = \left(\sum_{i=1}^{k} \textit{Weighted Cost Benefit} + \sum_{i=1}^{k} \textit{Weighted Health Benefit}\right)/2$$

Where: k = number of studies included in a sub-group analysis

By adding a weighting based on sample size to the cost benefit, the cumulative dominance ranking score can range from −1 to +1. Similarly, by weighting the health benefit, the cumulative ranking score can range from −1 to +1. Assuming that both cost and health benefits play an equal role in determining the overall ranking result, the weighed cost and health benefits can be averaged to obtain the overall dominance ranking score. Based on this approach, the dominance ranking scores are color-coded in Figure 1 to visually represent the level of dominance of the intervention.

If the overall score is in the green zone ($-1 \leq$ score < 0), then the result favors the intervention, with a score in the lighter green zone ($-0.5 \leq$ score < 0) showing a moderate dominance of the intervention, while a score in the darker green zone ($-1 \leq$ score < -0.5) showing a strong dominance of the intervention.

If the overall score is in the red zone ($0 <$ score ≤ 1), then the result favors the control, with a score in the lighter red zone ($0 <$ score ≤ 0.5) showing a moderate dominance of the control, while a score in the darker red zone ($0.5 <$ score ≤ 1) showing a strong dominance of the control.

In the case that the overall score is equal to 0, then it would mean that the intervention is equivalent to the control.

Note that for weighting the health benefit, to align the direction of the scoring to the cost benefit, a better health benefit for the intervention of interest would need to be given a negative sign. The legend key of the benefit values for the dominance ranking score is shown in Table 1.

The weightings are associated with a benefit value (−1, 0, +1) which is, itself, a categorical expression of the direction of dominance; therefore the starting point (i.e. the benefit value) is not a precise measure of dominance level. For example, in the scenario that all studies in a review have lower intervention cost outcome than control, this will mean that the cost benefit values assigned would all be −1. In such a case, regardless of the weightings, the calculated cost dominance level would always be −1. Hence, the

Table 1: Benefit values for dominance ranking score

Benefit value	Cost outcome	Health outcome
−1	Lower	Better
0	Equal	Equal
+1	Higher	Poorer

dominant ranking score is useful when studies have heterogeneous benefit values and can help to better differentiate the dominance level. The dominant ranking score is also useful when the dominant ranking framework shows an unclear interpretation (such as an equal number of studies in each band).

We do not claim that the methodology of determining the dominant ranking score developed for this review is comparable to the rigor of a quantitative meta-analysis. We have merely extended the dominant ranking framework to incorporate more differentiating information, thereby enabling a more informed analysis of dominance levels to be performed. In fact, we suggest that reviewers conduct a review tabulation using the dominant ranking framework and then supplement their analysis with the dominant ranking score, as has been performed in this paper.

Sub-group analyses were also conducted based on impairment levels (moderate/mild versus severe) and stages of stroke recovery (acute/sub-acute versus chronic). The authors had envisaged conducting a sub-group analysis to shed light on whether there were differences in robotic intervention costs due to upper limb training or lower limb training. However, as there was only one study which examined lower limb training (and this study had a mix of upper limb training),[30] a meaningful sub-group analysis based on limb extremity was not possible.

Results

Study inclusion

A total of 303 citations were generated from the database searches, and 81 were identified from other sources such as MedNar, ProQuest Dissertations and Theses and ClinicalTrials.gov (Figure 2).[31] After initial screening of titles and abstracts, the full texts of seven studies were retrieved and screened for eligibility. After full-text review, two studies were excluded, and the reference details of these excluded studies with reasons for their exclusion are listed in Appendix II. Consequently, five studies were appraised for quality, and no further studies were excluded at this stage. For the final review, these five studies were included (Figures 3–7).

Methodological quality

Overall, the methodological quality of the included studies was of moderate level. The included studies had relatively positive scores in aspects of providing sufficient details on intervention and control groups, as well as a reasonably accurate and credible breakdown of relevant costs and outcomes reported. All of the studies also measured the clinical effectiveness of their interventions using Fugl-Meyer Assessment or Motricity Index. Hence, these studies scored mainly "yes" for questions one through six on the JBI critical appraisal checklist for economic evaluations (Appendix III).

Of the five studies, only one (Wagner *et al.*[16]) attempted to further analyze economic effects beyond the cost minimization outcome. Wagner *et al.* analyzed both the incremental and sensitivity effects of different levels of resource use, such as number of patients using the robotics and the amount of therapist time involved in conducting robotic therapy sessions.[16] Although the authors did further analysis, they adopted a societal perspective in their computations. This rendered these additional analyses inapplicable for our review, as we were looking at costs from the perspective of healthcare organizations.

Due to the lack of in-depth economic analysis, the remaining four studies scored "no" for questions seven, eight and nine as these questions addressed aspects of incremental analysis, sensitivity analysis and discount rate used. Similarly, because of the insufficient exploration of the economic aspects, these four studies also scored a "no" for question 10, as the results were not comprehensive enough and did not address concerns relating to varying levels of key variables and robustness of the findings.

Two of the five studies (Bustamante Valles *et al.*[30] and Hesse *et al.*[18]) had a trial design using robotic circuit training. This circuit training included non-robotic devices and because of this, their cost computations were not reflective of purely robotic devices. The trial by Bustamante Valles *et al.* was also conducted in Mexico, where labor costs were not comparable to the other trials, which were

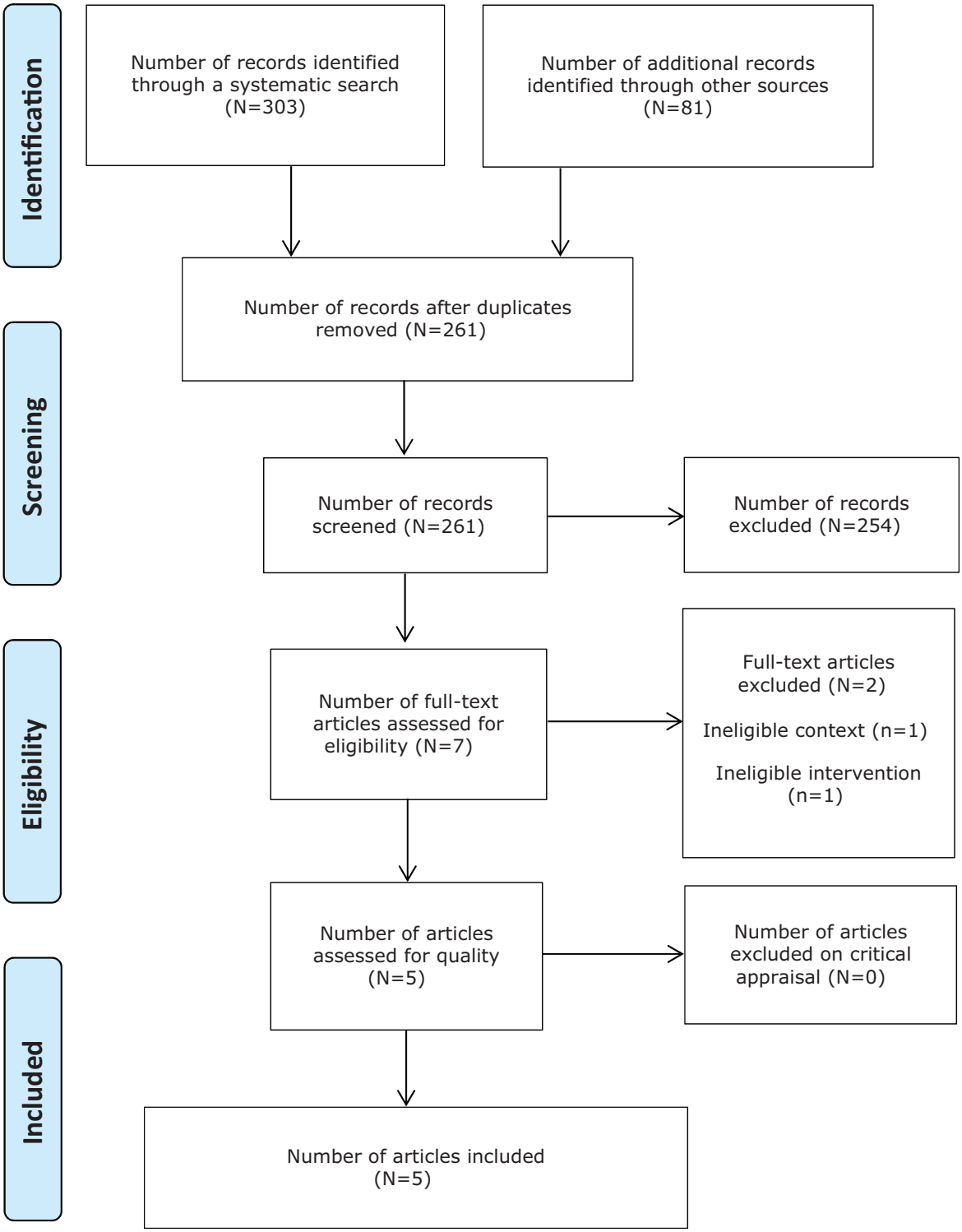

Figure 2: PRISMA flow diagram of search and study selection process[31]

conducted in developed countries such as Germany, Italy and the United States.[30] As a result, these two studies scored "no" for question 11, as their results were not generalizable to a purely robotic clinical setting that was typically found in developed countries. Appendix III outlines the appraisal of methodological quality for the included studies.

Characteristics of included studies

A total of five studies with 213 patients were included in this review. Four studies[16,18,32,33] examined upper limb interventions, and one study[30] evaluated both upper limb and lower limb interventions. Of the included studies, two[18,33] had acute/sub-acute patients and three[16,30,32] had chronic patients.

The studies came from various countries: Germany,[18] Italy,[33] Mexico[30] and the United States.[16,32] Trial participants were all adults and were predominantly older than 60 years old, although the robotic intervention group of Bustamante Valles *et al.*[30] had an average age of 44 years. In this trial, there was a significant difference between the mean ages of the robotic intervention group and the conventional control group, which had been acknowledged by the authors in their study report. Despite this age difference, in terms of their pre-intervention Fugl-Meyer scores, the authors stated no significant differences between the two groups.

The included studies had mainly cost minimization outcomes. These studies compared the costs of robotic therapy versus the cost of conventional therapy. Even though all these studies had measured clinical outcomes such as Fugl-Meyer Assessment or Motricity Index, there was no presentation of a cost effectiveness comparison, except for the study by Wagner *et al.*[16] This study did compute an Incremental Cost-Effectiveness Ratio,[34-36] but this was done by comparing the robotic arm versus the arm that had no formal rehabilitation therapy program, which was not the conventional therapy arm that we were examining. Furthermore, the cost perspective adopted by the study was from a societal perspective. None of the studies provided outcomes in terms of cost utility or cost benefit.

The trial with the largest sample size (Wagner *et al.*[16]) had a majority of male patients (around 96%). because it recruited veterans from four Veterans' Affairs medical centers. However, the average percentage of males across all included studies was 72%.

In terms of stroke types, more patients (81%) had ischemic stroke than hemorrhagic stroke. However, two studies (Bustamante Valles *et al.*[30] and McCabe *et al.*[32]) did not record the types of stroke for their participants.

The studies had various amounts of training durations, with total training hours ranging from 20 hours to 300 hours. However, within each study, the therapy dosage was the same for both the intervention and control groups (i.e. both groups were dose-matched).

Three studies (Bustamante Valles *et al.*,[30] Vanoglio *et al.*,[33] Wagner *et al.*[16]) compared purely robotic training to purely conventional training (i.e. the intervention group had no conventional training component), while two other studies (Hesse *et al.*,[18] and McCabe *et al.*[32]) had a mix of conventional and robotic training in the intervention group.

Two studies[16,32] had multiple-arm comparisons, but only results of the intervention arm with robotic rehabilitation were compared to the conventional therapy control arm. In one study,[32] the intervention arm with a combination of robotic devices and non-conventional therapy (functional electrical stimulation [FES]) was excluded from analysis. In the second study,[16] one of the three arms had no formal rehabilitation therapy program; therapy was administered as needed. The result of this arm was excluded from analysis.

In terms of trial design, two studies (Bustamante Valles *et al.*[30] and Hesse *et al.*[18]) adopted a robotic circuit training concept, whereby patients were cycled through various training stations during the therapy session. In the trial by Bustamante Valles *et al.*,[30] patients underwent training using a mix of upper limb/lower limb robotic devices, FES and cognitive devices. Patients in this robotic intervention group switched stations every half hour, working on four stations per day throughout the trial. For the trial by Hesse *et al.*,[18] the robotic circuit training consisted only of upper limb devices. However, the devices were a mix of robotic and non-assistive mechanical devices. Each patient practiced for 15 minutes on one device and worked with two devices during a therapy session. Although these trials had mixed training equipment in the intervention groups, they still compared the intervention groups to control groups, which had conventional therapy.

Because the therapy durations were also dose-matched, these trials were included for the review. Additional characteristics of the studies are presented in Appendix IV.

Review findings

Cost minimization

The included studies compared the cost of providing robotic intervention against the cost of providing conventional therapy in dose-matched therapy sessions. The studies computed the cost measures in terms of cost per patient session or cost per patient. Under cost per patient session, authors calculated the cost to treat one patient for one therapy session. Under cost per patient, authors calculated the cost to treat one patient for the entire intervention period. As part of their cost considerations, the studies included cost components such as robotic device cost, device depreciation period, device maintenance cost and cost of therapist.

For the trials by Hesse *et al.*,[18] Bustamante Valles *et al.*[30] and Wagner *et al.*,[16] the authors compared the intervention and control groups using cost per patient session. In the trial by Hesse *et al.*,[18] the intervention group had 30 minutes of robotic therapy and 30 minutes of conventional therapy, while the control group had two 30-minute sessions of conventional therapy. However, in calculating the cost per patient session, the authors compared only the cost of 30 minutes of robotic therapy against the cost of 30 minutes of conventional therapy. This was still a reasonably acceptable comparison, as both groups had the same therapy duration and the additional 30 minutes of conventional therapy in both groups would have negated each other. Although the magnitude of the comparison was affected, the direction of the comparison remained the same.

In the trial by Bustamante Valles *et al.*,[30] the cost per patient session was based on one therapy session of two hours. In the study by Wagner *et al.*,[16] the authors adopted a societal perspective for their cost computations, but in our review, we adopted a healthcare organization perspective. Nevertheless, Wagner *et al.*[16] listed directly in their report the intervention cost per patient for a therapy session of one hour (i.e. cost per patient session). We extracted this cost data to perform the relevant cost comparison based on our review perspective.

Four of the five studies showed a lower robotic therapy cost as compared to conventional therapy. Only one study (McCabe *et al.*[32]) had a higher robotic therapy cost. The cost comparisons of the included studies are summarized in Table 2.

Table 2: Cost comparison of included studies

Study	Currency	Annual cost of device (intervention group)	Annual cost of device maintenance (intervention group)	Device depreciation period (year)	Annual cost of therapist	Cost (control group)	Cost (intervention group)
Bustamante Valles *et al.*[30]	USD/MXN	USD $18,024 (MXN $216,296)	MXN $108,148	2*	USD $19,612 (MXN $235,344)	Cost/patient session: USD $19.21	Cost/patient session: USD $6.99
Hesse *et al.*[18]	Euro	€9,600	€2,400	4	Assistant therapist: €25,000 Experienced therapist: €35,000	Cost/patient session: €10.00	Cost/patient session: €4.15
McCabe *et al.*[32]	USD	$17,800	$8,000	5	$98,000	Cost/patient: $4570	Cost/patient: $5686
Vanoglio *et al.*[33]	Euro	€6,000	Not recorded	5	Annual value not provided, only cost per minute: €0.40/minute	Cost/patient: €480	Cost/patient: €237
Wagner *et al.*[16]	USD	$46,150	$15,000	5	Annual value not provided, only cost per hour: $218/hour	Cost/patient session: $218	Cost/patient session: $140

MXN = Mexican peso; USD = United States dollar.
*–The two years was the commercial payment period, which was used by the author for depreciation cost calculations. The actual depreciation period of the robotic device was not reported.

Cost effectiveness

Although all studies measured the clinical effectiveness of the interventions, none of the studies compared the cost data against the effectiveness measure. Four studies[16,18,30,32] used the Fugl-Meyer Assessment scale while one study[33] utilized the Motricity Index (upper limb).

Cost utility

None of the included studies examined the cost utility outcome.

Cost benefit

None of the included studies examined the cost benefit outcome.

Dominance ranking framework

We graded the studies using the dominance ranking framework, which ranks studies based on their cost and health benefit into three implications for decision making: reject intervention, unclear or favor intervention.[26] The studies were graded according to different health and cost outcomes, and we also presented sub-group analyses based on impairment levels and stages of stroke recovery.

All included studies

Four studies were ranked under the band that favors the intervention, while one study was ranked under "reject intervention" (Table 3). With most of the studies showing that robotic intervention was more favorable, it seemed to indicate that robotic therapy was preferable to conventional therapy.

Studies with acute/sub-acute patients

There were two studies that had acute and sub-acute patients, and when ranked, both studies were under the band that favored the robotic intervention,

Table 3: Dominance ranking framework (all studies)

Cost	Health benefit	Implication for decision makers	No. of studies
+	–	Reject intervention	None
0	–	Reject intervention	None
+	0	Reject intervention	1[32]
–	–	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
0	0	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
+	+	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
–	0	Favor intervention	3[16,18,30]
0	+	Favor intervention	None
–	+	Favor intervention	1[33]

(+) = higher cost/better health outcome; 0 = equal cost/equal health outcome; (–) = lower cost/poorer health outcome.

Table 4: Dominance ranking framework (acute/sub-acute patients)

Cost	Health benefit	Implication for decision makers	No. of studies
+	—	Reject intervention	None
0	—	Reject intervention	None
+	0	Reject intervention	None
—	—	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
0	0	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
+	+	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
—	0	Favor intervention	1[18]
0	+	Favor intervention	None
—	+	Favor intervention	1[33]

(+) = higher cost/better health outcome; 0 = equal cost/equal health outcome; (–) = lower cost/poorer health outcome.

which might indicate that robotic therapy was preferable for acute and sub-acute patients (Table 4).

Studies with chronic patients

There were three studies that included chronic patients. When ranked, two studies came under the band that favored the robotic intervention, and one was under the band that rejected the intervention (Table 5). Based on the higher number of studies in the "favor intervention" band, it seemed to indicate that robotic therapy was preferable for chronic patients.

Studies with mild/moderate patients

There were two studies that included mild/moderate patients. When ranked, one study was under the band that favored the robotic intervention, and one study was under the band that rejected the intervention (Table 6). This seemed to indicate no preference for either robotic therapy or conventional therapy for mild/moderate patients.

Studies with severe patients

There were three studies that included severe patients. When ranked, all studies were under the band that favored the robotic intervention, which might indicate that robotic therapy was preferable for severe patients (Table 7).

Dominance ranking score

The following dominance ranking scores were computed by taking into account the sample sizes of the studies, as illustrated in the methods section.

All included studies

In terms of the weighted cost benefit, the included studies had a score of −0.78, which showed a strong dominance of the robotic intervention. However, in terms of the weighted health benefit, the studies had a score of −0.13, which showed a moderate dominance of the intervention. Combined together, the overall dominance ranking score was −0.46, which indicated a moderate dominance of the robotic intervention.

Table 5: Dominance ranking framework (chronic patients)

Cost	Health benefit	Implication for decision makers	No. of studies
+	—	Reject intervention	None
0	—	Reject intervention	None
+	0	Reject intervention	1[32]
—	—	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
0	0	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
+	+	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
—	0	Favor intervention	2[16,30]
0	+	Favor intervention	None
—	+	Favor intervention	None

(+) = higher cost/better health outcome; 0 = equal cost/equal health outcome; (–) = lower cost/poorer health outcome.

Table 6: Dominance ranking framework (mild/moderate patients)

Cost	Health benefit	Implication for decision makers	No. of studies
+	—	Reject intervention	None
0	—	Reject intervention	None
+	0	Reject intervention	1[32]
—	—	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
0	0	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
+	+	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
—	0	Favor intervention	1[30]
0	+	Favor intervention	None
—	+	Favor intervention	None

(+) = higher cost/better health outcome; 0 = equal cost/equal health outcome; (–) = lower cost/poorer health outcome.

Table 7: Dominance ranking framework (severe patients)

Cost	Health benefit	Implication for decision makers	No. of studies
+	—	Reject intervention	None
0	—	Reject intervention	None
+	0	Reject intervention	None
—	—	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
0	0	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
+	+	Unclear: judgment required on whether intervention is preferable considering incremental cost effectiveness measures and priorities/willingness to pay	None
—	0	Favor intervention	2[16,18]
0	+	Favor intervention	None
—	+	Favor intervention	1[33]

(+) = higher cost/better health outcome; 0 = equal cost/equal health outcome; (–) = lower cost/poorer health outcome.

	Number of participants	Cost benefit	Weighted cost benefit	Health benefit	Weighted health benefit	Overall dominance score
Bustamante Valles et al.[30]	20	-1	-0.09	0	0.00	
Hesse et al.[18]	50	-1	-0.23	0	0.00	
McCabe et al.[32]	23	+1	+0.11	0	0.00	
Vanoglio et al.[33]	27	-1	-0.13	-1	-0.13	
Wagner et al.[16]	93	-1	-0.44	0	0.00	
Total	213		-0.78		-0.13	-0.46

Figure 3: Dominance ranking score (all studies)

	Number of participants	Cost benefit	Weighted cost benefit	Health benefit	Weighted health benefit	Overall dominance score
Hesse et al.[18]	50	-1	-0.65	0	0.00	
Vanoglio et al.[33]	27	-1	-0.35	-1	-0.35	
Total	77		-1.00		-0.35	-0.68

Figure 4: Dominance ranking score (acute/sub-acute patients)

Studies with acute/sub-acute patients

In terms of the weighted cost benefit, the included studies had a score of −1.00, which showed a strong dominance of the robotic intervention. However, in terms of the weighted health benefit, the studies had a score of −0.35, which showed a moderate dominance of the intervention. Combined together, the overall dominance ranking score was −0.68, which

	Number of participants	Cost benefit	Weighted cost benefit	Health benefit	Weighted health benefit	Overall dominance score
McCabe et al.[32]	23	+1	+0.17	0	0.00	
Bustamante Valles et al.[30]	20	-1	-0.15	0	0.00	
Wagner et al.[16]	93	-1	-0.68	0	0.00	
Total	136		-0.66		0.00	-0.33

Figure 5: Dominance ranking score (chronic patients)

indicated a strong dominance of the robotic intervention.

Studies with chronic patients

In terms of the weighted cost benefit, the included studies had a score of −0.66, which showed a strong dominance of the robotic intervention. However, in terms of the weighted health benefit, the studies had a score of 0.00, which showed that the robotic intervention was equivalent to the conventional control. Combined together, the overall dominance ranking score was −0.33, which indicated a moderate dominance of the robotic intervention.

Studies with mild/moderate patients

In terms of the weighted cost benefit, the included studies had a score of +0.07, which showed a moderate dominance of the conventional control. In terms of the weighted health benefit, the studies had a score of 0.00, which showed that the robotic intervention was equivalent to the conventional control. Combined together, the overall dominance ranking score was +0.03, which indicated a moderate dominance of the conventional control.

Studies with severe patients

In terms of the weighted cost benefit, the included studies had a score of −1.00, which showed a strong dominance of the robotic intervention. However, in terms of the weighted health benefit, the studies had a score of −0.16, which showed a moderate dominance of the intervention. Combined together, the overall dominance ranking score was −0.58, which indicated a strong dominance of the robotic intervention.

In summary, the results according to the different sub-groups are shown in Table 8 (based on dominance ranking framework) and Table 9 (based on the dominance ranking score).

	Number of participants	Cost benefit	Weighted cost benefit	Health benefit	Weighted health benefit	Overall dominance score
Bustamante Valles et al.[30]	20	-1	-0.47	0	0.00	
McCabe et al.[32]	23	+1	+0.53	0	0.00	
Total	43		+0.07		0.00	+0.03

Figure 6: Dominance ranking score (mild/moderate patients)

	Number of participants	Cost benefit	Weighted cost benefit	Health benefit	Weighted health benefit	Overall dominance score
Hesse et al.[18]	50	-1	-0.29	0	0.00	
Vanoglio et al.[33]	27	-1	-0.16	-1	-0.16	
Wagner et al.[16]	93	-1	-0.55	0	0.00	
Total	170		-1.00		-0.16	-0.58

Figure 7: Dominance ranking score (severe patients)

Table 8: Summary of dominance levels (based on dominance ranking framework)

Sub-group	Overall dominance level of the intervention	Number of studies (number of studies by implication)
All studies	Favor intervention	5 studies (1 reject; 4 favor)
Acute/sub-acute patients	Favor intervention	2 studies (2 favor)
Chronic patients	Favor intervention	3 studies (1 reject; 2 favor)
Mild/moderate patients	No preference	2 studies (1 reject; 1 favor)
Severe patients	Favor intervention	3 studies (3 favor)

Table 9: Summary heatmap of dominance levels (based on dominance ranking score)

Sub-group	Overall dominance level	Dominance level of cost benefit	Dominance level of health benefit
All studies	Moderate robotic	Strong robotic	Moderate robotic
Acute/sub-acute patients	Strong robotic	Strong robotic	Moderate robotic
Chronic patients	Moderate robotic	Strong robotic	Equivalent
Mild/moderate patients	Moderate control	Moderate control	Equivalent
Severe patients	Strong robotic	Strong robotic	Moderate robotic

Sensitivity analysis

In the study by Bustamante Valles *et al.*,[30] the authors found that there was no statistically significant difference in health benefit between robotic and conventional groups for upper limb motor movement; however, for lower limb motor movement, the authors found that there was a statistically significant difference in health benefit in favor of the robotic group. The prior dominance ranking score analysis had used an equivalent health benefit for this study but to account for the better health outcome of the lower limb, a sensitivity analysis was conducted to assess the effect of changing the health outcome from equal (0) to better (−1). Table 10 and

Table 10: Summary heatmap of dominance levels (after sensitivity analysis)

Sub-group	Overall dominance level	Dominance level of cost benefit	Dominance level of health benefit
All studies	Moderate robotic	Strong robotic	Moderate robotic
Acute/sub-acute patients	Strong robotic	Strong robotic	Moderate robotic
Chronic patients	Moderate robotic	Strong robotic	Moderate robotic
Mild/moderate patients	Moderate robotic	Moderate control	Moderate robotic
Severe patients	Strong robotic	Strong robotic	Moderate robotic

Sub-group: all studies	Number of participants	Cost benefit	Weighted cost benefit	Health benefit	Weighted health benefit	Overall dominance score
Bustamante Valles et al.[30]	20	-1	-0.09	-1	-0.09	
Hesse et al.[18]	50	-1	-0.23	0	0.00	
McCabe et al.[32]	23	+1	+0.11	0	0.00	
Vanoglio et al.[33]	27	-1	-0.13	-1	-0.13	
Wagner et al.[16]	93	-1	-0.44	0	0.00	
Total	213		-0.78		-0.22	-0.50

Sub-group: chronic patients	Number of participants	Cost benefit	Weighted cost benefit	Health benefit	Weighted health benefit	Overall dominance score
McCabe et al.[32]	23	+1	+0.17	0	0.00	
Bustamante Valles et al.[30]	20	-1	-0.15	-1	-0.15	
Wagner et al.[16]	93	-1	-0.68	0	0.00	
Total	136		-0.66		-0.15	-0.40

Sub-group: mild/moderate patients	Number of participants	Cost benefit	Weighted cost benefit	Health benefit	Weighted health benefit	Overall dominance score
Bustamante Valles et al.[30]	20	-1	-0.47	-1	-0.47	
McCabe et al.[32]	23	+1	+0.53	0	0.00	
Total	43		0.07		-0.47	-0.20

Figure 8: Sub-groups affected by sensitivity analysis

Figure 8 showed the summary heatmap and sub-groups that were affected by the sensitivity analysis.

Discussion

We conducted a cost comparison of the included studies and reviewed the data based on two approaches: the dominance ranking framework and the dominance ranking score. By simply comparing the cost outcome of each study, four of the five studies showed lower cost data for the robotic intervention group. Under the dominance ranking framework, as most sub-groups favored robotic intervention, it also seemed to indicate that robotic therapy had better cost and health benefits. Under the dominance ranking score, the overall dominance levels for most sub-groups favored robotic intervention and seemed to indicate that robotic therapy had better cost and health benefits. Overall, the results appeared to be promising that robotic therapy could potentially have better economic cost benefits than conventional therapy. However, the limited number of studies in this review required us to view the results with caution.

Despite the limited number of studies, we did see some corresponding similarities between our dominance ranking scores and previous systematic reviews. Under the dominance ranking score, an equivalent health benefit was shown between robotic intervention and conventional therapy for mild/moderate patients. However, for severe patients, a moderate dominance in health benefit favoring robotic intervention was found. Robotic intervention was also found to be more beneficial for severely affected patients in the systematic reviews of Lo *et al.*[5] and Mehrholz *et al.*[2] The authors found that robotic training was more effective for patients with severe impairment, although their review finding was for training lower limbs. For mild/moderate patients, the weighted dominance ranking score for health benefit was 0, which was

also similar to the finding of Lo *et al.*[5] that robotic therapy was equivalent to conventional therapy for the sub-group of mild/moderate patients.

Comparing the cost benefit under the dominance ranking score between the sub-groups of mild/moderate and severe patients, there was a moderate dominance for conventional control for mild/moderate patients and a strong dominance for robotic intervention for severe patients. The better cost benefit of robotic intervention for severely impaired patients might be due to the need for more one-to-one therapist time during conventional therapy to gain the same health benefits as robotic therapy. In conventional therapy, therapists manually support and exercise the impaired limbs of patients, which is physically demanding for therapists to sustain at high intensity, especially for severely impaired patients with minimal volitional movements.[11] Furthermore, during conventional therapy for lower limbs of severe patients, because of the weight and muscle spasticity (i.e. stiffness) of the legs, the number of walking steps that can be facilitated by therapists is also limited. Because severely affected patients had less motor movement ability, therapists would need to spend more time exercising the limbs of patients to achieve the same number of repetitions during conventional therapy as robotic devices, which would increase the cost of therapy.

In the review, the cost comparison was based on the cost measure: cost per patient and cost per patient session. For both measures, the result was dependent on the number of patients who can be treated in a given time period. If a robotic therapy session was able to treat more patients in a given time period, then the cost would be further reduced. For example, in the trials by Bustamante Valles *et al.*[30] and Hesse *et al.*,[18] the number of patients who could be treated under robotic training was, respectively, six times and two times more than that under conventional training. The higher number of patients who can be treated within a given time period helped to spread the cost of the robotic therapy across more patients and this, in turn, resulted in a lower cost outcome for robotic intervention. This relation to the number of patients treated in a given time period was also mentioned by Wagner *et al.* during his sensitivity analysis.[16] From the sensitivity analysis, the authors found that their results were most sensitive to how efficiently (in terms of the number of patients per robotic session) the robotic device was used and the time therapists spent with patients during a robotic session. If more patients could be treated per robotic session, then cost would decrease. Similarly, if less therapist involvement was needed during robotic training, then cost would decrease. Our review was in line with the sensitivity factors identified by Wagner *et al.*[16] that i) robotic sessions that could treat more patients than conventional sessions in a given time period would have lower costs and ii) patients with severe impairment would require less therapist time to achieve a high number of training repetitions during robotic therapy and therefore incur a lower cost.

Limitations of the review

Heterogeneity of studies

A potential limitation of our analysis was the heterogeneity of studies. The main sources of heterogeneity were study design, types of robotic devices, cost of therapist and cost computation methods for robotic intervention and conventional control groups.

Study design

Two of the included studies (Bustamante Valles *et al.*[30] and Hesse *et al.*[18]) utilized a robotic circuit training program, whereby a mix of robotic and non-robotic devices were used for the robotic intervention group. The studies provided no breakdown on the cost of each individual device used, and as a result, the robotic cost computed included the cost of the non-robotic devices. As such, the overall cost of the intervention would have been inflated by the non-robotic devices. Despite the mixed robotic circuit training increasing the cost of therapy, the cost of robotic intervention was still lower than conventional therapy. Although the magnitude of the cost was affected by the non-robotic components, the direction of the comparison would have remained the same, even if we were able to remove the cost of the non-robotic devices. However, the health benefit might not be attributable to just robotic training, as some of these non-robotic devices were FES equipment or pure mechanical arm trainers. In terms of the health benefits, the use of both robotic and non-robotic devices in the intervention group was a source of uncertainty.

Types of robotic devices

Various types of robotic devices were used in the studies, with different levels of complexity and costs.

Looking at the annual cost of device (intervention group) in Table 2, we could see the annualized device cost ranged from €6000 (approximately USD $7000) for a hand robotic device to USD $46,150 for an upper limb robotic device. This wide range of costs depends on the nature of the robotic devices, with more complex devices costing more. If studies used more complex robotic devices, it could increase the intervention cost and alter the economic outcome. The various types and complexities of robotic devices and their associated variable costs might lead to imprecise economic outcomes.[37]

Cost of therapist

Under annual cost of therapist in Table 2, the cost of therapist ranged from USD $19,612 to USD $98,000, which is a wide variance. In the study by Wagner *et al.*,[16] only the hourly cost of a therapist was provided. If we were to work out the annual cost based on this hourly rate, we would have an annual cost of USD $408,096 (based on annual work days of 234 days and eight work hours per day). It is likely that the cost of therapist in the study by Wagner *et al.*[16] included other cost factors such as overhead and administrative charges. Nevertheless, the wide variability of therapist cost would have an impact on the economic outcome, especially since the resource use of therapist had been identified as a main cost sensitivity factor.

Cost computation methods for robotic intervention and conventional control groups

In calculating the cost of the robotic intervention group, different cost components were considered. The studies by Bustamante Valles *et al.*[30] and Hesse *et al.*[18] considered robotic device cost (depreciated to an annual amount), an overhead that covered annual device maintenance and consumables cost and annual cost of therapist. It should be noted that Hesse *et al.*[18] considered the cost of electrical consumption of the robotic device under the overhead, but it was not mentioned if cost of power was included in the Bustamante Valles *et al.* study.[30]

For the trial by McCabe *et al.*,[32] robotic device cost (depreciated to an annual amount), annual device maintenance cost and annual cost of therapist were considered. In the study by Vanoglio *et al.*,[33] robotic device cost (depreciated to an annual amount) and annual cost of therapist were considered, but there was no mention of annual device maintenance cost or cost of consumables or electrical power. In the study by Wagner *et al.*,[16] robotic device cost (depreciated to an annual amount), annual device maintenance cost and annual cost of therapist (which includes an overhead and fixed expenses) were considered, but the authors also considered additional cost components such as financing and facility overhead expenses.

Furthermore, the cost of robotic devices was depreciated to calculate the annual device cost, and this depended on the depreciation period used. Most studies used five years as the depreciation period, but Hesse *et al.*[18] used four years while Bustamante Valles *et al.*[30] used two years. In the study by Bustamante Valles *et al.*,[30] the two years was actually based on their commercial payment period, while the device depreciation period was not reported.

Similarly, for the cost computation of conventional control group, different cost components were utilized. In the study by Bustamante Valles *et al.*,[30] cost of therapist, cost of maintenance and consumables for conventional therapy equipment were included. However, cost of the conventional therapy equipment was excluded. For Hesse at al.,[18] only the cost of therapist with an overhead was included. For McCabe *et al.*,[32] annual salary of therapist was included. In the study by Vanoglio *et al.*,[33] cost of therapist was used, and for the study by Wagner *et al.*,[16] annual cost of therapist (which included an overhead and fixed expenses) was considered.

The inconsistency of cost components used to compute the cost of robotic and conventional therapies and the device depreciation period that the authors used to compute the annual cost of robotic device were sources of heterogeneity.

Limited number of studies and small sample sizes

The limited number of included studies and the relatively small sample sizes (except in the trial by Wagner *et al.*[16]) do not lend confidence to our results. Because there will be variability among the salary levels of therapists, types and prices of robotic devices, and device depreciation periods, economic studies should have large sample sizes to be sufficiently powered for both cost and clinical outcomes, especially when resource use variables have a skewed statistical distribution pattern, while clinical variables are usually normally disrtibuted.[38] One such

method has been presented by Briggs *et al.*[39] but it requires a maximum acceptable incremental cost-effectiveness ratio[35,40] to be pre-determined. Typically, sample sizes required for economic variables will be overpowered for clinical outcomes, which raises the ethical question on whether it would be inappropriate to carry out a trial beyond the sample size at which clinical effectiveness has been demonstrated.[38] With inclusion of studies with larger sample sizes, there would be sufficient sampling data to ensure that resource variations can be adequately powered to detect cost differences and give a more definitive result.[38] This is an important consideration, given that the distribution of cost data for resource use can be skewed, which would mean that sampling sizes for cost outcomes need to be much larger than that for clinical outcomes.[38]

Better comparison of cost and clinical effectiveness measures

The included studies were conducted in various countries using different motor impairment scales, different currencies and over different time points. If the motor impairment scale and currency value could be standardized, it would allow for a better comparison across studies in terms of the cost and health benefits using a cost-effective (CE) plane. The CE plane is a two-dimensional space with the x-axis being the average difference (treatment minus control) in effectiveness (ΔE) per patient and the y-axis being the average difference in cost (ΔC) per patient.[34,35] If each economic trial is able to compute ΔE and ΔC, it would be possible to plot these point estimates on the CE plane for several trials. With a scatter plot on the CE plane, depending on which quadrant the scatter is most prominent, it would give us a simple but clear view of the direction of the economic outcome.[34]

Data extraction issues

We faced some challenges when extracting data. The study by Bustamante Valles *et al.*[30] included both upper and lower limb training in the robotic intervention group. Based on the Fugl-Meyer Assessment, the authors reached different clinical effectiveness conclusions for upper and lower limbs. For upper limb, the authors found that there was no statistically significant difference between robotic and conventional groups, but for the lower limb, the authors found that there was a statistically significant difference in favor of the robotic group. However, this finding was complicated by the fact that the average age of the intervention group was much younger. This might have contributed to the intervention group gaining more improvements during their lower limb training due to the younger ages of patients. Under the dominance ranking framework, we can only have one grading for health benefit, so we have taken the more conservative value of no statistically significant difference, i.e. health benefit is graded as 0. Nevertheless, even if we had graded the health benefit as ''better'' (+), the study would still be within the band favoring the robotic intervention. In terms of the dominance ranking framework, we would still have had the study placed in the same band, regardless of the grading for the health benefit.

In terms of the dominance ranking score, a sensitivity analysis was performed and there were changes not only in terms of the values of dominance scores but also in terms of the bands of the dominance levels. For subgroups of chronic and mild/moderate patients, a moderate dominance in health benefit for robotic intervention was shown, which was previously equivalent. For the overall dominance level of sub-group mild/moderate patients, instead of the previous moderate dominance of control, a moderate dominance for robotic intervention was shown. Overall, the sensitivity analysis generated a more pronounced shift towards favoring the robotic intervention.

Another point to note was that in the study by Wagner *et al.*,[16] using a societal perspective, the authors had an uncertain conclusion when comparing the costs between robotic therapy and conventional therapy. However, when using a healthcare organization perspective in our review, the cost conclusion favored robotic therapy.

Another restriction is the lack of reporting on the quantities of resources used. Some studies included cost of consumables, electrical power and overheads in their cost computations, but there were no details of the quantities and unit prices for these resources. If these had been stated, it would allow for reviewers to extract resource use data of interest to the review and thereby enable cost computations that could be more comparable across studies.

Generalizability to healthcare settings and external validity of review findings

Various factors limit the findings of this review to be generalizable to healthcare providers in a developed

economic setting. The labor cost of Bustamante Valles *et al.*,[30] which was conducted in a developing economy, affects the cost applicability of our findings to a developed economy. There could also be differing clinical practice patterns among the studies, as each country might use different levels of clinical resources to treat their patients.[41] The difference in study designs (i.e. some studies used robotic circuit training with non-robotic devices) adds uncertainty to the cost and health benefits, thus limiting external validity of the review results. Most of the studies examined upper limb outcomes, and only one study (Bustamante Valles *et al.*[30]) examined upper and lower limbs. The predominance of studies for upper limb might limit the economic outcome only to this limb extremity.

Conclusion

Our review indicated that robotic therapy had a better economic outcome than conventional therapy. For patients with severe effects from stroke, a moderate dominance favoring robotic therapy was found for health benefit, and a strong dominance for robotic therapy was found for cost benefit. However, the limited number of studies in the review required us to view the results with caution. Key sensitivity factors affecting robotic therapy were the number of patients who could be treated per robotic session and the time therapists spent with patients during a robotic session. If more patients could be treated per robotic session, then the cost would decrease. Similarly, if less therapist involvement was needed during robotic training, then the cost would decrease.

The main sources of heterogeneity were study design, types of robotic devices, cost of therapist and cost computation methods for robotic intervention and conventional control groups. Key among these factors was the cost computation method. There were many inconsistencies in the resources used, which could affect the cost computations and economic outcomes.

Recommendations for practice

Robotic therapy seemed to have a better economic outcome, especially for patients with severe effects from stroke, where a dominance for robotic therapy was found. In view of this, robotic therapy could be prescribed more for adult patients with severe impairments after stroke. However, this needed to be considered with caution, as there was a limited number of studies in our review. (Grade B; JBI Grades of Recommendation[42])

As robotic therapy was associated with the sensitivity factors of number of patients per robotic session and the time of therapists, hospital providers might wish to organize their robotic therapy program accordingly to maximize the cost economics of robotics. Hospital providers could increase the number of patients treated during a robotic therapy session and minimize the involvement of therapists as far as possible, while still maintaining patient safety. (Grade B; JBI Grades of Recommendation[42])

Recommendations for research

More comparable cost computations

To achieve more comparable cost computations among studies, researchers ought to report both the quantities of resource use and their unit prices, especially for device consumables and electrical power consumption, if included in their trials. As a minimum, researchers should include the following resources and their associated cost per unit prices:

i) Resources for robotic intervention group
   For annual cost of robotic device:
   - Purchase price of robotic device
   - Depreciation period of the robotic device
   - Annual cost of device maintenance/warranty

   Time of therapist based on annual gross salary
ii) Computation for conventional control group
   For annual cost of conventional therapy equipment:
   - Purchase price of therapy equipment
   - Depreciation period of the therapy equipment
   - Annual cost of equipment maintenance/warranty

   Time of therapist based on annual gross salary

Researchers should also report their computation steps so that readers are able to calculate how values of the cost per patient or cost per patient session measures are derived. It would also allow for reviewers to extract resource use data that were of interest to the review and thereby enable cost computations that could be more comparable across studies.

Larger trial sample sizes

As there will be variability among resource use, economic studies should have large sample sizes to be sufficiently powered for both cost and clinical outcomes. As sample sizes required for economic

variables will be overpowered for clinical outcomes, this brings up the ethical question of whether it would be inappropriate to carry out a trial beyond the sample size at which clinical effectiveness has been demonstrated.[38] If ethical barriers limit patient sample size, then this will affect the reliability of cost outcomes, and we may have to accept higher error rates for economic trials.[39] While research into power and sample size calculations that are suitable for trials with economic and clinical outcomes is suggested, the ethical perspectives of acquiring greater patient sample sizes for cost outcomes also needs to be addressed.

Cost effectiveness plane

If each economic study is able to compute the measures ΔE and ΔC, it would be possible to plot these point estimates on the CE plane for several trials. Depending on which quadrant the scatter is most prominent, it would give us a simple but clear view of the direction of the cost economic outcome.[34] Thus, it may be advisable for researchers to compute ΔE and ΔC for their trials. In terms of ΔE, researchers should preferably use a common motor impairment scale such as Fugl-Meyer Assessment (upper limb or lower limb) to have ΔE comparable across various studies. While systematic reviewers would need to set costs to a common currency and price year, researchers ought to use a standardized cost outcome measure such as cost per patient session hour (i.e. the cost to treat a patient for one hour of therapy). Standardizing the therapy duration to one hour will allow reviewers to compare ΔC across studies. Currently, we have the measure cost per patient session, but the duration of therapy session varies among studies. The trial therapy dosage also has to be dose-matched for both intervention and control groups.

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References

1. Mackay J, Mensah G. The atlas of heart disease and stroke: part 3 - the burden: global burden of stroke [Internet] Geneva: World Health Organization; 2004 [cited 5 January 2018]. Available from: http://www.who.int/cardiovascular_diseases/resources/atlas/en/.
2. Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke (Review). Cochrane Database Syst Rev (7):2013:CD006185.
3. Mehrholz J, Pohl M, Platz T, Kugler J, Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. Cochrane Database Syst Rev (11):2015:CD006876.
4. Prange GB, Jannink MJA, Groothuis-Oudshoorn CGM, Hermens HJ, Ijzerman MJ. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. J Rehabil Res Dev 2006;43(2):171–84.
5. Lo K, Stephenson M, Lockwood C. Effectiveness of robotic assisted rehabilitation for mobility and functional ability in adult stroke patients: a systematic review. JBI Database System Rev Implement Rep 2017;15(12):3049–91.
6. Van Peppen R, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? Clin Rehabil 2004;18(8):833–62.
7. French B, Thomas LH, Leathley MJ, Sutton CJ, McAdam J, Forster A, *et al*. Repetitive task training for improving functional ability after stroke. Cochrane Database Syst Rev (4):2007:CD006073.
8. Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. Science 1996;272(5269):1791–4.
9. Whitall J. Stroke rehabilitation research: time to answer more specific questions? Neurorehabil Neural Repair 2004;18(1):3–11.
10. Yakub F, Md Khudzari AZ, Mori Y. Recent trends for practical rehabilitation robotics, current challenges and the future. Int J Rehabil Res 2014;37(1):9–21.
11. Masiero S, Poli P, Rosati G, Zanotto D, Iosa M, Paolucci S, *et al*. The value of robotic systems in stroke rehabilitation. Expert Rev Med Devices 2014;11(2):187–98.
12. Krebs HI, Hogan N. Robotic therapy: the tipping point. Am J Phys Med Rehabil 2012;91(11 suppl 3):S290–7.
13. Husemann B, Muller F, Krewer C, Heller S, Koenig E. Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke 2007;38(2):349–54.
14. Rosati G. The place of robotics in post-stroke rehabilitation. Expert Rev Med Devices 2010;7(6):753–8.
15. Fazekas G. Robotics in rehabilitation: successes and expectations. Int J Rehabil Res 2013;36(2):95–6.
16. Wagner TH, Lo AC, Peduzzi P, Bravata DM, Huang GD, Krebs HI, *et al*. An economic analysis of robot-assisted therapy for long-term upper-limb impairment after stroke. Stroke 2011;42(9):2630–2.
17. Masiero S, Poli P, Armani M, Gregorio F, Roberto R, Giulio R. Robotic upper limb rehabilitation after acute stroke by NeReBot: evaluation of treatment costs. Biomed Res Int 2014;2014:265634.

18. Hesse S, Hess A, Werner CC, Kabbert N, Buschfort R. Effect on arm function and cost of robot-assisted group therapy in subacute patients with stroke and a moderately to severely affected arm: a randomized controlled trial. Clin Rehabil 2014;28(7):637–47.
19. Lo K, Stephenson M, Lockwood C. The economic cost of robotic rehabilitation for adult stroke patients: a systematic review protocol. JBI Database System Rev Implement Rep 2018;16(8):1593–8.
20. Canadian Partnership for Stroke Recovery. Fugl-Meyer Assessment of Sensorimotor Recovery After Stroke (FMA) [Internet]. [cited 20 February 2018]. Available from: http://www.strokengine.ca/indepth/fma_indepth/.
21. Collin C, Wade D. Assessing motor impairment after stroke: a pilot reliability study. J Neurol Neurosurg Psychiatry 1990;53(7):576–9.
22. Canadian Partnership for Stroke Recovery. Functional Ambulation Categories (FAC) [Internet]. [cited 20 February 2018]. Available from: http://www.strokengine.ca/indepth/fac_indepth/.
23. Canadian Partnership for Stroke Recovery. Barthel Index (BI) [Internet]. [cited 21 February 2018]. Available from: http://www.strokengine.ca/indepth/bi_indepth/.
24. Canadian Partnership for Stroke Recovery. Functional Independence Measure (FIM) [Internet]. [cited 21 February 2018]. Available from: http://www.strokengine.ca/indepth/fim_indepth/.
25. Gomersall J, Jadotte Y, Xue Y, Lockwood S, Riddle D, Preda A. Conducting systematic reviews of economic evaluations. Int J Evid Based Healthc 2015;13:170–8.
26. Gomersall JS, Jadotte YT, Xue Y, Lockwood S, Riddle D, Preda A. Chapter 6: Systematic reviews of economic evidence. In: Aromataris E, Munn Z, editors. Joanna Briggs Institute Reviewer's Manual [Internet]. Adelaide: Joanna Briggs Institute, 2014. [cited DATE]. Available from: https://reviewersmanual.joannabriggs.org/.
27. Nixon J, Khan KS, Kleijnen J. Summarising economic evaluations in systematic reviews: a new approach. BMJ 2001;322(7302):1596–8.
28. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315(7109):629–34.
29. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1(2):97–111.
30. Bustamante Valles K, Montes S, Madrigal Mde J, Burciaga A, Martinez ME, Johnson MJ. Technology-assisted stroke rehabilitation in Mexico: a pilot randomized trial comparing traditional therapy to circuit training in a robot/technology-assisted therapy gym. J Neuroeng Rehabil 2016;13(1):83.
31. Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
32. McCabe J, Monkiewicz M, Holcomb J, Pundik S, Daly JJ. Comparison of robotics, functional electrical stimulation, and motor learning methods for treatment of persistent upper extremity dysfunction after stroke: a randomized controlled trial. Arch Phys Med Rehabil 2015;96(6):981–90.
33. Vanoglio F, Bernocchi P, Mule C, Garofali F, Mora C, Taveggia G, *et al*. Feasibility and efficacy of a robotic device for hand rehabilitation in hemiplegic stroke patients: A randomized pilot controlled study. Clin Rehabil 2016;31(3):351–60.
34. Black WC. The CE plane: a graphic representation of cost-effectiveness. Med Decis Making 1990;10(3):212–4.
35. Briggs AH, O'Brien BJ, Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. Annu Rev Public Health 2002;23:377–401.
36. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves – facts, fallacies and frequently asked questions. Health Econ 2004;13(5):405–15.
37. Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, *et al*. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. J Clin Epidemiol 2013;66(2):140–50.
38. Briggs A. Economic evaluation and clinical trials: size matters. BMJ 2000;321(7273):1362–3.
39. Briggs AH, Gray AM. Power and sample size calculations for stochastic cost-effectiveness analysis. Med Decis Making 1998;18(2 Suppl):S81–92.
40. Cook J, Drummond M, Heyse JF. Economic endpoints in clinical trials. Stat Methods Med Res 2004;13(2):157–76.
41. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, *et al*. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force Report. Value Health 2009;12(4):409–18.
42. The Joanna Briggs Institute. The JBI approach: Grades of recommendation [Internet]. 2014 [cited 20 February 2018]. Available from: http://joannabriggs.org/assets/docs/approach/JBI-grades-of-recommendation_2014.pdf

Appendix I: Search strategies

Database	Search terms	Returns
PubMed	Robotics[mh] OR Robot*[tw] OR Exoskeleton Device[mh] OR Exoskeleton*[tw] OR Gait Trainer[tw] OR Lokomat[tw]) AND (Rehabilitation[mh] OR Rehabilitation[tw] OR Habilitation[tw]) AND (Stroke[mh] OR Stroke*[tw] OR "Cerebrovascular Accident" OR Cerebral[tw] OR "Cerebral Stroke" OR "Cerebrovascular Stroke" OR "Acute Stroke" OR "Sub-acute Stroke" OR "Subacute Stroke") AND (Economics[mh] OR Cost-Benefit Analysis[mh] OR Costs and Cost Analysis[mh] OR Health Care Costs[mh] OR Technology Assessment, Biomedical[mh] OR Cost*[tw]	92
Embase	Robotics/exp OR Robotics/syn OR Robot*:ti,ab OR 'robotic exoskeleton'/exp OR 'robotic exoskeleton'/syn OR 'exoskeleton (rehabilitation)'/exp OR 'exoskeleton (rehabilitation)'/syn OR Exoskeleton*:ti,ab OR 'Gait Trainer':ti,ab OR Lokomat:ti,ab AND Rehabilitation/exp OR Rehabilitation/syn OR Rehabilitation:ti,ab OR Habilitation:ti,ab AND Stroke/exp OR Stroke/syn OR Stroke*:ti,ab OR 'Cerebrovascular Accident'/exp OR 'Cerebrovascular Accident'/syn OR 'Cerebrovascular Accident':ti,ab OR Cerebral:ti,ab OR 'Cerebral Stroke':ti,ab OR 'Cerebrovascular Stroke':ti,ab OR 'Acute Stroke':ti,ab OR 'Sub-acute Stroke':ti,ab OR 'Subacute Stroke':ti,ab AND 'Health Economics'/exp OR 'Health Economics'/syn OR 'Health Economics':ti,ab OR 'Cost Benefit Analysis'/exp OR 'Cost Benefit Analysis'/syn OR 'Cost Benefit Analysis':ti,ab OR 'Health Care Cost'/exp OR 'Health Care Cost'/syn OR 'Health Care Cost':ti,ab OR 'Biomedical Technology Assessment'/exp OR 'Biomedical Technology Assessment'/syn OR 'Biomedical Technology Assessment':ti,ab OR 'Cost Effectiveness Analysis'/exp OR 'Cost Effectiveness Analysis'/syn OR 'Cost Effectiveness Analysis':ti,ab OR Cost/exp OR Cost/syn OR Cost*:ti,ab	126
CINAHL	MH Robotics+ OR TI Robot* OR AB Robot* OR MH Assistive Technology Devices+ OR TI "Assistive Technology Devices" OR AB "Assistive Technology Devices" OR TI Exoskeleton* OR AB Exoskeleton* OR TI 'Gait Trainer' OR AB 'Gait Trainer' OR TI Lokomat OR AB Lokomat AND MH Rehabilitation+ OR TI Rehabilitation OR AB Rehabilitation OR TI Habilitation OR AB Habilitation AND MH Stroke+ OR TI Stroke* OR AB Stroke* OR TI "Cerebrovascular Accident" OR AB "Cerebrovascular Accident" OR TI Cerebral OR AB Cerebral OR TI "Cerebral Stroke" OR AB "Cerebral Stroke" OR TI "Cerebrovascular Stroke" OR AB "Cerebrovascular Stroke" OR TI "Acute Stroke" OR AB "Acute Stroke" OR TI "Sub-acute Stroke" OR AB "Sub-acute Stroke" OR TI "Subacute Stroke" OR AB "Subacute Stroke" AND MH Economics in Healthcare+ OR TI "Economics in Healthcare" OR AB "Economics in Healthcare" OR MH Cost Benefit Analysis or Cost Effectiveness+ OR TI "Cost Benefit Analysis or Cost Effectiveness" OR AB "Cost Benefit Analysis or Cost Effectiveness" OR MH Costs and Cost Analysis+ OR TI "Costs and Cost Analysis" OR AB "Costs and Cost Analysis" OR MH Health Care Costs+ OR TI "Health Care Costs" OR AB "Health Care Costs" OR MH Technology Assessment, Biomedical+ OR TI "Technology Assessment, Biomedical" OR AB "Technology Assessment, Biomedical" OR MH Cost Effectiveness+ OR TI "Cost Effectiveness" OR AB "Cost Effectiveness" OR MH Cost Effective+ OR TI "Cost Effective" OR AB "Cost Effective" OR MH Cost Benefit Analysis+ OR TI "Cost Benefit Analysis" OR AB "Cost Benefit Analysis" OR MH Cost+ OR TI Cost* OR AB Cost*	38

(*Continued*)

Database	Search terms	Returns
Cochrane (CENTRAL)	robot* and rehabilitation and stroke and cost*	25
PEDro	robot* rehabilitation stroke cost*	6
NHS Economic Evaluation Database (NHS EED)	robot* and rehabilitation and stroke	1
Cost Effectiveness Analysis (CEA) Registry	robot	14
Health Technology Assessment (HTA) Database	robot* and rehabilitation and stroke	1
MedNar	robot* and rehabilitation and stroke and cost*	60
ProQuest Dissertations and Theses	robot* and rehabilitation and stroke and cost*	17
ClinicalTrials.gov	robot* and rehabilitation and stroke and cost*	4

Appendix II: Excluded studies

Study	Reason for exclusion
Housley SN, Garlow AR, Ducote K, Howard A, Thomas T, Wu D, *et al*. Increasing access to cost effective home-based rehabilitation for rural veteran stroke survivors. Austin J Cerebrovasc Dis Stroke. 2016;3(2):1-11.	Ineligible context: trial was for home-based rehabilitation
Masiero S, Poli P, Armani M, Gregorio F, Roberto R, Giulio R. Robotic upper limb rehabilitation after acute stroke by NeReBot: evaluation of treatment costs. Biomed Res Int. 2014;2014:265634.	Ineligible intervention: trial discussed a ''mixed protocol'' approach, which was hypothetical. No actual clinical trial was done for this approach. Actual trial was done for ''additional protocol,'' which was not dose-matched.

Appendix III: Critical appraisal results of eligible studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Bustamante Valles *et al.*[30]	Y	Y	Y	Y	Y	Y	N	N	N	N	N
Hesse *et al.*[18]	Y	Y	Y	Y	Y	Y	N	N	N	N	N
McCabe *et al.*[32]	N	Y	Y	Y	Y	Y	N	N	N	N	Y
Vanoglio *et al.*[33]	Y	Y	Y	Y	Y	Y	N	N	N	N	Y
Wagner *et al.*[16]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Total %	80%	100%	100%	100%	100%	100%	20%	20%	20%	20%	60%

Y = yes; N = no.
JBI critical appraisal checklist for economic evaluations:
Q1. Is there a well-defined question?
Q2. Is there comprehensive description of alternatives?
Q3. Are all important and relevant costs and outcomes for each alternative identified?
Q4. Has clinical effectiveness been established?
Q5. Are costs and outcomes measured accurately?
Q6. Are costs and outcomes valued credibly?
Q7. Are costs and outcomes adjusted for differential timing?
Q8. Is there an incremental analysis of costs and consequences?
Q9. Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?
Q10. Do study results include all issues of concern to users?
Q11. Are the results generalizable to the setting of interest in the review?

Appendix IV: Characteristics of included studies

Clinical characteristics

Study	Location	Age, mean ± SD	Male (n)	Ischemic stroke (n)	Hemorrhagic stroke (n)	Acute/sub-acute	Chronic	Severe	Moderate/mild	Upper limb	Lower limb	Total training hours	IG (n)	CG (n)	Outcome measure of interest
Bustamante Valles et al.[30]	Mexico	IG: 44.1 ± 12.55 CG: 64.1 ± 8.38	7	NR	NR		x		x	x	x	48	10	10	Cost per patient per session Fugl-Meyer (upper limb) Fugl-Meyer (lower limb)
Hesse et al.[18]	Germany	IG: 71.4 ± 15.5 CG: 69.7 ± 16.6	28	41	9	x		x		x		20	25	25	Cost per patient per session Fugl-Meyer (upper limb)
McCabe et al.[32]	USA	IG: 21-49 (n = 2); 50-81 (n = 10) CG: 21-49 (n = 2); 50-81 (n = 9)	16	NR	NR		x		x	x		300	12	11	Cost per patient (over intervention period) Fugl-Meyer (upper limb)
Vanoglio et al.[33]	Italy	IG: 72 ± 11 CG: 73 ± 14	14	17	10	x		x		x		20	14	13	Cost per patient (over intervention period) Motricity Index (upper limb)
Wagner et al.[16]	USA	IG: 66 ± 11 CG: 64 ± 11	89	80	13		x	x		x		36	47	46	Cost per patient per session Fugl-Meyer (upper limb)

IG: intervention group; CG: control group; n: sample size; SD: standard deviation; NR: not recorded.

Economic characteristics

Study	Currency	Annual cost of device (IG)	Annual cost of device maintenance (IG)	Device depreciation period (years)	Annual cost of therapist	Cost (CG)	Cost (IG)	Price year	Analytic viewpoints	Trial time horizons	Study design	TPR/day (IG)	TPR/day (CG)	Authors' economic conclusion
Bustamante Valles *et al.*[30]	USD/ Mexican pesos (MXN)	USD $18,024 (MXN $216,296)	MXN $108,148	2	USD $19,612 (MXN $235,344)	Cost/ patient session: USD $19.21	Cost/ patient session: USD $6.99	2011 (USD)	NR	January 2012 to September 2013 (21 months)	IG used a circuit robotic gym concept that had both upper and lower limb robotic devices, FES and cognitive devices (total of six stations). Robotic equipment cost included FES and cognitive training devices. CG had conventional training.	24	4	Robotic cheaper than conventional
Hesse *et al.*[18]	Euro	€9,600	€2,400	4	Assistant therapist: €25,000 Experienced therapist: €35,000	Cost/ patient session: €10.00	Cost/ patient session: €4.15	NR	NR	18 months	IG used a circuit "arm studio" concept that had six training devices. The devices consisted of robotic and non-assistive mechanical devices such as Reha-Slide and Reha-Digit. Robotic equipment cost included non-robotic training devices. CG had conventional training.	35	15	Robotic cheaper than conventional
McCabe *et al.*[32]	USD	$17,800	$8,000	5	USD $98,000	Cost/ patient: USD $4570	Cost/ patient: USD $5686	NR	NR	NR	Trial had three arms: robotic and conventional, FES and conventional, and conventional IG used an upper limb robotic device. CG had conventional training.	One therapist to three patients (five hours/ day)	NR	Robotic more expensive than conventional
Vanoglio *et al.*[33]	Euro	€6,000	NR	5	Annual value not provided, only cost per minute: €0.40/minute	Cost/ patient: Euro €480	Cost/ patient: Euro €237	NR	NR	May 2013 and January 2014 (9 months)	IG used a hand robotic glove. CG had conventional training.	8	NR	Robotic cheaper than conventional
Wagner *et al.*[16]	USD	$46,150	$15,000	5	Annual value not provided, only cost per hour: USD $218/ hour	Cost/ patient session: USD $218	Cost/ patient session: USD $140	2009	Societal	November 2006 to October 2008 (24 months)	Trial had three arms: robotic, conventional, and usual care (i.e. treatment as needed). IG used an upper limb robotic device. CG had conventional training.	7	NR	Robotic equivalent to conventional

IG: intervention group; CG: control group; NR: not recorded; FES: functional electrical stimulation; TPR: therapist-to-patient ratio; USD: U.S. dollar; MXN: Mexican peso.

Statement of Authorship

Title of Paper	The economic cost of robotic rehabilitation for adult stroke patients: a systematic review protocol.
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Principal Author

Name of Principal Author (Candidate)	Kenneth Lo		
Contribution to the Paper	I was responsible for the overall creation of this paper. As the primary author I developed the protocol, conducted the literature searches, retrieved papers, and assessed each paper for their eligibility. I subsequently undertook critical appraisal, data extraction and data analysis. I was also responsible for responses to reviewers and revisions to the paper. The review was conducted using tools provided by the Joanna Briggs Institute.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	October 2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr. Matthew Stephenson		
Contribution to the Paper	Supervisor: provided conceptualization and methodological guidance to the manuscript. Contributed to the writing and revision of the paper, including responding to peer review comments, and reviewing the findings and conclusion.		
Signature		Date	October 2019

Name of Co-Author	Assoc. Prof. Craig Lockwood		
Contribution to the Paper	Supervisor: provided conceptualization and methodological guidance to the manuscript. Contributed to the writing and revision of the paper, including responding to peer review comments, and reviewing the findings and conclusion.		
Signature		Date	October 2019

Please cut and paste additional co-author panels here as required.

The economic cost of robotic rehabilitation for adult stroke patients: a systematic review protocol

Kenneth Lo • Matthew Stephenson • Craig Lockwood

Joanna Briggs Institute, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, Australia

Review question/objective: The objective of this review is to identify the best available evidence on the economic cost of robotic rehabilitation for adult stroke patients to improve their motor movement abilities. More specifically, the objective is to identify the evidence on the economic cost of robotic training compared to conventional physiotherapy for adult stroke patients, from the perspective of hospitals.

Keywords Stroke; Robotics; rehabilitation; Economic; Systematic Review Protocol

JBI Database System Rev Implement Rep 2018; 16(8):1593–1598.

Introduction

Stroke is a leading cause of disability with 15 million people suffering a stroke yearly.[1] In the United States, the annual healthcare spending for stroke patients is USD80 billion.[2] Given the large social and economic burden of stroke, it is important to identify appropriate treatment methods that can not only reduce the disability of stroke survivors, but also do so cost effectively. Traditionally, stroke patients would undergo rehabilitation post stroke and, depending on the nature of the disability, rehabilitation would be administered by a multi-disciplinary team of physiotherapists, occupational therapists, speech therapists and neuropsychologists, who work together to offer integrated, holistic rehabilitation therapy.[3] For physical impairments, stroke patients will usually undergo conventional physiotherapy, which involves patients undergoing repetitive, high intensity, task-specific exercises that enable them to regain their motor and functional abilities.[4,5] In animal studies, it has been shown that test subjects regain motor abilities after intensive and repetitive task training.[6] This was associated with a reorganization of the undamaged motor cortex to enable recovery of motor abilities of the affected limbs.[7] This ''neuroplasticity'' is the underlying principle of motor learning involving repetitive, high intensity, task-specific exercises.[8] However, conventional physiotherapy trainings are labor intensive and places physical strain on physiotherapists.[9]

To facilitate the high repetitions required, robotic devices have been used to assist therapists to rehabilitate patients based on high repetitions of task specific exercises.[10] These robotic devices provide intensive, consistent and repetitive cycles over long periods to train the impaired limbs of patients. There are two main types of robotic devices: exoskeletons or end-effectors. Exoskeletons are devices that wrap around limbs and are able to assist each limb joint to move. End-effectors are devices that assist only the extremities of a limb (either hands or feet).[9] Regardless of the design mechanism, one key feature of robotic devices is the ability to automatically assist patients to move their limbs when they are unable to do so by themselves. This automated assistive feature enables high repetitions to be achieved.

Systematic reviews conducted on these robotic devices showed varying degrees of effectiveness. One systematic review that assessed lower limb outcomes found that robotic-assisted gait training increased the odds of participants being able to walk independently.[11] For the sub-group of severely impaired patients, findings indicated that robotic treatment was more effective.[11] In terms of upper limb outcomes, systematic reviews have found that robot-assisted arm training improved arm motor movement[12,13] and activities of daily living scores.[12] A recent systematic review found that robotic training was just as effective as conventional

Correspondence: Kenneth Lo, kenneth.lo@adelaide.edu.au

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physiotherapy for upper limb motor movement, lower limb walking and activities of daily living, but for severely impaired lower limb patients, robotic training was found to be more effective than conventional training.[14] Overall, these reviews showed that robotic devices, at a minimum, offered equivalent treatment outcomes as conventional physiotherapy.

While robotic devices enable a high intensity training regime that can be just as effective as conventional therapy, the robotic training equipment can cost up to several hundred thousand dollars[15] per device, which is a significant capital outlay for hospitals. Hence, the decision to introduce robotic devices into clinical settings and offer robotic stroke rehabilitation to patients has an important cost consideration for healthcare providers. Despite its cost, robotic devices may increase the work efficiency of therapists, hence more patients can be treated and this could lead to an overall reduction in cost of treatment per patient.[16] There have been clinical studies to determine the economic cost of robotic devices in the rehabilitation of stroke patients.[17] However, these studies presented a mixed picture of the cost impact of robotic devices. One study[18] that compared the cost-effectiveness of robotic rehabilitation with conventional rehabilitation had an uncertain finding, while another study[19] found that robotic devices were economically sustainable. A third study[20] compared the treatment costs and found that robotic training was less expensive than conventional training. A preliminary search of PubMed, Embase, *JBI Database of Systematic Reviews and Implementation Reports*, Cochrane Library and PROSPERO was carried out to identify systematic reviews that had been conducted on this topic area and no reviews were found.

The current literature does not provide a clear determination of the cost impact of using robotic devices for stroke rehabilitation and it is the aim of this review to provide clarity to the discussion and assist healthcare providers to understand the economic cost of robotic rehabilitation.

Inclusion criteria

Participants

This review will consider studies that include adult stroke patients (18 years and over) of all genders, regardless if stroke is due to ischemic or hemorrhagic causes. Patients with pre-existing impairments that are not caused by stroke, such as disabilities due to spinal cord injuries, Parkinson's disease, multiple sclerosis and traumatic brain injuries, will be excluded. Study participants may be new stroke patients or repeat stroke patients at acute, sub-acute or chronic stages of their stroke, as long as they have been accepted into a rehabilitation program.

Intervention and comparator

The review will consider studies that evaluate rehabilitation of stroke patients using robotic devices and compare the outcomes to control groups which use conventional physiotherapy. The types of robotic devices can be varied (e.g. either robotic exoskeletons or end-effectors for gait training), as long as interventions involve electro-mechanical devices with automated assistive feature to help patients regain their motor abilities.

Interventions involving the devices below are not considered as robotic rehabilitation devices as they do not exhibit assistive automation that robotic devices have:

- Non-interactive devices that deliver passive motion such as treadmills, static body-weight assisted treadmills, bicycles, static walking aids, static orthoses (such as ankle-foot orthoses addressing foot drop) or pure mechanical trainers (e.g. Reha-Slide, Reha-Slide duo).
- Standalone video games controlled solely by patient without automated assistive feature, such as Nintendo Wii.
- Rehabilitation programs using non-conventional therapies such as acupuncture, functional electrical stimulation (FES), transcranial direct current stimulation, motor imagery, biofeedback and constrain induced therapy (CIT).

The intervention group can have an added conventional physiotherapy component or not. If the intervention group has an added conventional physiotherapy component, this can involve non-interactive static devices. The intervention should not contain other types of non-conventional therapy (e.g. FES, transcranial direct current stimulation, motor imagery or CIT). For multiple-arm studies, only results of the intervention arm with robotic rehabilitation will be compared to the conventional therapy control arm. The intervention arm with a combination of robotic devices and non-conventional therapy will be excluded from analysis.

As control groups, patients do not receive robotic rehabilitation but receive only conventional physiotherapy. The conventional physiotherapy treatment may include non-interactive static devices (e.g. bicycles, treadmills, acupuncture). The amount of therapy treatment in both intervention and control groups should be the same in terms of duration, i.e. dose-matched. For example, if patients in the intervention group undergo 60 minutes of therapy using a robotic device on top of a conventional physiotherapy component, then in the control group the patients should also undergo an additional 60 minutes of conventional physiotherapy. Therefore, the total amount of therapy time planned for patients (over the intervention period) should be the same for both groups.

Context

Studies where the rehabilitation setting is either inpatient or outpatient will be included. Home rehabilitation patients will be excluded due to potential confounding of treatment adherence. The rehabilitation program can be conducted in hospitals, nursing facilities or across multi-centers, and only physical impairments related to upper and lower limbs will be considered.

Outcomes

This review will consider studies that include the following outcomes:

- Cost minimization:
  Studies that aim to compare the cost of providing robotic rehabilitation against the cost of providing conventional physiotherapy will be included.
- Cost-effectiveness:
  Studies that aim to compare the cost of providing robotic rehabilitation against the cost of providing conventional physiotherapy will be included, whereby the outcome is presented as relative costs to achieve a unit of effect. The unit of effect should reflect the motor movement ability of patients and should involve the following measurement scales:
  - For measurement scale of upper limbs, the Fugl-Meyer Assessment[21] (upper extremity score) is the preferred scale. If a study does not use this scale, then an alternative measurement scale that quantifies upper limb motor movement (e.g. upper limb Motricity Index[22]) will be considered.
  - For measurement scale of lower limbs, the Functional Ambulation Category[23] is the preferred scale. If a study does not use this scale, then an alternative measurement scale that quantifies walking will be considered, e.g. Barthel Index[24] (ambulation item) or Functional Independence Measure[25] (walking item).
- Cost utility:
  Studies that aim to compare the cost of providing robotic rehabilitation against the cost of providing conventional physiotherapy will be included, whereby the outcome is presented as relative costs to achieve a unit of utility, which is measured in quality adjusted life years (QALY).
- Cost benefit:
  Studies that aim to compare the cost of providing robotic rehabilitation against the cost of providing conventional physiotherapy will be included, whereby the outcome is presented as relative costs to achieve a unit of benefit, which is also measured in monetary units.

The cost perspective adopted is from the viewpoint of hospitals, as hospitals are the main decision makers for introducing robotic rehabilitation to stroke patients in a clinical setting. As such, only direct medical costs (e.g. therapist time, medical devices) will be considered. Indirect costs, such as cost of patients' caregivers or patients' travel expenses, will be excluded. Direct non-medical costs (e.g. hospital administrative cost) will also be excluded as this type of cost is common to all patients, regardless of robotic or conventional training. Cost components during the follow-up period will be excluded, as it is the intent of the review to examine the costs associated with providing the intervention during the treatment period.

Types of studies

Economic studies of robotic training involving upper and lower limbs will be included. The economic component of the review will consider cost minimization, cost-effectiveness, cost utility and cost benefit studies, which compare robotic rehabilitation to conventional physiotherapy in dose-matched therapy sessions. Partial economic evaluations (i.e. cost analysis, cost-description studies and cost-outcome descriptions) of robotic rehabilitation versus dose-matched conventional physiotherapy will also be considered for inclusion. Modeling studies will not

be considered, as the review aims to collect empirical data from prospective clinical trials.

Studies published in English will be considered for inclusion in this review and a date limit starting from 2000 will be set, as automated robotic devices have increasingly been used since 2000, together with an associated increase in the number of studies undertaken.

Methods

Search strategy

The search strategy will aim to find both published and unpublished studies. An initial limited search of PubMed will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the articles. This will inform the development of a search strategy which will be tailored for each information source. A full search strategy for PubMed is detailed in Appendix I. The reference list of studies selected for critical appraisal will also be screened for additional studies.

Information sources

The databases to be searched include: PubMed, Embase, CINAHL, Cochrane (CENTRAL), PEDro (Physiotherapy Evidence Database), NHS Economic Evaluation Database (NHS EED), Cost Effectiveness Analysis (CEA) registry, and Health Technology Assessment (HTA) database.

The search for unpublished studies will include: MedNar, ProQuest Dissertations and Theses and ClinicalTrials.gov

Study selection

Following the search, all identified citations will be collated and uploaded into bibliographic software or citation management system and duplicates removed. Titles and abstracts will then be screened for assessment against the inclusion criteria for the review. Studies that meet the inclusion criteria will be retrieved in full and assessed in detail against the inclusion criteria. Full text studies that do not meet the inclusion criteria will be excluded and reasons for exclusion will be provided in an appendix in the final systematic review report. Included studies will undergo a process of critical appraisal. The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram.

Assessment of methodological quality

Selected studies will be critically appraised by two independent reviewers at the study level for methodological quality using the standardized critical appraisal instruments from the Joanna Briggs Institute for Economic Evaluation.[26] Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer.

As economic analysis of robotic devices is an emerging research area, all studies regardless of their methodological quality will undergo data extraction and synthesis (where possible) to maximize data collection. However, study quality will be considered in the interpretation of review findings.

Data extraction

Data will be extracted by two independent reviewers from papers included in the review using the standardized data extraction tool from Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI). The data extracted will include: firstly, descriptive data about the intervention/s and comparator/s examined, study population/participants and context, study methods; and secondly, results for the resource use, cost and cost-effectiveness measures; thirdly, where possible, author conclusions about factors that promote (impede) cost-effectiveness of the intervention. In the event of specific key data of interest being absent from published articles, corresponding authors will be contacted.

Data synthesis

Economic findings will, where possible, be synthesized and presented in a tabular summary. Where this is not possible, findings will be presented in narrative form. In general, depending on quantity, quality and nature of the economic papers identified, economic results will be subjected to:

- Narrative summary, or
- Sorting in tables by comparisons/outcomes, or
- Tabulated in a permutation matrix.[27,28]

Data permitting, sub-group analysis may be conducted to shed light on whether there are differences in costs due to: i) upper limb; ii) lower limb; iii) impairment levels; and iv) stages of stroke recovery (acute/sub-acute/chronic).

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References

1. Mackay J, Mensah G. The Atlas of Heart Disease and Stroke: Part 3 - The Burden: Global burden of stroke: World Health Organization; [cited 2018 5 January]. Available from: http://www.who.int/cardiovascular_diseases/resources/atlas/en/.
2. Censullo JL. The Economics of Health Care for Stroke Patients. New Jersey State Stroke Conference, USA. 2014.
3. Gresham GE, Alexander D, Bishop DS, Giuliani C, Goldberg G, Holland A, *et al*. Rehabilitation. Stroke 1997;28(7):1522–6.
4. Van Peppen R, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? Clin Rehabil 2004;18(8):833–62.
5. French B, Thomas LH, Leathley MJ, Sutton CJ, McAdam J, Forster A, *et al*. Repetitive task training for improving functional ability after stroke. Cochrane Database Syst Rev (4):2007:CD006073.
6. Kleim JA, Barbay S, Nudo RJ. Functional Reorganization of the Rat Motor Cortex Following Motor Skill Learning. J Neurophysiol 1998;80(6):3321–5.
7. Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural Substrates for the Effects of Rehabilitative Training on Motor Recovery After Ischemic Infarct. Science 1996;272(5269):1791–4.
8. Whitall J. Stroke Rehabilitation Research: Time to Answer More Specific Questions? Neurorehabil Neural Repair 2004;18(1):3–11.
9. Masiero S, Poli P, Rosati G, Zanotto D, Iosa M, Paolucci S, *et al*. The value of robotic systems in stroke rehabilitation. Expert Rev Med Devices 2014;11(2):187–98.
10. Yakub F, Md Khudzari AZ, Mori Y. Recent trends for practical rehabilitation robotics, current challenges and the future. Int J Rehabil Res 2014;37(1):9–21.
11. Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke (Review). Cochrane Database Syst Rev (7):2013:CD006185.
12. Mehrholz J, Pohl M, Platz T, Kugler J, Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. Cochrane Database Syst Rev (11):2015:CD006876.
13. Prange GB, Jannink MJA, Groothuis-Oudshoorn CGM, Hermens HJ, Ijzerman MJ. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. J Rehabil Res Dev 2006;43(2):171–84.
14. Lo K, Stephenson M, Lockwood C. Effectiveness of Robotic Assisted Rehabilitation for Mobility and Functional Ability in Adult Stroke Patients: A Systematic Review. JBI Database System Rev Implement Rep 2017;15(1):39–48.
15. Krebs HI, Hogan N. Robotic Therapy: The Tipping Point. Am J Phys Med Rehabil 2012;91(11 0 3):S290–7.
16. Husemann B, Muller F, Krewer C, Heller S, Koenig E. Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke 2007;38(2):349–54.
17. Fazekas G. Robotics in rehabilitation: successes and expectations. Int J Rehabil Res 2013;36(2):95–6.
18. Wagner TH, Lo AC, Peduzzi P, Bravata DM, Huang GD, Krebs HI, *et al*. An economic analysis of robot-assisted therapy for long-term upper-limb impairment after stroke. Stroke 2011;42(9):2630–2.
19. Masiero S, Poli P, Armani M, Gregorio F, Roberto R, Giulio R. Robotic upper limb rehabilitation after acute stroke by NeReBot: evaluation of treatment costs. Biomed Res Int 2014;2014:265634.
20. Hesse S, Hess A, Werner CC, Kabbert N, Buschfort R. Effect on arm function and cost of robot-assisted group therapy in subacute patients with stroke and a moderately to severely affected arm: a randomized controlled trial. Clin Rehabil 2014;28(7):637–47.
21. Canadian Partnership for Stroke Recovery. Fugl-Meyer Assessment of Sensorimotor Recovery After Stroke (FMA); [Internet]. [cited 2016 April 18]. Available from: http://www.strokengine.ca/indepth/fma_indepth/.
22. Collin C, Wade D. Assessing motor impairment after stroke: a pilot reliability study. J Neurol Neurosurg Psychiatry 1990;53(7):576–9.
23. Canadian Partnership for Stroke Recovery. Functional Ambulation Categories (FAC); [Internet]. [cited 2016 April 18]. Available from: http://www.strokengine.ca/indepth/fac_indepth/.
24. Canadian Partnership for Stroke Recovery. Barthel Index (BI); [Internet]. [cited 2016 April 18]. Available from: http://www.strokengine.ca/indepth/bi_indepth/.
25. Canadian Partnership for Stroke Recovery. Functional Independence Measure (FIM); [Internet]. [cited 2016 April 18]. Available from: http://www.strokengine.ca/indepth/fim_indepth/.
26. Gomersall J, Jadotte Y, Xue Y, Lockwood S, Riddle D, Preda A. Conducting systematic reviews of economic evaluations. Int J Evid Based Healthc 2015;13(3):170–8.
27. The Joanna Briggs Institute, The University of Adelaide. Joanna Briggs Institute Reviewers' Manual: 2014 edition Joanna Briggs Institute; 2014.
28. The Systematic Review of Economic Evaluation Evidence. In: Joanna Briggs Institute Reviewers' Manual: 2014 edition [Internet]. Australia: The Joanna Briggs Institute; 2014 [cited 2016 April 182]. Available from http://joannabriggs.org/assets/docs/sumari/ReviewersManual-The-Systematic-Review-of-Economic-Evaluation-Evidence-2014_v2.pdf.

Appendix I: Search strategy for PubMed

PubMed search terms:

(Robotics[mh] OR Robot*[tw] OR Exoskeleton Device[mh] OR Exoskeleton*[tw] OR Gait Trainer[tw] OR Lokomat[tw]) AND (Rehabilitation[mh] OR Rehabilitation[tw] OR Habilitation[tw]) AND (Stroke[mh] OR Stroke*[tw] OR "Cerebrovascular Accident" OR Cerebral[tw] OR "Cerebral Stroke" OR "Cerebrovascular Stroke" OR "Acute Stroke" OR "Sub-acute Stroke" OR "Subacute Stroke") AND (Economics[mh] OR Cost-Benefit Analysis[mh] OR Costs and Cost Analysis[mh] OR Health Care Costs[mh] OR Technology Assessment, Biomedical[mh] OR Cost*[tw])

Breakdown of search terms based on key search concepts:

Robotic	Rehabilitation	Stroke	Cost
Robotics[mh] OR Robot*[tw] OR Exoskeleton Device[mh] OR Exoskeleton*[tw] OR Gait Trainer[tw] OR Lokomat[tw]	Rehabilitation[mh] OR Rehabilitation[tw] OR Habilitation[tw]	Stroke[mh] OR Stroke*[tw] OR "Cerebrovascular Accident" OR Cerebral[tw] OR "Cerebral Stroke" OR "Cerebrovascular Stroke" OR "Acute Stroke" OR "Sub-acute Stroke" OR "Subacute Stroke"	Economics[mh] OR Cost-Benefit Analysis[mh] OR Costs and Cost Analysis[mh] OR Health Care Costs[mh] OR Technology Assessment, Biomedical[mh] OR Cost*[tw]

Chapter Five: Dominance Ranking Score (Paper Six - Submitted for publication, under peer review)

Paper 6: Lo K, Stephenson M, Lockwood C. Extending the hierarchical decision matrix to incorporate a dominance ranking score for economic systematic reviews. 2019.

Statement of Contribution

Kenneth Lo (Candidate)

I was responsible for the overall creation of this paper. As the primary author I developed the method concept, drafted the content, and structured the paper for journal submission. I was also responsible for responses to reviewers and revisions to the paper.

Statement of Authorship

Title of Paper	Extending the hierarchical decision matrix to incorporate a dominance ranking score for economic systematic reviews.
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Journal: Elsevier Methods X

Principal Author

Name of Principal Author (Candidate)	Kenneth Lo		
Contribution to the Paper	I was responsible for the overall creation of this paper. As the primary author I developed the method concept, drafted the content, and structured the paper for journal submission. I was also responsible for responses to reviewers and revisions to the paper.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	October 2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr. Matthew Stephenson		
Contribution to the Paper	Supervisor: provided conceptualization and methodological guidance to the manuscript. Contributed to the writing and revision of the paper, including responding to peer review comments, and reviewing the findings and conclusion.		
Signature		Date	October 2019

Name of Co-Author	Assoc. Prof. Craig Lockwood		
Contribution to the Paper	Supervisor: provided conceptualization and methodological guidance to the manuscript. Contributed to the writing and revision of the paper, including responding to peer review comments, and reviewing the findings and conclusion.		
Signature		Date	October 2019

Please cut and paste additional co-author panels here as required.

Method Article

Title

Extending the hierarchical decision matrix to incorporate a dominance ranking score for economic systematic reviews

Keywords

Cost-Benefit Analysis; Costs and Cost Analysis; Economics, Medical; Economics, Pharmaceutical; Evidence-Based Medicine.

Abstract

As the base of clinical evidence grows, it is increasingly common to conduct economic evaluations in addition to clinical evaluations of effectiveness in order to inform health policies. For economic systematic reviews there is currently no agreed-upon quantitative method to obtain a pooled economic effect size. With no suitable quantitative method available, the hierarchical decision matrix stands out as a tool that enables a visual summary of different types of economic studies, but there are limitations with the hierarchical decision matrix. We extended the hierarchical decision matrix with a weighted scoring system (termed dominance ranking score) to allow for useful information of a study design to be incorporated.

- The scoring system of the dominance ranking score incorporates weighting factors that are based on sample size, effect size and methodological quality of a study.
- The dominance ranking score enables a more differentiating analysis of dominance levels.
- For systematic reviews that include partial economic studies, both the hierarchical decision matrix and the dominance ranking score assist to indicate the level of economic potential for a particular intervention, which facilitates the conduct of subsequent full economic studies.

SPECIFICATIONS TABLE

Subject Area	*Medicine and Dentistry*

More specific subject area:	*Economic systematic review*
Method name:	*Dominance ranking score*
Name and reference of original method	*Hierarchical decision matrix* *Nixon J, Khan KS, Kleijnen J. Summarising economic evaluations in systematic reviews: a new approach. BMJ. 2001;322(7302):1596-8.*
Resource availability	*Not applicable*

Background

Systematic review of clinical effectiveness has become the gold standard for evidence-based medical research. As the base of clinical evidence grows, it is increasingly common to conduct economic evaluations in addition to clinical evaluations of effectiveness in order to inform health policies.[1,2] Economic evaluations can be classified into two main types: empirical economic evaluations which collect patient-level data on costs and outcomes, and decision model (simulation) based economic analyses.[2] Empirical economic evaluations involve data collection and synthesis of existing evidence using the framework of a systematic review, while economic decision modeling involves the data collection and synthesis of existing evidence in order to generate a new economic evaluation using the framework of a decision model.[3] For either type of economic evaluation, the economic outcomes are expressed using a variety of measures, such as cost effectiveness, cost utility, cost benefit and incremental cost effectiveness ratios (which measure relative efficiency and are expressed as incremental gains in clinical effectiveness, health utility values or monetary valuations).[3-5]

Systematic reviews of empirical economic studies involve several stages of research which are similar to systematic reviews of clinical effectiveness: defining the review question and inclusion criteria for study eligibility; identifying and collecting data; appraising methodological quality; analyzing collected data and undertaking meta-analysis (where appropriate); and summarizing and presenting results.[4,5] On the other hand, economic decision modelling involves computing the expected costs and outcomes of alternative interventions, based on a synthesis of evidence for the probabilities, costs and outcomes associated with each event in the pathway flow of the intervention.[3]

However, in the systematic review of empirical economic studies, there are currently no agreed-upon methods to obtain a pooled economic effect size from included empirical trials using meta-analysis or other quantitative synthesis methods.[4,6] The main reasons are the generalizability and transferability of the empirical economic studies. Economic trials are context and time sensitive,[3] as resource use and unit costs are dependent on local settings, clinical practices and currency values at a particular time. This generates high heterogeneity if the economic studies in a systematic review come from different clinical contexts in different countries. Only if the studies have similar resource use and unit costs, with economic outcomes expressed in a common metric, then meta-analysis could be appropriate.[4]

Given the current lack of quantitative synthesis methods, systematic reviews of economic studies have been restricted to methods of using descriptive narratives (via summaries or tables)[4] or plotting the magnitude and direction of cost and effectiveness using the CE-plane,[7] or applying visual summaries in a hierarchical decision matrix.[1,5] Here, we propose methods to extend the hierarchical decision matrix in order to enhance its use and address some of its limitations.

Hierarchical decision matrix

The hierarchical decision matrix (also known as dominance ranking framework)[1,5] enables a visual summary of various economic studies that have different economic outcome measures (e.g. cost-effectiveness, cost-utility, cost-benefit), which would otherwise not be possible in a quantitative meta-analysis approach.[8] Although the hierarchical decision matrix is not a quantitative synthesis method, its hierarchical structure enables an interpretation of the dominance levels of an intervention based on assessment of benefits for both cost and health outcomes within a trial. If there are more studies in a certain color band, it would indicate a dominance level which is associated with that band.

Another advantage of the hierarchical decision matrix is that it allows for economic synthesis even when only partial economic data (e.g. cost minimization data) is available. For emerging research areas, basic economic cost data is usually collected in parallel to a trial on clinical effectiveness. These trials do not usually incorporate extensive economic analysis, such as calculations of incremental cost effectiveness ratio or acceptability curves. In such a scenario, the hierarchical decision matrix allows for rudimentary economic studies with only cost minimization data to be synthesized.

Limitations of Hierarchical decision matrix/Dominance ranking framework

The hierarchical decision matrix shows the distribution of studies in the three different bands, where a predominance of the number of studies in a certain band will indicate the likely implication of the intervention. However, if there are equal numbers of studies across two or three bands, no clear conclusion can be drawn.

As the basis of the distribution is based on the number of studies, this approach also does not take into account sample sizes of the clinical trials, which affect the statistical power of a trial to detect an effect. To illustrate, in an example where there are three studies and one of them is within the band that favors the intervention, while the other two studies are within the band that rejects the intervention. Under the current hierarchical decision matrix, it will imply that the intervention is to be rejected. However, the two studies that reject the intervention could be smaller trials while the study that favors the intervention may have a larger sample size and greater precision. Rejecting the intervention in such a scenario may lead to an inaccurate conclusion.

The current hierarchical decision matrix does not give a clear interpretation in certain scenarios and also does not incorporate considerations of other aspects of a study design, such as sample sizes of the studies. If we can extend the hierarchical decision matrix to incorporate additional study aspects, it may provide more informative analysis of dominance levels.

Methods

We extend the hierarchical decision matrix using a weighted scoring system which is described here. We term this method the dominance ranking score.

The data transformation of the benefit value to make it suitable for use in the dominance ranking score is shown in Table 1. To calculate the traditional dominance ranking we transform the qualitative expression of the benefits in terms of '+' and '-' into quantitative data that can be calculated. This process of converting qualitative data into quantitative data is called quantitizing[9] and this approach of data transformation is commonly used in mixed method analysis and synthesis.[10-12] For the dominance

ranking score, in order to align the direction of the scoring for health outcome to be the same as the direction for cost outcome, a better health outcome for the intervention of interest is given a negative sign. Note that this is in opposite contrast to the hierarchical decision matrix, where a better health outcome is given a positive sign.[1]

Table 1: Benefit values for dominance ranking score

Benefit Value	Cost Outcome	Health outcome
-1	Lower	Better
0	Same	Same
+1	Higher	Poorer

We know the sample size of a trial improves the precision of the trial and the larger the sample size, the smaller the confidence interval.[13] We also know that under the fixed effects model for meta-analysis, studies are weighted by their variance, with larger studies having more weight.[14] To give a similar weighting to larger studies, which should have more precision in their effects, we can modify the existing hierarchical decision matrix by adding a weighting to the cost and health benefits that is based on their sample sizes.

The weighting calculation schema are as follows:

$$\text{Weighted Benefit} = \frac{n}{N} \times \text{Benefit Value}$$

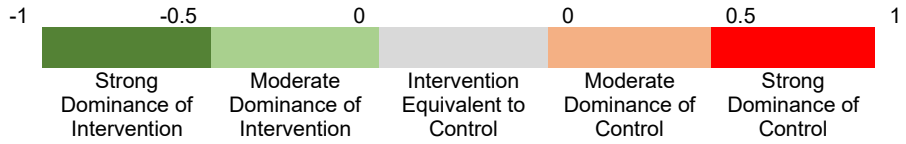
Where: n = sample size of a study; N = total sample size of studies in a sub-group analysis; Benefit Value = -1, 0 or +1

$$\text{Overall Dominance Ranking Score} = \left(\sum_{i=1}^{k} Weighted\ Cost\ Benefit + \sum_{i=1}^{k} Weighted\ Health\ Benefit \right) / 2$$

Where: k = number of studies included in a sub-group analysis

By adding a weighting based on sample size to the cost benefit, the cumulative dominance ranking score will range from -1 to +1. Similarly, by weighting the health benefit, the cumulative ranking score will range from -1 to +1. Assuming that both cost and health benefits play an equal role in determining the overall ranking result, the weighed cost and health benefits can be averaged to obtain the overall dominance ranking score. Based on this approach, we can color-code the dominance ranking scores per Table 2 to visually represent the level of dominance of the intervention.

Table 2: Dominance ranking score scale



If the overall score is in the green zone (-1 ≤ score < 0), then the result favors the intervention, with a score in the lighter green zone (-0.5 ≤ score < 0) showing a moderate dominance of the intervention and a score in the deeper green zone (-1 ≤ score < -0.5) showing a strong dominance of the intervention. If the overall score is in the red zone (0 < score ≤1), then the result favors the control, with a score in the lighter red zone (0 < score ≤ 0.5) showing a moderate dominance of the control and a score in the deeper red zone (0.5 < score ≤1) showing a strong dominance of the control. In the case that the overall score is equal to 0, then it would mean that the intervention is equivalent to the control.

Results

Using an example from a published economic review,[15] we illustrate calculations of the dominance ranking score and presentation of its color-coded scale. In the example, five studies were included for economic review and Tables 3 and 4 show the results of the original review. From Table 3, there are more studies under the green band, which indicates that the intervention is favored. For the sub-groups analysis (Table 4), all sub-groups except for the sub-group "mild/moderate", indicate that the intervention is favored. Under the "mild/moderate" sub-group, there is one study favoring the intervention and one study rejecting the intervention, which leads to an inconclusive result.

Table 3: Hierarchical decision matrix/Dominance ranking framework (all studies)

Cost	No. of studies	Health benefit	Implication for decision makers
+	0	-	Reject intervention
0	0	-	Reject intervention
+	1[16]	0	Reject intervention
-	0	-	Unclear – Judgment required on whether intervention preferable considering incremental cost effectiveness measures and priorities/willingness to pay

0	0	0	Unclear - Judgment required on whether intervention preferable considering incremental cost effectiveness measures and priorities/willingness to pay
+	0	+	Unclear - Judgment required on whether intervention preferable considering incremental cost effectiveness measures and priorities/willingness to pay
-	3[17-19]	0	Favor intervention
0	0	+	Favor intervention
-	1[20]	+	Favor intervention

Table 4: Summary of dominance levels (based on hierarchical decision matrix)

Sub-groups	Overall Dominance Level of the Intervention	Number of Studies (number of studies by implication)
All Studies	Favor intervention	5 studies (1: Reject Intervention 4: Favor Intervention)
Acute/sub-acute Patients	Favor intervention	2 studies (2: Favor Intervention)
Chronic Patients	Favor intervention	3 studies (1: Reject Intervention 2: Favor Intervention)
Mild/moderate Patients	No preference	2 studies (1: Reject Intervention 1: Favor Intervention)
Severe Patients	Favor intervention	3 studies (3: Favor Intervention)

Using the data transformation key in Table 1, these studies were assigned values of either -1, 0, +1 for their cost and health benefits. Thereafter the cost and health benefits were weighted based on sample sizes of the studies (Table 5).

Table 5: Dominance ranking score (all studies)

	Number of Participants	Cost Benefit	Weighted Cost Benefit	Health Benefit	Weighted Health Benefit	Overall Dominance Score
Bustamante Valles et al.[18]	20	-1	-0.09	0	0.00	
Hesse et al.[17]	50	-1	-0.23	0	0.00	
McCabe et al.[16]	23	1	+0.11	0	0.00	
Vanoglio et al.[20]	27	-1	-0.13	-1	-0.13	

Wagner et al.[19]	93	-1	-0.44	0	0.00	
Total	213		-0.78		-0.13	-0.46

The calculations are then repeated for every subgroup and a summary can be tabulated as shown in Table 6. As a comparison, the results using the hierarchical decision matrix and its summary tabulation are shown in Tables 3 and 4 respectively.

Table 6: Summary heatmap of dominance levels (based on dominance ranking score)

Sub-groups	Overall Dominance Level	Dominance Level of Cost Benefit	Dominance Level of Health Benefit
All Studies	Moderate Robotic	Strong Robotic	Moderate Robotic
Acute/sub-acute Patients	Strong Robotic	Strong Robotic	Moderate Robotic
Chronic Patients	Moderate Robotic	Strong Robotic	Equivalent
Mild/moderate Patients	Moderate Control	Moderate Control	Equivalent
Severe Patients	Strong Robotic	Strong Robotic	Moderate Robotic

In Table 4, for “mild/moderate” subgroup, as there was one study in each band, no clear interpretation can be drawn; whereas under the dominance ranking score (Table 6), we can glean further analysis. In this case, that overall, for the “mild/moderate” subgroup, there is a moderate dominance for control. For the cost benefit, moderate dominance for control is shown and for the health benefit, equivalent dominance is shown. Under a dominance ranking score which incorporates sample sizes, we can have not only a more differentiated analysis for overall dominance level, but also analysis which can be specific to dominance levels of cost and health benefits.

Discussion

Weighting the effects of cost and health outcomes

In the example illustrated above, we had assumed that cost and health outcomes had an equal role in determining the overall dominance ranking score. For certain trials this may not be so, for example in certain infectious diseases with high mortality rates, the health outcome might have a larger emphasis. With sufficient evidence and justification provided, reviewers can alter the weights of the cost and health outcomes for the dominance ranking score, thus enabling researchers the flexibility to determine the

ranking score that is applicable to their research context. The revised calculation schema incorporating weights to cost and health outcomes is:

$$\text{Overall Dominance Ranking Score} = \left(W_{cost} \times \sum_{i=1}^{k} Weighted\ Cost\ Benefit \right) + \left(W_{health} \times \sum_{i=1}^{k} Weighted\ Health\ Benefit \right)$$

$$W_{cost} + W_{health} = 1$$

Where: W_{cost} = weight applied to cost outcome; W_{health} = weight applied to health outcome; k = number of studies included in a sub-group analysis

Incorporating multiple weighting factors

With a weighting scheme, various aspects of a study design can be incorporated as multiple weighting factors. In our method, besides the sample sizes, we could incorporate two other weighting factors that mirror key considerations when conducting a systematic review: effect sizes of trials and methodological quality of studies.

Effect Size Weighting

If effect size data is available, it could be an additional weighting factor. Studies that show greater effect sizes will have more weight and the effect size weighting will shift the dominance ranking score towards such studies. Effect sizes are proposed as a weighting factor, as a greater effect size indicates a larger difference between the mean effects of experimental and control groups,[4] which would imply that there is likely a clinical difference between the two groups. The use of effect size weighting is also contingent upon studies having sufficient power and are methodologically well conducted.

The calculation schema to incorporate effect size weighting is:

$$\text{Weighted Benefit (Effect Size)} = \frac{|e|}{E} \text{ x Benefit Value}$$

$$E = \Sigma_{i=1}^{k} |e|$$

$$\text{Overall Dominance Ranking Score} = \left(W_{cost} \times \frac{\left(\sum_{i=1}^{k} \frac{n}{N} \times Cost\ Benefit + \sum_{i=1}^{k} \left[\frac{|e|}{E}\right]_{cost} \times Cost\ Benefit \right)}{F} \right) + \left(W_{health} \times \frac{\left(\sum_{i=1}^{k} \frac{n}{N} \times Health\ Benefit + \sum_{i=1}^{k} \left[\frac{|e|}{E}\right]_{health} \times Health\ Benefit \right)}{F} \right)$$

Where: $|e|$ = modulus of effect size of a study; E = sum of effect sizes of studies in a sub-group analysis; $\left[\frac{|e|}{E}\right]_{cost}$ is the effect size weight for cost data; $\left[\frac{|e|}{E}\right]_{health}$ is the effect size weight for health data; *F* = number of weighting factors applied (here *F* = 2); n = sample size of a study; N = total sample size of studies in a sub-group analysis; W_{cost} = weight applied to cost outcome; W_{health} = weight applied to health outcome; k = number of studies included in a sub-group analysis; Benefit Value = -1, 0 or +1

Note: Effect sizes can have positive or negative values, depending on whether intervention is favored, or control is favored. As the direction of effect size is already indicated by the sign of the benefit value, only the modulus (i.e. absolute value) of the effect size is needed for calculation of effect size weighting. As there are both cost and health (i.e. clinical effectiveness) outcomes, there will also be two effect size data: one for cost outcome and one for health outcome. It is also to note that the presented weighting scheme applies to effect sizes of continuous data (i.e. weighted mean difference, standardized mean difference), as the meta-analysis of such data is centered on a neutral value of “0”, with either side representing effects favoring intervention or control on symmetrical scales.

Methodological Quality Weighting

Another weighting factor that can be incorporated is the methodological quality of studies. During critical appraisal, systematic reviewers can assign a score to rate the quality of a study. With this appraisal score, we can incorporate quality aspects of study design into the dominance ranking score. Studies that have better methodological quality will have more weight and the quality weighting will shift the dominance ranking score towards such studies. The calculation schema to incorporate quality weighting is:

$$\text{Weighted Benefit (Quality)} = \frac{q}{Q} \text{ x Benefit Value}$$

$$Q = \Sigma_{i=1}^{k}\, q$$

$$\text{Overall Dominance Ranking Score} = \left(W_{cost} \times \frac{\left(\sum_{i=1}^{k} \frac{n}{N} \times Cost\ Benefit + \sum_{i=1}^{k} \left[\frac{|e|}{E}\right]_{cost} \times Cost\ Benefit + \sum_{i=1}^{k} \frac{q}{Q} \times Cost\ Benefit \right)}{F} \right) + \left(W_{health} \times \frac{\left(\sum_{i=1}^{k} \frac{n}{N} \times Health\ Benefit + \sum_{i=1}^{k} \left[\frac{|e|}{E}\right]_{health} \times Health\ Benefit + \sum_{i=1}^{k} \frac{q}{Q} \times Health\ Benefit \right)}{F} \right)$$

Where: q is the methodological quality score of a study; Q is the total methodological quality score in a sub-group analysis; $|e|$ = modulus of effect size of a study; E = total effect size of studies in a sub-group analysis; $[\frac{|e|}{E}]_{cost}$ is the effect size weight for cost data; $[\frac{|e|}{E}]_{health}$ is the effect size weight for health data; *F* = number of weighting factors applied (here *F* = 3); n = sample size of a study; N = total sample size of studies in a sub-group analysis; W_{cost} = weight applied to cost outcome; W_{health} = weight applied to health outcome; k = number of studies included in a sub-group analysis; Benefit Value = -1, 0 or +1

Limitations

Weighting Factors

We have shown how weights based on factors relevant and important to most reviews, namely: sample size, effect size and methodological quality of studies can be considered in the analysis. The weighting factors serve to incorporate useful aspects of a study design into the hierarchical decision matrix/dominance ranking framework and helps to provide more information for analysis and understanding of dominance levels. In our example, we have demonstrated a technique to increase precision in the analysis, through incorporating a weighting scheme that is based on sample sizes of the included studies.

Effect size weighting factor

With additional weighting factors that incorporate effect size and methodological quality, the dominance ranking score can be further enhanced for a better analysis of dominance levels. However, effect size data for economic cost measures is often not available, as meta-analysis for economic cost data is not encouraged due to resource use and cost data that are sensitive to variability across settings and between countries.[8] Even if economic effect size data is available, the different economic outcome measures used in economic trials (e.g. cost-effectiveness, cost-utility, cost-benefit, cost minimization) also make the comparison of effect sizes currently not possible, so we urge caution when incorporating effect size weighting. For economic studies where the cost setting is similar, with low variability across resource use or clinical practice, and the economic outcome measure is the same, effect size weighting

may be appropriate. If only effect size data for clinical effectiveness is available, it is not suggested to conduct effect size weighting for the health benefit without a similar effect size weighting for the cost benefit. Such an approach, while incorporating more information for health benefit analysis, will render an unbalanced weighting approach towards the overall interpretation of dominance levels.

Another consideration to incorporating effect size weighting factor is that outlying studies in a meta-analysis would skew the dominance ranking score towards such studies. Unless the causes for the outlying effect can be explained, such outliers should be viewed with caution and be justified if included.

Methodological quality weighting factor

For methodological quality weighting, the quality score assigned to a study after critical appraisal would depend on the appraisal tool used. There are various appraisal tools available and some of these tools are scales or checklists. For checklists, there is usually no scoring mechanism reported for these tools and to obtain a summary quality score, review authors would need to apply their own scoring mechanism. Even for tools that are scales, there is also debate on the validity of the summary quality score.[8] Although incorporation of the quality weighting in the dominance ranking score is independent of the tools, because of the subjective nature of quality scores, review authors ought to exercise caution when applying the quality weighting. To add credibility and reliability, it is suggested that the scoring matrix be made clear in the systematic review and, preferably, be pre-specified in a review protocol. There should also be two appraisers to rate a study and the quality score be averaged for use in the dominance ranking score.

Sample size weighting factor

The dominance ranking score is flexible to allow multiple weighting factors to be incorporated. However, reviewers might wish to limit their weighting factors and only incorporate those factors that are most relevant to their review. Given that effect size and methodological quality weightings have their limitations and are to be used with caution, we would recommend that sample size weighting be the preferred weighting factor. Sample sizes are usually reported (unlike economic effect sizes) and can be easily extracted from studies. It is also a form of objective data, in that it is not subject to interpretation by reviewers, unlike the methodological quality score.

Benefit Values

It is important to note that the weightings are associated with a benefit value (-1, 0, +1) which is, itself, a categorical expression of the direction of dominance. As such, it may not be appropriate to have too many weighting factors, as the starting point (i.e. the benefit value) is not a precise measure of dominance level. For example, in the scenario that all studies in a review have lower intervention cost outcome than control, this will mean that the cost benefit values assigned would all be -1. In such a case, regardless of the weightings, the calculated cost dominance level would always be -1. Hence the dominance ranking score is useful when studies have heterogeneous benefit values and can help to better differentiate the dominance level. The dominance ranking score is also useful when the hierarchical decision matrix shows an unclear interpretation (such as equal number of studies in each band).

Extending the hierarchical decision matrix

In no sense do we claim that the dominance ranking score is able to perform a quantitative meta-analysis of economic data or that the hierarchical decision matrix is irrelevant. We merely extend the hierarchical decision matrix tool to have more differentiating information incorporated into it and thereby enable a more informed analysis of dominance levels to be performed. In fact, we suggest reviewers conduct a review tabulation using the hierarchical decision matrix and then supplement their analysis with the dominance ranking score.

We also recognize that for decision making, good quality economic trials or models that represent the specific context of the healthcare system is necessary. However, the proposed dominance ranking score and the associated hierarchical decision matrix are still useful when evaluating partial economic studies, such as studies with only cost minimization data. Such cost minimization studies are usually conducted for emergent research areas where basic economic data is collected, in parallel to a trial on clinical effectiveness. On this spectrum of rudimentary economic studies, we see a role for the hierarchical decision matrix and the dominance ranking score to provide some degree of dominance analysis. Through such a ‘pilot’ analysis, it could indicate the level of economic potential and pave the way for a full economic study.

Sub-weighting of weighting factors

If the use of multiple weighting factors is appropriate, it is possible to further weight each individual weighting factor, such that one can assign more priority to a certain factor. For example, if methodological quality is more relevant to a review, the methodological quality weighting can be given a higher weight. This will shift the direction of the dominance ranking score towards studies that have better methodological quality. If such further sub-weights are adopted, it is suggested that justifications for the levels of sub-weightings be reported and that these sub-weights be consistently applied for both cost and health benefit calculations. The sum of the sub-weights should always add up to 1.

Conclusion

For economic systematic reviews there is currently no agreed-upon quantitative method to obtain a pooled economic effect size. With no suitable quantitative method available, the hierarchical decision matrix stands out as a tool that enables a visual summary of different types of economic studies. Extending the hierarchical decision matrix with a weighted scoring system (termed dominance ranking score) allows for useful information of a study design to be incorporated and enables a more differentiating analysis of dominance levels.

Various study characteristics can be incorporated via weighting factors in the dominance ranking score, although the appropriate use of each weighting factor needs to be considered. In this paper, we have incorporated weights based on factors that we deem are relevant to most reviews, namely: sample size, effect size and methodological quality of studies. Given that effect size and methodological quality weightings have their limitations, we would recommend that sample size weighting be the preferred weighting factor, as sample sizes are usually reported and are a more objective form of data.

For systematic reviews that include partial economic studies, we see a role for the hierarchical decision matrix and the dominance ranking score to provide some degree of dominance analysis, which would otherwise not be possible. This analysis could improve the utility of such reviews by indicating the level of economic potential for a particular intervention, which may facilitate the conduct of subsequent full economic studies.

References

1. Nixon J, Khan KS, Kleijnen J. Summarising economic evaluations in systematic reviews: a new approach. BMJ. 2001;322(7302):1596-8.
2. Anderson R. Systematic reviews of economic evaluations: utility or futility? Health Econ. 2010;19(3):350-64.
3. Shemilt I, Mugford M, Vale L, Marsh K, Donaldson C, Drummond M. Evidence synthesis, economics and public policy. Research synthesis methods. 2010;1(2):126-35.
4. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011.
5. Gomersall J, Jadotte Y, Xue Y, Lockwood S, Riddle D, Preda A. Chapter 6: Systematic reviews of economic evidence. In: Aromataris E, Munn Z, editors. Joanna Briggs Institute Reviewer's Manual [Internet]. Adelaide: Joanna Briggs Institute, 2014.Available from: https://reviewersmanual.joannabriggs.org/.
6. van Mastrigt GA, Hiligsmann M, Arts JJ, Broos PH, Kleijnen J, Evers SM, et al. How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: a five-step approach (part 1/3). Expert Rev Pharmacoecon Outcomes Res. 2016;16(6):689-704.
7. Black WC. The CE plane: a graphic representation of cost-effectiveness. Med Decis Making. 1990;10(3):212-4.
8. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011] [Internet]. The Cochrane Collaboration. 2011 [cited 25 April 2018].
9. Sandelowski M. Combining qualitative and quantitative sampling, data collection, and analysis techniques in mixed-method studies. Res Nurs Health. 2000;23(3):246-55.
10. Sandelowski M, Voils CI, Barroso J. Defining and Designing Mixed Research Synthesis Studies. Research in the schools : a nationally refereed journal sponsored by the Mid-South Educational Research Association and the University of Alabama. 2006;13(1):29.
11. Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs-principles and practices. Health Serv Res. 2013;48(6 Pt 2):2134-56.
12. Frantzen KK, Fetters MD. Meta-integration for synthesizing data in a systematic mixed studies review: insights from research on autism spectrum disorder. Quality & quantity. 2016;50(5):2251–77.
13. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
14. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Research synthesis methods. 2010;1(2):97-111.
15. Lo K, Stephenson M, Lockwood C. The economic cost of robotic rehabilitation for adult stroke patients: a systematic review. JBI Database System Rev Implement Rep. 2019;17(4):520-47.
16. McCabe J, Monkiewicz M, Holcomb J, Pundik S, Daly JJ. Comparison of robotics, functional electrical stimulation, and motor learning methods for treatment of persistent upper extremity dysfunction after stroke: a randomized controlled trial. Arch Phys Med Rehabil. 2015;96(6):981-90.
17. Hesse S, Hess A, Werner CC, Kabbert N, Buschfort R. Effect on arm function and cost of robot-assisted group therapy in subacute patients with stroke and a moderately to severely affected arm: a randomized controlled trial. Clin Rehabil. 2014;28(7):637-47.
18. Bustamante Valles K, Montes S, Madrigal Mde J, Burciaga A, Martinez ME, Johnson MJ. Technology-assisted stroke rehabilitation in Mexico: a pilot randomized trial comparing traditional therapy to circuit training in a Robot/technology-assisted therapy gym. J Neuroeng Rehabil. 2016;13(1):83.
19. Wagner TH, Lo AC, Peduzzi P, Bravata DM, Huang GD, Krebs HI, et al. An economic analysis of robot-assisted therapy for long-term upper-limb impairment after stroke. Stroke. 2011;42(9):2630-2.

20. Vanoglio F, Bernocchi P, Mule C, Garofali F, Mora C, Taveggia G, et al. Feasibility and efficacy of a robotic device for hand rehabilitation in hemiplegic stroke patients: A randomized pilot controlled study. Clin Rehabil. 2016;31(3):351-60.

Chapter Six: Adoption of Robotic Stroke Rehabilitation (Paper Seven - Submitted for publication, under peer review)

Paper 7: Lo K, Stephenson M, Lockwood C. Adoption of robotic stroke rehabilitation into clinical settings: a qualitative descriptive analysis. 2019.

Statement of Contribution

Kenneth Lo (Candidate)

I was responsible for the overall creation of this paper. As the primary author, I developed the analysis concept, drafted the content, and structured the paper for journal submission. I was also responsible for responses to reviewers and revisions to the paper.

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Kenneth Lo		
Contribution to the Paper	I was responsible for the overall creation of this paper. As the primary author, I developed the analysis concept, drafted the content, and structured the paper for journal submission. I was also responsible for responses to reviewers and revisions to the paper.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	October 2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr. Matthew Stephenson		
Contribution to the Paper	Supervisor: provided conceptualization and methodological guidance to the manuscript. Contributed to the writing and revision of the paper, including responding to peer review comments, and reviewing the findings and conclusion.		
Signature		Date	October 2019

Name of Co-Author	Assoc. Prof. Craig Lockwood		
Contribution to the Paper	Supervisor: provided conceptualization and methodological guidance to the manuscript. Contributed to the writing and revision of the paper, including responding to peer review comments, and reviewing the findings and conclusion.		
Signature		Date	October 2019

Please cut and paste additional co-author panels here as required.

Manuscript Title

Adoption of robotic stroke rehabilitation into clinical settings: a qualitative descriptive analysis

Abstract

A qualitative descriptive study was conducted to interview stroke therapists about their experiences and interactions with robotic rehabilitation. Perspectives pertaining to the clinical, human behavioural and organizational factors of adopting robotic stroke rehabilitation into clinical settings were examined in order to inform rehabilitation clinicians about the various aspects of adopting and integrating robotic stroke therapy into clinical settings. Overall, we found that a structured plan addressing various factors was necessary, and that both therapist attitude and device benefit worked together to shape the motivations of therapists to adopt robotics. It would be worthwhile to have an adoption plan that actively generated positive attitudes and expounded the benefits of robotic training, and that the plan be well thought-through and be all-encompassing. We hope that findings of this study would assist to inform stroke clinicians in formulating such plans.

Introduction

One of the main goals in stroke rehabilitation is the restoration of motor skills and this involves the patient undergoing repetitive, high intensity, task-specific exercises that enables them to regain their motor movements and functional abilities.[1,2] Over the years, a number of robotic devices have been developed to assist therapists to rehabilitate patients, and these devices are complex in nature involving interactive automation, sensors and dynamic control logic to enable patients to keep repeating their exercises over long periods, without much intervention from therapists. There are two main types of robotic devices: exoskeletons and end-effectors. Exoskeletons are devices that wrap around limbs and are able to assist each limb joint to move, while end-effectors are devices that assist only the extremities of a limb (either hands or feet).[3] Regardless of design mechanism, one key feature of robotic devices is the ability to automatically assist patients to move their limbs when they are unable to do so by themselves. Conventional therapy, on the other hand, is labour-intensive in nature and places physical strain on therapists,[3] and it is hoped that with robotic devices improved rehabilitation progress can be achieved for patients, such that therapists could offer appropriate levels of personalized treatment for patients and increase their efficiency.[3]

The end goal of rehabilitation is to improve the functional ability of patients.[4] For physical disability, this requires gradual training of minimal movements then progressing to more complex functional actions. Depending on patient needs, rehabilitation can be a multi-disciplinary approach, involving not just physical/occupational therapists but also speech and cognitive therapists.[5] There are also various types of robotic devices with different functionalities, adding to the complexity of adopting robotic rehabilitation.[6] The complexity of interaction between these multiple rehabilitation disciplines and types of devices raises

questions on implementation, such as how therapists can work with robotics to improve rehabilitation outcomes of patients.

Robotic devices also do not work alone but are part of a wider spectrum of clinical care that involves clinicians, patients and hospital administrators. This interconnection to other parties could affect adoption into a clinical setting in various ways. For example, what would be the work scope of therapists when robotic devices are doing the rehabilitation? How would patients respond to robotic treatment that has less human contact? What are the optimal treatment protocols for a rehabilitation unit that has both therapists and robotic devices? The presence of robotic devices could change the way clinicians work and how patients are handled in a rehabilitation unit. However, the clinical, human behavioural and organisational dimensions can present challenges to the adoption of robotic devices.

A recent paper discussed the limits of robotic stroke rehabilitation and identified barriers such as technological, behavioural, organizational, and economic factors.[7] While the paper identified the broad ranging considerations that goes into adoption, no interviews were conducted to obtain direct perspectives from stroke therapists who work with robotic rehabilitation devices. Another paper[8] approached the topic of technology adoption with the aim of identifying priorities for the development of assistive stroke rehabilitation technologies and generating ideas to improve its adoption. However, the focus of this paper was broad and did not specifically consider adoption of robotic stroke rehabilitation devices in the context of a clinical setting.[3] With a need for more primary research into the adoption of robotic rehabilitation for stroke patients, the aim of this study was to interview clinical therapists involved with robotic rehabilitation in order to understand how clinicians experienced robotic training and its relationship to conventional therapy, what factors to consider when introducing

robotic devices into clinical settings, and how best to conduct robotic training. Through the data gathered, we seek to inform rehabilitation clinicians and clinical managers about the various aspects of adopting and integrating robotic stroke rehabilitation into clinical settings.

Methods

Design of study

The study applied a qualitative description design,[9] which involved the identification of findings that was close to the data, with minimal transformation (i.e. with little imputation of meaning by researchers).[9] This descriptive analysis approach enabled us to identify and extract data that described specific adoption considerations, such as what worked/did not work as expressed by participants, i.e. manifest context is described with low interpretation of data.[9] We used qualitative description as it allowed us to understand the actual nature of the situations faced by those involved, thereby giving us a sharper resolution of the events that were being encountered on the ground, without any loss of details or contextual meaning.[9] Data collection involved interviewing therapists who worked with robotic devices in clinical settings that provided rehabilitation services to adult patients. The semi-structured interview format offered not only allowed us tap into their knowledge, past experiences and learning points, but also enabled the collection of further information to uncover and probe deeper into specific points during the interviews. From the data collected, qualitative descriptive analysis was used to inductively identify codes, categories and central themes.

Participants

Purposive sampling[10] was used to recruit interview participants. In terms of sample size, as qualitative studies were exploratory in nature and not hypothesis testing, the participants were selected based on criteria that could best contribute to the research aim, and not based on certain participant sizes which were statistically representative.[11] In addition, the therapists

interviewed were all very experienced in robotic rehabilitation and thus had higher information power, which states that a study can have less extensive sample participants when these participants have characteristics that are highly relevant and specific for the study aim.[12] Inclusion criteria were physiotherapists, and occupational therapists involved in adult rehabilitation units with robotic training devices. As we sought a broader perspective on robotic rehabilitation, the participants were geographically distributed across Asia, Australia, Europe, and the United States. Altogether we interviewed eight therapists from five hospitals across the above regions.

Data collection

The interviews lasted from 45 to 100 minutes and were conducted from October 2017 to February 2018. Data collection was primarily directed toward discovering the who, what and why of events and experiences, and involved one-to-one interviews with participants. For participants based in Australia, interviews were conducted either face-to-face at the rehabilitation hospital or over phone, and for participants based internationally, online communication media [such as Skype® (Skype Communications SARL)] was used. All interviews were audio recorded and transcribed verbatim. At the beginning of the interview, warm up questions related to demographics and establishing an understanding of the specific clinical settings were used. This was followed by questions on their robotic rehabilitation programs and therapy experiences. The list of interview questions was piloted by co-authors and is included under Appendix 1.

Data analysis

The method guiding the data analysis was qualitative descriptive analysis, which involved the identification of findings that were close to the data.[9] Following the interviews, the recorded

data was transcribed then reviewed and coded using QDA Miner Lite® (Provalis Research). From the transcripts, the authors identified various concepts and arranged similar concepts into codes. The codes were then sorted based on their relationships and linkages into higher level categories. From these categories, central themes were inductively derived. Numerous readings of the transcripts and discussions among the authors were necessary to reach consensus on the coding and category structure.

Researcher influence

A reflexivity approach was taken during data collection and analysis stages in order to ensure an adequate balance between objective and purposeful analysis, as opposed to self-indulgent, personal analysis.[13-15] Findings were reported as they were presented by the participants, and discussed observations flowed directly from the findings. In addition, all findings and observations were jointly reviewed among the primary and co-authors who have clinical backgrounds and are experienced in conducting qualitative research. In this study, all participants were not known to any of the authors until the day of interview. This provided a measure of independent feedback to our interview questions, as there were no relational elements which could influence the findings. During the interviews, the primary author asked the same questions in the same sequence to each participant, although in some cases where interesting aspects were raised, the primary author would ask additional questions in order to better understand and interpret the context of a particular feedback. Although the intention was to gain a deeper and clearer understanding, this could potentially lead to some influence on the responses provided by participants.

Ethical considerations

This research was approved by the University of Adelaide Human Research Ethics Committees

and all participants provided informed written consent to be interviewed (approval number H-2017-151). Anonymity and confidentiality of findings were maintained by assigning codes to the participants, and participants also received their own individual transcripts to verify the authenticity of the raw data.

Results

Demographics

The eight interview participants from five hospitals were all rehabilitation therapists who had worked with adult patients using robotic devices. Seven of the participants were based at public hospitals (funded via national budgets, private insurances, or a mix of both), and one was based at a private hospital (receives both in-country and international patients). Except for the private hospital which specialized in rehabilitation, the other four hospitals were large general hospitals. Four of the eight participants were recruited from a single hospital, as the hospital was undergoing transition during the interview period, and there was a need to interview further participants to understand the rehabilitation practices before and after the transition.

The average rehabilitation experience of the participants was around 12 years, of which an average of 5 years was with robotic rehabilitation. In terms of the number of rehabilitation in-patients treated per month, the private hospital treated around 15 patients, while three other hospitals treated on average 45 patients per month. One public hospital treated around 2500 rehabilitation patients per month (both in- and out-patients). Except for the private hospital which had 20 beds, three public hospitals had on average 50 beds for inpatient rehabilitation (the public hospital that treated 2500 patients did not indicate its number of beds). Two hospitals had mainly stroke patients, while the other three hospitals treated patients with various neurological conditions such as stroke, spinal cord injury, multiple sclerosis, brain tumours and traumatic brain injuries. The average age of in-patients at four hospitals was

around 60 years old, while at the private hospital it ranged from 40 to 60 years. In terms of robotic equipment, three hospitals had robotic devices for upper and lower limb training, while two hospitals had upper limb robotic devices only.

Study findings

Three main themes emerged from the study findings: clinical considerations, benefits of robotic training, and robotic improvements. Figure 1 provides an overview of the themes and their associated categories. In the following sections, we describe and illustrate the main findings under these themes and categories with relevant participant quotes. For a detailed listing of all the codes and their associated participant quotes, the authors are able to provide a supplementary data sheet upon request.

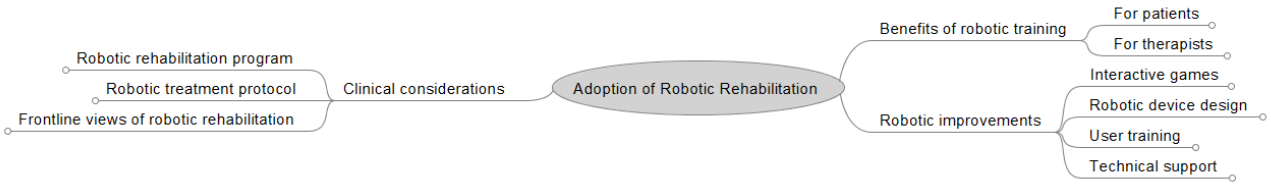

Figure 1: Organization of themes and categories

To maintain anonymity, the eight participants were assigned codes from A to H, and to reflect their clinical backgrounds, we have used the abbreviations: "OT" (denoting occupational therapist) and "PT" (denoting physiotherapist). However, it is to be noted that some participants have clinical managerial responsibilities and provided more organizationally focused responses.

Theme: Clinical Considerations

This theme covered aspects regarding the interactions, opinions and experiences of therapists and patients, in the context of the rehabilitation service program. The theme was informed by three categories: robotic rehabilitation program, robotic treatment protocol, and frontline views of robotic rehabilitation. The category "robotic rehabilitation program" encompassed codes pertaining to the organizational aspects of robotic rehabilitation program (i.e. how to adopt robotic rehabilitation? What were the various factors to consider?). The category "robotic treatment protocol" described the treatment protocol for robotic training (i.e. how was robotic training conducted? What was the patient inclusion criteria?), and the category "frontline views of robotic rehabilitation" detailed the attitudes and opinions of therapists towards robotic rehabilitation, and the training experiences of patients (as narrated by therapists). Figure 2 illustrates the organization of the theme "clinical considerations", and its associated categories and codes.

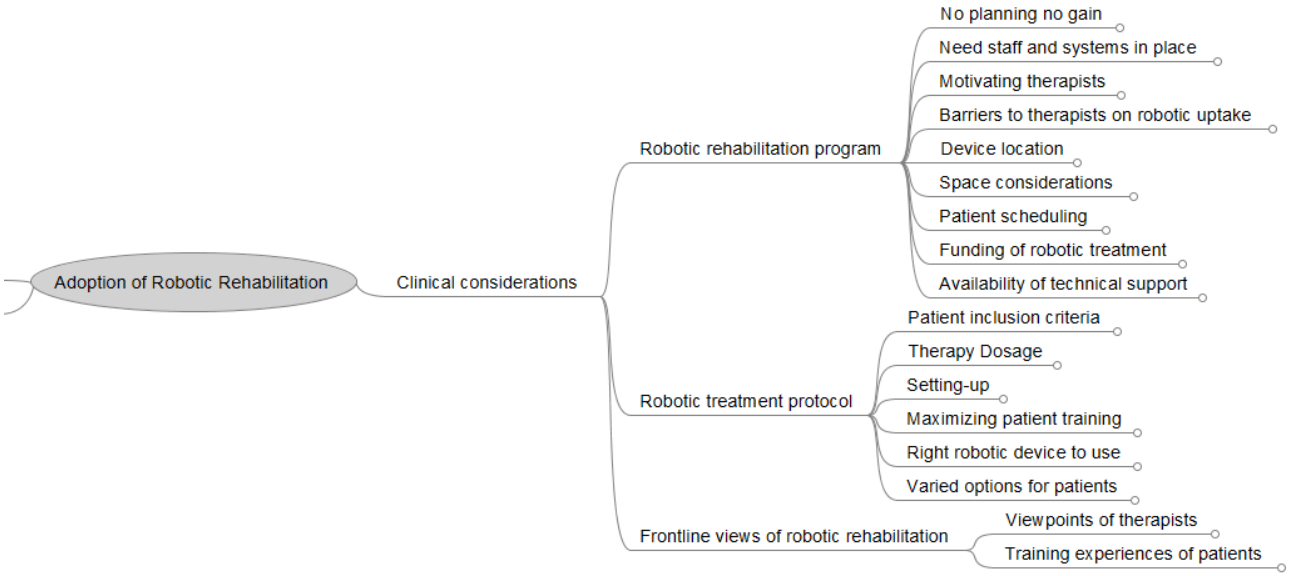

Figure 2: Organization of theme "clinical considerations", its categories and codes

Category: Robotic rehabilitation program

Under this category, there were nine codes pertaining to organizational considerations when introducing robotic rehabilitation into clinical settings (see Figure 2). These codes were

associated with different aspects of rehabilitation program planning, delivery and financing. Some experiences included therapists being given a robotic device with no organizational support for integration into existing rehabilitation services, with one interviewee noting:

> "The medical team, actually, acquired it for us, … and told us that we've got it. And then it was our responsibility to get trained in it, train everyone else up in using it and to make sure that it is used as much as possible." [D/OT]

The lack of adequate pre-implementation planning to ensure staff and systems were in place also led to increased stress levels and decreased motivation to enable robotic training. Participants indicated that the ad-hoc implementation of robotics was leading to sub-optimal rehabilitation. There were also practical barriers when robotics was introduced without consideration for patient transfers within the organization, distances from ward to the robotic devices, and sufficient physical space. In one hospital, the robotic device was initially placed near the inpatient ward, but after some time, it was relocated away from the ward, which led to a decline in usage. Location and space considerations were often overlooked in the implementation but yet had an impact on the organization and delivery (scheduling) of care.

> "I've faced a lot of the challenges for…making sure patients are ready, on time, toileted, dressed and getting here. Essentially, I have done the running around to do that and driven myself crazy doing that. Because those systems aren't in place and it's very intensive." [F/PT]

The funding arrangements for robotic training also played a part in determining the patient inclusion criteria for robotic rehabilitation. In one of the hospitals, conventional therapy was

subsidized by a national health insurance plan, but robotic therapy was not. This affected which patients had access to the robotic training. Instead of a needs-based approach, patients who could afford the more expensive robotic therapy had access to it.

> "… the services of robotic devices are not covered by the national health insurance and that makes the price of robotic gait training services much higher than conventional." [H/PT]

Category: Robotic treatment protocol

This second category for the theme of Clinical Considerations included six codes that illustrated how robotic training was conducted in terms of patient inclusion criteria, duration (dosage) of robotic therapy, and setup and supervision of robotic training. From the interviews, we found that robotics seemed to be the preferred treatment option for patients with severe impairments.

> "If they can't move, then they shouldn't be on the *'arm-weight supported device'*. They should be on the *'powered robotic device'*." [D/OT]

In terms of the dose of a robotic therapy session, we found that an upper limb training session lasted either 30 or 60 minutes, while for lower limb training it was either 45 or 60 minutes. Within each session, the amount of exercise time was inversely proportional to the impairment levels of patients. There was also variation in terms of the number of robotic therapy sessions per week for a patient. Some hospitals scheduled two robotic sessions per patient over a week for upper or lower limb treatment, while others scheduled a daily robotic session over five days.

The staffing, resources and time needed to set-up a patient also varied between robotic lower and upper limb training. The set-up took longer for lower limb devices, as the patient had to be transferred from a wheelchair onto the device and be secured into a body-weight support harness. Generally, the participants mentioned that the time for the initial set-up and down a patient in an upper limb device was around 10 to 15 minutes; while for lower limb devices, it was around 15 to 20 minutes. There was also a difference in the number of staff needed for robotic setup between upper and lower limb devices. For upper limb robotics, one staff was required as such devices did not require physical patient transfer to a body-weight support harness; while for lower limb two were needed. Some hospitals had assistants that worked alongside therapists but the training parameters during setup were still determined by the therapists, due to the need for clinical reasoning in evaluating the progress of a patient.

> "All therapy exercises and the degree of difficulty is set by the therapist. That's why, the therapist has to review it every week." [C/OT]

After setup, some participants mentioned that there was no need for a qualified therapist to monitor the patient performing the exercise; that such a task could be assigned to a therapist aid who need not have a clinical degree. However, not all participants shared this view. Some thought that it was necessary for a therapist to be around to monitor the patient performing the exercises and provide training guidance.

> "But then after the initial setup, the COTA *(Certified Occupational Therapist Assistants)* can end up helping to carry out the program." [B/PT]

> "We thought about a rehab aid being able to do that after I set it up but, I'm

> not speaking for all robotics, I'm just speaking specifically for the *(upper limb device)*. I think you need someone knowledgeable there to observe the session." [G/OT]

On maximizing patients' training during the robotic exercise, participants shared on several training tips, ranging from encouraging patients to participate actively in the training, discouraging compensatory movements of patients, and to challenging the limits of patients.

> "Obviously, we hope patients improve, maybe every session, maybe every week, you're always trying to bring those parameters down to make it harder as they improve, if you can." [F/PT]

Category: Frontline views of robotic rehabilitation

The third category, consisting of two key codes, described how therapists perceived robotic rehabilitation in relation to existing conventional training, their own abilities and work attitudes, and narrated the robotic training experiences of patients as a core aspect of the clinical considerations in adoption of robotic rehabilitation.

<u>Viewpoints of therapists</u>

The participants perceived robotic training as one of many treatment options, that robotic training was supplemental to existing conventional training as a way to increase training repetitions. Participants also viewed robotic training as a lead-in for patients to ultimately achieve functional outcomes.

> "They complement. I would never use it as the sole means of treatment. I

> think it helps to increase the repetitions and therefore maybe the intensity and overall really the dose. We're looking at dose." [D/OT]

The way robotic training was organized affected how some of therapists at this hospital saw themselves professionally. Some therapists did not have a sense of patient ownership and felt that they were no longer clinicians.

> "You become a technician and we're not technicians, we're clinicians who use our clinical reasoning." [E/PT]

In relation to their own abilities, therapists felt that it required skill to use robotic devices well, but on the other hand, that they could also lose their conventional therapy skills depending on the amount of time they spent with robotics. The respondents also shared a mix of positive and negative attitudes towards robotic training. The positive attitudes stemmed from the fact that therapists did not view robotics as a threat to their job; instead participants recognized the need for a therapist to be involved during robotics training. Some participants even commented that robotics helped fill gaps in conventional training.

> "Because you will lose your physio skill as well, if you're just on the robot the whole time. You still need to be able to do some sort of clinical work, so that you're not losing skill and you want to continue to upskill as well." [E/PT]

<u>Training experiences of patients</u>

Participants shared a spectrum of positive and negative experiences that had been related by

their patients. On the positive side, the patients enjoyed the training, felt that it was beneficial, and were motivated by the animated training games. This beneficial view of robotics, in turn, motivated patients to want more robotic training. Interestingly, seeing the motivated patient exercising also created a positive work experience for therapists.

> "Patients would definitely comment to us that: "Oh, it's just so nice to be up and walking." And even though they are not doing it themselves, completely obviously, it's just so nice for them to be out of bed, out of the chair and upright and doing something, you know, walk and walking." [F/PT]

Another aspect of robotic devices that helped to motivate patients was the ability to keep score and display analytic data on exercise movements. Some patients were motivated by having a deeper understanding of how they performed during the robotic exercise.

However, a number of patients experienced discomfort when using robotic devices. For lower limb robotic training, this mainly involved the body-weight support harness, as it exerts pressure in the groin region. For both upper and lower limb devices, the cuffs that secured the frame of robotic devices onto limbs were also a source of discomfort. Such discomfort could be amplified for patients, due to hypersensitivity after a stroke incident. Overall, despite these discomforts, there were no safety concerns for patients. Other negative experiences were that patients felt exhausted after a robotic training session, they found the number of games limited, and for a small number that they were unable to move in tune with the robotics. Due to such patients resisting the robotic assisted movements, therapists had to take them off robotic training.

> "It's becomes not that effective because what we call 'fighting with it'. As I said, the machine moves in this pattern, in this time, and there's no change to that. If they don't join in with that, it's not helping their therapies…We had a few that we actually had to say: "You know what, this isn't the right therapy for them" because of that reason." [F/PT]

Theme: Benefits of robotic training

The second theme identified through this study described the returns that patients gain from receiving robotic training, and the benefits to therapists from using robotics to conduct rehabilitation training. The theme was developed from two categories: 'for patients' and 'for therapists', in order to illustrate the specific benefits experienced by each of the two main user groups. Figure 3 illustrates the organization of the theme and its associated categories and codes.

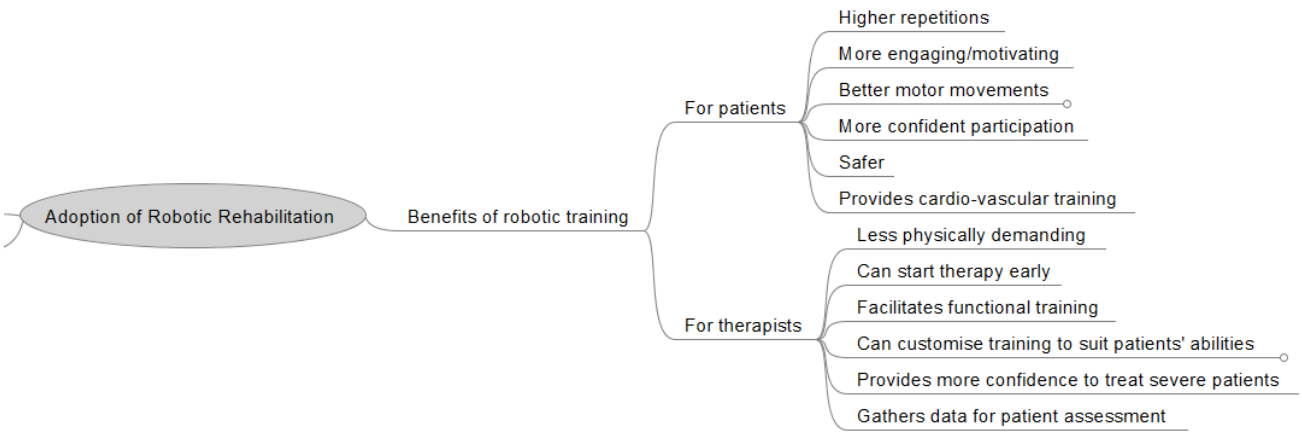

Figure 3: Organization of theme "benefits of robotic training", its categories and codes

Category: For patients

With robotic rehabilitation, patients were able to have a higher intensity of training with more repetitions, which provided a cardio-vascular work out that was safe and engaging (through

interactive games). All this helped patients to have a better recovery.

> "People would perform far greater number of steps on the robotic than they would in conventional physiotherapy." [F/PT]

The robotic devices also enabled a better quality of motor movement for patients. The upper limb devices enabled patients to focus on improving their motor movements, without being impeded by the weight of their weakened arms. For lower limb devices, patients had a more physiologically correct walking pattern.

> "In terms of the quality of the gait, after stroke patients often have very asymmetrical type gait patterns. The '*lower limb device'* takes them through a somewhat normal walking pattern, you've got that symmetry between step length, between cadence, timings and things like that." [E/PT]

Interestingly, as patients did not need to rely on cues from therapists during robotic training, they had more confidence and actively exerted their limbs, without expecting the therapists to help them.

> "And because it *(i.e. conventional therapy)* was hands-on, therapists; patients really were not confident in what part of it they were doing and what part of it the therapist was doing. And they were relying on the therapists to give them that feedback." [D/OT]

Category: For therapists

One of the main benefits for therapists was that they experienced less physical strain when using robotic devices to perform rehabilitation training, as the devices took over the task of supporting the limbs of patients.

> "Manual handling, sort of that active assisted ranging, functional tasks were very burdensome for the therapist. The load of holding the arms and doing all of that sort of stuff." [D/OT]

Robotics also offered a range of other benefits, such as enabling therapists to start rehabilitation early, and helping to progress their patients towards functional training. The ease of adjusting the training parameters also permitted therapists to adapt robotic training to suit the abilities of patients, where therapists could safely challenge patients to their limits. As the robotic devices could record various training parameters, therapists had accurate, up-to-date data to assess the progress of patients.

Therapists also had more confidence to treat severely impaired patients, which needed a fair amount of clinical experience in order to recognize deficits and prescribe the right type of training. Because the robotic devices could finely calibrate a patient's range of motion during the initial setup, this assisted therapists to determine the training needed.

> "And they're like: well, actually they *(i.e. patients)* have got this, that and they *(i.e. therapists)* just haven't been able to know how to look for, how to set a patient up to get an analysis of that movement. Whereas the robotic is easier for that to just happen." [D/OT]

Theme: Robotic improvements

From the interviews, we received a number of suggestions for device manufacturers to improve the robotic devices. These suggestions pertained to various aspects of the devices: interactive games, design of the devices, user training and technical support. Figure 4 shows the categories and codes under this theme.

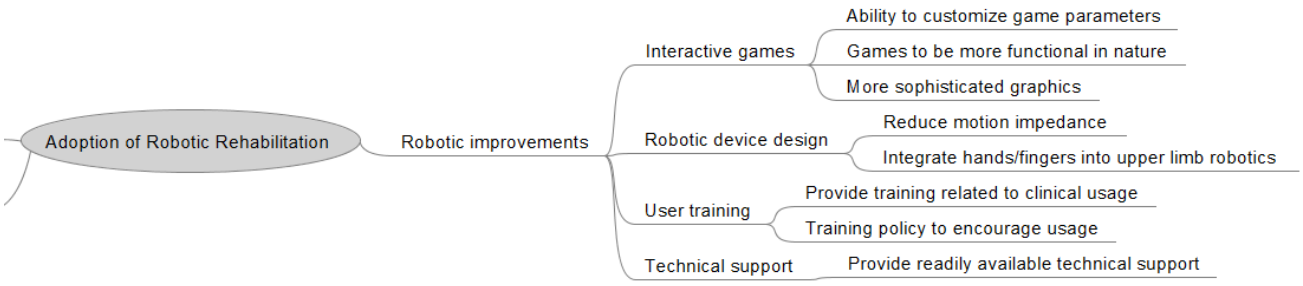

Figure 4: Organization of theme "robotic improvements", its categories and codes

Category: Interactive games

Therapists commented that they needed to adjust the game training parameters in order to customize the exercises for individual patients. Other improvements were related to the functionalities of the games, that games should reflect the real-world use of limbs. There was also a need to have more sophisticated game graphics that matched existing computer games.

> "They *(i.e. manufacturers)* try and make them *(i.e. games)* functional, to be honest, I don't think they're as functional as they can be." [D/OT]

Category: Robotic device design

Some patients found the upper limb devices hard to move, even though active assistance was provided by the device. Manufacturers should examine this inertia which impeded movements by patients.

Targeting both distal and proximal parts of the upper limb was necessary to provide a holistic training. However the upper limb robotic devices used by the therapists did not include training appendages for the hand.

> "You don't use the hand for any *(robotic exercise)* activities. At the end you have one of the most important or the most important part of the arm neglected. It is the part that you need for all functional activities, you need to use the hand for grasping, opening, everything." [A/OT]

Category: User training

To help therapists understand how to best use the device for patients with different levels and types of impairments, user training should identify which training exercises/games would facilitate what types of rehabilitation goals.

> "…when the people from the different companies they come, they tell you how to use the devices but very general way. They mainly tell you the safety information but they are not really clinicians. Normally they don't know too much about therapy. At the end you have to find yourself the way to use the devices with different patients." [A/OT]

The model of user training also affected the adoption and usage of robotic devices, for example a train-the-trainers model would facilitate the usage of the devices, as trainers could conveniently train other colleagues.

Category: Technical support

Without accessible technical support, the onus was on therapist to trouble-shoot issues that came up. This could hinder the adoption of robotics and would be a relevant aspect for suppliers to consider.

> "We're having to spend time out of our clinical day trying to fix the problems. That is a negative in that it is sometimes quite burdensome to try and overcome some of the problems that come up with it and it's just the general wear and tear that comes with the use of them day to day." [D/OT]

Discussion

We conducted a qualitative descriptive study to understand the clinical, human behavioural and organizational factors of adopting robotic rehabilitation in clinical settings. Our findings indicated that a structured plan was needed to adopt robotic training into an existing rehabilitation program, and such a plan would need to consider the factors of staff (capacity, capability and motivation), patient flow and transport, location and physical space of the robotic devices, financial funding model of robotic therapy, and availability of technical support. Not only does intra-coordination within the physical rehabilitation unit need to be considered, but also inter-disciplinary coordination between the rehabilitation unit and other hospital disciplines was needed.

Robotics more suitable for severely impaired patients

From the study, we found that powered robotic devices were the preferred treatment option for severely impaired patients. This could imply that such devices could be more for inpatient use, as inpatients usually have more severe impairments than outpatients.[16] This findings is also

similar to the results from two quantitative systematic reviews conducted on robotic stroke rehabilitation, which found that robotic therapy produced better outcomes for more severely impaired patients.[6,17,18] This could then imply that such powered robotic devices should ideally be located near to inpatient wards in order to facilitate patient preparations and transport. This may also make sense, as from our interviews we found that most of the patients for robotic devices came from acute inpatient care. Nevertheless, we are also mindful that this could be due to the funding arrangement, which provided inpatients with more access to robotic devices than outpatients.

Although powered robotic devices could be more suitable for inpatients with severe impairments, this does not mean that non-powered robotic devices were not useful.[19,20] From our interviews with therapists who work with upper limb impairments, we found that the powered upper limb devices were sometimes found by patients to be 'heavy', and that non-powered devices with arm weight support was more suitable instead. Hence it could be ideal to co-locate all types of robotic devices (whether powered or non-powered, upper or lower limb) together, into a kind of robotic gym.[21] This can also provide therapists and patients with more robotic training options.

Robotic training protocol

Setting up

During the setting up of robotic devices, it is necessary that the therapist determines the training parameters, as this required clinical reasoning in evaluating the progress of a patient.[22,23] Regular reviews of patients' progress are also necessary[5] and, as the devices are able to record the training performance of patients, therapists should tap into such data to assist in evaluating the progress of patients.

In determining the durations of robotic training, therapists should take into account the time differences for setting up patients, which has also been alluded to in trials on robotic rehabilitation.[24,25] From our study, due to the need for bodily transfer, we found that the amount of time for setting-up/down lower limb patients is longer than for upper limb patients, and the set-up time for the first therapy session is longer than subsequent sessions. Again, because of the body transfer, the setup for lower limb robotics requires two staff, whereas upper limb robotics require only one staff.

Supervision of patients

After patients have been setup, there were differing views on who should supervise patients while they trained. Some therapists mentioned that it was not necessary for a fully qualified therapist to be monitoring the patient throughout the training session, and that an assistant without a clinical degree would suffice. The clinical therapist would only need to be in close proximity to the patient. However some other therapists were of the view that it was necessary for a therapist to be present in order to observe the movements of patients and provide real-time guidance to help patients perform better. Nevertheless, some participants also provided the feedback that it could be a more effective use of therapist resources if therapists could treat another patient whilst one patient was on robotic training. Such a "multi-patient tasking" concept has been tested in clinical trials, and these trials have demonstrated equivalent or better clinical and cost outcomes as compared to one-on-one conventional therapy.[21,26] Hence it could be feasible for one therapist to simultaneously treat more than one patient.

Robotic training dosage

From the participants, we found that, in terms of the duration per training session, an upper

limb session lasted either 30 or 60 minutes, while a lower limb session was 45 or 60 minutes. There is still debate regarding the optimal duration of a robotic training session,[27,28] but from studies included in systematic reviews conducted, most of the therapy durations were between 20 to 90 minutes for upper limb training[28] and 20 to 50 minutes for lower limb training.[27] It is also recommended in a stroke clinical guideline to offer at least 45 minutes of rehabilitation training per therapy session.[29] We believe our findings are within the ranges of these studies and the clinical guideline.

It is also to note that the actual time that a patient spends on robotic training would be dependent on the patient's impairment level.[29] For more severe patients, they would tire faster due to general cardiovascular deconditioning post stroke and would need more rest breaks, which would reduce the amount of time they spend training. Hence, due to the time for setup and rest breaks, the effective training duration would be less than the allocated schedule. Taken together, in determining the duration of a robotic therapy session, therapists would need to consider the minimum amount of exercise time that a patient is required to have, while taking into account the time needed for setting patients up/down and rest breaks of patients.[30] Therapists should also note that, within the daily working hours, a shorter therapy duration would provide more training slots per day and hence more patients can train on the devices, which would improve the utility of the robotic devices.

Another consideration to note is to align the duration of a therapy session between in- and out-patients, which would facilitate the flexible booking of therapy sessions between both patient groups. As robotic devices are costly investments, it would make sense to offer such devices to both in- and out-patients in order to maximize the device usage. This would be in line with an economic systematic review, where the authors had found that the number of patients treated

during a single robotic session should be maximised in order to optimise the cost economics of robotic devices.[31]

Therapists and robotics

The way robotic therapy was structured affected the attitudes and motivations of therapists towards the robotic devices. In one hospital where robotic training was structured as a standalone service, into which in- and out-patents were referred, the therapist felt that the work was not rewarding. This could be caused by a number of factors. In such a standalone setup, the robotic therapist did not have an assigned patient load. They only provided robotic training but did not see how patients progressed overall. This lack of patient ownership and follow through from robotic training to other rehabilitation goals did not fulfil the provision of care to patients and the exercise of clinical judgment that therapists were trained to provide. This then subsequently led to a perception that they were not clinicians but were more like robotic technicians. That the therapist worked at a separate location from other therapists who were based at the inpatient wards, could also have contributed to this 'non-clinician' perception. Another associated finding was that such a standalone robotic model could affect the skills of therapists. While working full-time with the robotic devices enhanced their skills to use the robotic devices well and provide better robotic benefits to patients, it also reduced their conventional therapy skillsets over time. Conversely, if someone is not working regularly with the robotic devices, they would enhance their conventional skills but reduce their robotic skills. These findings regarding satisfaction and acceptability by clinicians have also been recognised as an important factor to consider in studies on adoption of robotic rehabilitaion.[7,32] Therefore clinical managers should note the implications that a therapy model would have on staff motivation, job fulfilment and skill levels.

The benefits that robotic devices offer should be explained to therapists not just by using evidence examples but also 'lived' experiences of patients who had progressed after robotic training. Therapists, upon directly seeing the patient benefits themselves, would be more motivated to adopt robotic rehabilitation. The use of 'lived' experience as a training approach has been shown to be useful and effective,[33,34] and could enhance the acceptability of robotic rehabilitation by therapists. For hospitals where robotics was offered as part of a standard rehabilitation program, therapists should also take note not to neglect the human relational aspect of rehabilitation but remember to engage patients in a meaningful way, even though most of the therapy is performed by the devices.

One barrier to the uptake of robotic devices was the capacity of therapists to learn new technologies, with a participant commenting that it was easier for newly recruited staff to adopt robotic devices when such use was already included into their job descriptions, i.e. that the use of robotic devices was facilitated when it was expected and determined upfront. It has been found that undergraduate education and a structured training curriculum are useful in learning new skills[35,36] and by extending this principle further, it could be worthwhile to include robotic devices as a standard module in the undergraduate educational curriculum of therapists. This would enable future therapists to be familiar with robotic rehabilitation and facilitate the adoption of robotic therapy as a routine clinical practice.

Patients and robotics

To encourage usage by patients, it is necessary to understand how robotics motivate them. From our study, we found that when patients saw their impaired limbs moving (although they knew this was robotic assisted), they experienced a positive sense of recovery, which motivated them psychologically. Patients' motivation was also augmented by the interactive games they

played as part of their training regimes. It was not just the animations but also that the games were scored. This score-keeping presented itself as a goal, and it was likely that patients associated higher scores with better limb movements. This then motivated patients to train more in order to improve their scores. Our finding is generally in line with the positive patient engagement effects of virtual interactive games that have been described in other studies, where virtual reality games have been shown to be particularly motivating, especially interactive games with functionally meaningful reactions to motor performance.[37-39] However our finding on the positive effect of competitive score-keeping of games is in contrast to a study which found that competitive games did not increase patient engagement.[37]

Patients should also be made aware that robotic training is an exhausting experience. This is due to therapists actively seeking patients to participate in each movement by constantly challenging them to their limits.[25] If patients progress in their training, the level of robotic support would actually reduce in order to keep challenging them.

Despite patients finding robotic devices beneficial, care should be taken that patients do not over emphasize the use of robotics and neglect other rehabilitation goals. Patients should be made aware that robotic training is one component of the overall rehabilitation treatment plan that includes conventional, speech, cognitive and other group/pool therapies, and that all components are equally important for their rehabilitation.[4,29] It is also to note that a small number of patients would not be able to move in sync with the robotic assistive movements and would actually resist it. Such patients would not be suitable for robotic training and therapists would have to excuse them from robotic training.

Manufacturers and robotics

The study uncovered suggested improvements for manufacturers of robotic devices. Several participants asked for the ability to customize game parameters, that they could adjust the game complexity as their patients improved. It is likely that therapists, given their clinical training, would like to able to exercise their clinical judgment in progressing a patient. This should be encouraged as it could lead to customized training exercises for each individual patient, which could potentially maximize the benefits that robotic devices could offer.[39]

Additional feedback was to have more games that were functional in nature, and which mimicked real-life activities of patients. Currently some games were seen as being 'gamey', even though they served to illicit the desired locomotor movement. This observation is in line with a similar finding that games with functionally meaningful activities increased patient engagement.[37] Another aspect related to the games is the sophistication of the game graphics. Computer games are nowadays very detailed with life-like graphics but in comparison the robotic game graphics are rudimentary, although the robotic devices themselves are complex machines.

Motivation of therapists

The adoption of robotic rehabilitation ultimately depends on the motivation of therapists to use the robotic devices, which in turn flows from their attitudes towards robotic devices and the benefits that robotics can offer. Hence, it would be worthwhile to have an adoption plan that actively generated positive attitudes and expounded the benefits of robotic training. A well thought-through adoption plan with seamless integration into existing settings would then sustain the motivations of therapists on a daily work basis. Therapists also need to be convinced of the benefits that robotics bring, not just the direct benefits to themselves (e.g. less physical strain) but also witnessing the benefits that their patients can gain. Manufacturers, through the

device functionalities and after-sales policies, also play a part in shaping the attitudes of therapists and the benefits that they experience. These organizational, user, vendor, and benefit-related factors have been identified in studies on the adoption of generic healthcare technologies,[40-42] and our study on robotic stroke rehabilitation have also uncovered these similar considerations.

Study limitations

Type of robotic devices

Although most of the robotic rehabilitation devices that the hospitals had were of the exoskeleton type, we believed most of our findings still applied to robotic devices in general. However our findings on the amount of time and staff resources needed for setting up/down a patient, and certain aspects of patient training experiences (such as the discomfort of cuffs to secure the exoskeleton frame to patients, and the inability of patients to move in sync with the exoskeleton frame) would be more applicable to exoskeleton devices.

Mainly acute inpatients

The clinical therapists we interviewed worked mainly with acute inpatients, and this might have limited the scope of their answers to our questions, although we did not limit the therapist interviewees to any patient group.

Only clinical participants

Our interviews involved only clinical therapists and no patients were included, due to resource and time limitations on recruiting patients from different countries. While we did ask clinicians about patient experiences, the lack of direct data from patients might have reduced the validity of patients' perspectives reported here and the level of insights that could have been gained. Despite this, we believe that therapists, as part of their professional therapeutic relations with

patients, would have provided bona fide and patient-centred insights.

Generalizability to other healthcare settings

Our findings would be more relevant for multi-discipline hospitals in an urban setting of higher socio-economic countries, given the profiles of the hospitals where the interviewed therapists worked. Having said this, we had interviewed only eight therapists from five hospitals, and this small number of participants and hospitals might not be representative of the hospital setting that we had postulated. Nevertheless, to maximize the generalizability of our findings, we have attempted to incorporate a global perspective on robotic rehabilitation via recruiting study participants in Asia, Australia, Europe, and the United States. This provided us with a broader perspective across various countries in different continents. Another point to note was that none of the hospital rehabilitation units treated solely stroke patients. Although two hospitals had mainly stroke patients, all hospitals had a mix of stroke and other neurological conditions such as spinal cord injury, multiple sclerosis, and traumatic brain injury. While the findings were not only related to stroke patients, the findings did reflect the real-world patient mix of rehabilitation units, which would enhance the external validity of the findings.

Conclusion

We had conducted a study to understand the various aspects of adopting robotic stroke rehabilitation in clinical settings. The study found that a structured plan addressing various factors (such as staff capacity, patient flow and transport, location and physical space of the robotic devices, financial funding model of robotic therapy, and availability of technical support from suppliers) needed to be in place in order to ensure the successful adoption of robotic rehabilitation in a multi-discipline hospital located in an urban setting. The study also examined the attitudes and views of therapists and patients (as expressed via their treating therapists) towards robotic rehabilitation, and discussed the benefits that robotic training

brought to these two user groups. Both therapist attitude and device benefit work together to shape the motivation of therapists to adopt robotics, and it would be worthwhile to have an adoption plan that actively generated positive attitudes and expounded the benefits of robotic training. Overall, an adoption plan needs to be well thought through and be all-encompassing, and we hope that the findings of this study can assist to inform this plan.

References

1. Van Peppen R, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? Clin Rehabil. 2004;18(8):833-62.
2. French B, Thomas LH, Leathley MJ, Sutton CJ, McAdam J, Forster A, et al. Repetitive task training for improving functional ability after stroke. Cochrane Database Syst Rev. 2007(4).
3. Masiero S, Poli P, Rosati G, Zanotto D, Iosa M, Paolucci S, et al. The value of robotic systems in stroke rehabilitation. Expert Rev Med Devices. 2014;11(2):187-98.
4. Gresham GE, Alexander D, Bishop DS, Giuliani C, Goldberg G, Holland A, et al. Rehabilitation. Stroke. 1997;28(7):1522-6.
5. Dobkin BH. Rehabilitation after Stroke. N Engl J Med. 2005;352(16):1677-84.
6. Lo K, Stephenson M, Lockwood C. Effectiveness of robotic assisted rehabilitation for mobility and functional ability in adult stroke patients: a systematic review. JBI Database System Rev Implement Rep. 2017;15(12):3049-91.
7. Turchetti G, Vitiello N, Trieste L, Romiti S, Geisler E, Micera S. Why effectiveness of robot-mediated neurorehabilitation does not necessarily influence its adoption. IEEE reviews in biomedical engineering. 2014;7:143-53.
8. Kerr A, Smith M, Reid L, Baillie L. Adoption of Stroke Rehabilitation Technologies by the User Community: Qualitative Study. JMIR rehabilitation and assistive technologies. 2018;5(2):e15.
9. Sandelowski M. Whatever happened to qualitative description? Res Nurs Health. 2000(23):334–40.
10. Patton MQ. Qualitative research and evaluation methods (4th ed.). Thousand Oaks, CA: Sage. 2014(Module 30 Purposeful sampling and case selection: Overview of strategies and options; Module 40 Sample size for qualitative designs).
11. Pope C, van Royen P, Baker R. Qualitative methods in research on healthcare quality. Quality and Safety in Health Care. 2002;11(2):148.
12. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. Qual Health Res. 2016;26(13):1753-60.
13. Finlay L. "Outing" the researcher: the provenance, process, and practice of reflexivity. Qual Health Res. 2002;12(4):531-45.
14. Dodgson JE. Reflexivity in Qualitative Research. J Hum Lact. 2019;35(2):220-2.
15. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. Nurse Educ Today. 2004;24(2):105-12.
16. Masiero S, Armani M, Ferlini G, Rosati G, Rossi A. Randomized Trial of a Robotic Assistive Device for the Upper Extremity During Early Inpatient Stroke Rehabilitation. Neurorehabil Neural Repair. 2014;28(4):377-86.
17. Mehrholz J, Werner C, Kugler J, Pohl M, Elsner B. Electromechanical-assisted training for walking after stroke. What is the evidence so far? What have we learnt? Physiotherapy (United Kingdom). 2015;101:eS990-eS1.
18. Mehrholz J, Thomas S, Werner C, Kugler J, Pohl M, Elsner B. Electromechanical-Assisted Training for Walking After Stroke: A Major Update of the Evidence. Stroke. 2017.
19. Hsieh YW, Wu CY, Wang WE, Lin KC, Chang KC, Chen CC, et al. Bilateral robotic priming before task-oriented approach in subacute stroke rehabilitation: A pilot randomized controlled trial. Clin Rehabil. 2016.
20. Conroy SS, Whitall J, Dipietro L, Jones-Lush LM, Zhan M, Finley MA, et al. Effect of gravity on robot-assisted motor training after chronic stroke: a randomized trial. Arch Phys Med Rehabil. 2011;92(11):1754-61.
21. Bustamante Valles K, Montes S, Madrigal Mde J, Burciaga A, Martinez ME, Johnson MJ. Technology-assisted stroke rehabilitation in Mexico: a pilot randomized trial comparing traditional therapy to circuit training in a Robot/technology-assisted therapy gym. J Neuroeng Rehabil. 2016;13(1):83.

22. Nunen MP, Gerrits KH, Konijnenbelt M, Janssen TW, Haan A. Recovery of walking ability using a robotic device in subacute stroke patients: a randomized controlled study. Disability and rehabilitation Assistive technology. 2015;10(2):141-8.
23. Westlake KP, Patten C. Pilot study of Lokomat versus manual-assisted treadmill training for locomotor recovery post-stroke. J Neuroeng Rehabil. 2009;6(1):18.
24. Burgar CG, Lum PS, Scremin AM, Garber SL, Van der Loos HF, Kenney D, et al. Robot-assisted upper-limb therapy in acute rehabilitation setting following stroke: Department of Veterans Affairs multisite clinical trial. J Rehabil Res Dev. 2011;48(4):445-58.
25. Schwartz I, Sajin A, Fisher I, Neeb M, Shochina M, Katz-Leurer M, et al. The effectiveness of locomotor therapy using robotic-assisted gait training in subacute stroke patients: A randomized controlled trial. PM & R : the journal of injury, function, and rehabilitation. 2009;1(6):516-23.
26. Hesse S, Hess A, Werner CC, Kabbert N, Buschfort R. Effect on arm function and cost of robot-assisted group therapy in subacute patients with stroke and a moderately to severely affected arm: a randomized controlled trial. Clin Rehabil. 2014;28(7):637-47.
27. Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke (Review). Cochrane Database Syst Rev. 2013(7):Cd006185.
28. Mehrholz J, Pohl M, Platz T, Kugler J, Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. Cochrane Database Syst Rev. 2018;9:Cd006876.
29. Intercollegiate Stroke Working Party. National Clinical Guideline for Stroke. 5th ed. London: Royal College of Physicians; 2016.
30. Ng MF, Tong RK, Li LS. A pilot study of randomized clinical controlled trial of gait training in subacute stroke patients with partial body-weight support electromechanical gait trainer and functional electrical stimulation: six-month follow-up. Stroke. 2008;39(1):154-60.
31. Lo K, Stephenson M, Lockwood C. The economic cost of robotic rehabilitation for adult stroke patients: a systematic review. JBI Database System Rev Implement Rep. 2019;17(4):520-47.
32. Turchetti G, Mazzoleni S, Dario P, Saldì D, Guglielmelli E. The impact of robotic technology on neuro-rehabilitation: Preliminary results on acceptability and effectiveness. Value Health. 2015;18(7):A363-A4.
33. Roussy V, Thomacos N, Rudd A, Crockett B. Enhancing health-care workers' understanding and thinking about people living with co-occurring mental health and substance use issues through consumer-led training. Health Expect. 2015;18(5):1567-81.
34. Happell B, Bennetts W, Harris S, Platania-Phung C, Tohotoa J, Byrne L, et al. Lived experience in teaching mental health nursing: issues of fear and power. Int J Ment Health Nurs. 2015;24(1):19-27.
35. Vlak T, Soso D, Poljicanin A, Becir B, Marinovic I, Pivalica D, et al. Physical and rehabilitation medicine training center in Split, Croatia: striving to achieve excellence in education of a rehabilitation team. Disabil Rehabil. 2014;36(9):781-6.
36. Gozen AS, Akin Y. Are structured curriculums for laparoscopic training useful? A review of current literature. Current opinion in urology. 2015;25(2):163-7.
37. Zimmerli L, Jacky M, Lunenburger L, Riener R, Bolliger M. Increasing patient engagement during virtual reality-based motor rehabilitation. Arch Phys Med Rehabil. 2013;94(9):1737-46.
38. Keshner EA. Virtual reality and physical rehabilitation: a new toy or a new research and rehabilitation tool? J Neuroeng Rehabil. 2004;1(1):8.
39. Keshner EA, Fung J. The quest to apply VR technology to rehabilitation: tribulations and treasures. J Vestib Res. 2017;27(1):1-5.
40. Varabyova Y, Blankart CR, Greer AL, Schreyogg J. The determinants of medical technology adoption in different decisional systems: A systematic literature review. Health Policy. 2017;121(3):230-42.
41. Schoville RR, Titler MG. Guiding healthcare technology implementation: a new integrated technology implementation model. Comput Inform Nurs. 2015;33(3):99-107; quiz E1.
42. Gücin NÖ, Berk ÖS. Technology Acceptance in Health Care: An Integrative Review of Predictive Factors and Intervention Programs. Procedia - Social and Behavioral Sciences. 2015;195:1698-704.

Appendix 1 – Interview Questions

1. Demographics & Clinical Setting
    - What is your occupation title?
    - How many years have you worked in stroke rehabilitation?
    - How many years have you worked with robotic rehabilitation devices?
    - Where is your hospital located (country, state, city)?
    - How many patients does the stroke rehabilitation unit handle per month?
    - How many clinicians are working at the stroke rehabilitation unit?
    - What types of robotic training (upper limb, lower limb) are offered at your unit?
    - What are the makes and models of the robotic devices?

2. How is robotic therapy conducted? What are the differences when providing robotic training compared with providing conventional rehabilitation?

3. To what extent do you think robotics could enhance or complement the work of therapists?
    - What are the major areas of potential for robotic rehabilitation training?

4. What effects do robotic devices have on rehabilitation outcomes for patients? Why do you think it has that effect?

5. Could you tell me about your stroke unit's experience during the transition from conventional training to the current therapy program utilizing robotic devices?
    - What were the impacts on clinical care? Were there changes to the way clinicians worked and how patients are managed?

6. What barriers were experienced when implementing robotics therapy?
    - What organisational, work, cultural, belief or behaviour-based barriers were encountered?
    - Has the introduction of robotics influenced staffing profiles within your unit?
    - Are staff generally open to or resistant to robotic therapy?

7. Could you tell me about your perceptions of robotic therapy?
    - Can you expand on what attitudes and values influenced your perceptions?

8. What feedback have you had from patients about their views or feelings when offered robotic therapy? Would you classify their experiences as generally positive, or generally negative – why?

Chapter Seven: Conclusion – Discussion of thesis findings and Conceptual Framework for implementation of Robotic Rehabilitation

Aim of thesis

Robotic rehabilitation in various formats and levels of technology has been offered to stroke patients since early 2000,[37,38] in order to assist therapists to provide high intensity training which is required for recovery of stroke impairments. However, it is uncertain if robotic rehabilitation is effective, for which patient groups,[39] or whether it is economically feasible.[40] Methods for operationalisation and integration of robotic rehabilitation with other clinical services are also unclear.[41] In view of these uncertainties, this thesis sought to answer the following research questions:

1. Can robotic devices help adult stroke patients to regain motor movement of their upper and lower limbs?
2. Can robotic devices rehabilitate adult stroke patients cost economically?
3. What are the clinical views and experiences of utilizing robotic rehabilitation? What are the factors to consider when introducing robotic devices into the clinical care environment?
4. How can findings from the effectiveness, economic cost and adoption studies be aggregated to create a conceptual framework for providing robotic rehabilitation?

In the prior chapters, the first three questions have been examined, namely regarding the clinical effectiveness, economic cost effectiveness, and considerations involved with clinical adoption of robotic rehabilitation. In this concluding chapter, we seek to answer the final research question of the thesis, i.e. how to amalgamate the findings from the prior studies and to generate a conceptual framework that models integration of robotic rehabilitation services. However, before we delve into the conceptual framework, the implications and significance of the prior thesis findings are first discussed. This discussion would also provide the foreground information which is incorporated into the framework, and illustrate the reasoning for doing so.

Discussion of thesis findings

Clinical Effectiveness

To investigate the clinical effectiveness of robotic rehabilitation among adult stroke patients, a systematic review which included 51 studies and 1,798 patients was conducted.[42] The Joanna Briggs Institute (JBI) systematic review methodology has been applied in our research as it offers a robust method for finding and reviewing the available evidence, and to undertake meta-analyses of individual study results.[32,43] Rehabilitation outcomes for both upper and lower limbs were examined, with 30 studies evaluating upper limb interventions and 21 studies evaluating lower limb gait training. Overall, the systematic review found that robotic training was just as effective as conventional physiotherapy for outcomes of upper limb motor movement, lower limb walking and activities of daily living. However, for severely impaired lower limb patients, robotic training was found to be more effective than conventional training.[42] Previous systematic reviews on the clinical effectiveness of robotic rehabilitation devices for lower limb patients,[44-46] found that robotic-assisted gait training increased the odds of participants becoming independent in walking, and for the sub-group of severely impaired patients the findings indicated that robotic treatment was more effective. In terms of upper limb outcomes, two systematic reviews found that robot-assisted arm training improved arm motor movement[39,47] and activities of daily living scores.[39] In our effectiveness systematic review, we found that robotic therapy was as effective as conventional therapy for both upper and lower limb patients, and we identified severely impaired lower limb patients as a key patient subgroup that would benefit from robotic rehabilitation. Our finding that robotic rehabilitation was more beneficial for patients with severe lower limb impairments is in concordance with previous systematic reviews, and in terms of the clinical significance, this could imply that lower limb patients should be treated using robotic gait training devices. However for patients with upper limb impairments, our finding is in contrast to the two other systematic reviews.[39,47] These reviews had shown improvements in outcomes, but in our review both robotic and conventional therapies had equivalent outcomes. As explained in our published manuscript, this could be due to the method of data analysis. In the other systematic reviews, the authors had pooled together data from different intervention arms (containing robotic training, and robotic training that is combined with other interventions such as electroencephalography-based brain computer interface[48] or functional electrical stimulation[26]) and compared it with the conventional training control arm. In our review, we only compared robotic interventions (without any concurrent therapy methods) with conventional therapy.

Overall, the effectiveness systematic review of this thesis has contributed additional knowledge to the body of evidence regarding the clinical effectiveness of robotic rehabilitation for stroke patients, but for the sub-group of severely impaired lower limb

patients, our evidence assists to corroborate the findings of previously conducted systematic reviews.

Economic cost effectiveness

A systematic review of cost-related data was undertaken to examine the economic implications, which included a total of five studies with 213 patients.[49] As with the effectiveness systematic review, the economic review methodology of JBI[50,51] has been adopted for this project. The included studies compared the cost of providing robotic intervention against the cost of providing conventional therapy in dose-matched therapy sessions, and computed the cost measures in terms of cost/patient session or cost/patient. The review found that robotic therapy had better economic outcomes than conventional therapy. For patients with severe disability from significant stroke, in terms of the health benefit, a moderate preference favoring robotic therapy was found. However, in terms of the cost benefit, a strong preference for robotic intervention was found. Practice-wise, this may imply that robotic therapy could be prescribed for severely impaired adult stroke patients. That robotic intervention had better cost benefit for severely impaired patients might be due to the need for more one-to-one therapist time during conventional therapy in order to gain the same health benefits as robotic therapy. In conventional therapy, therapists manually support and exercise the impaired limbs of patients, which is physically demanding for therapists to sustain at high intensity, especially for severely impaired patients with minimal volitional movements.[23] Robotic devices, on the other hand, were designed to specifically support the limbs and provide higher training repetitions.[52]

Two factors which highly influence the economic cost benefits of robotic therapy (i.e. sensitivity factors) were also identified from our review: the number of patients that could be treated per robotic session and the time therapists spent with patients during a robotic session. If more patients could be treated per robotic session, then cost would decrease. Similarly, if less therapist involvement was needed during robotic training, then cost would decrease. Hence, to maximize the cost benefits of robotics in view of these sensitivity factors, healthcare providers might wish to increase the number of patients treated during a robotic therapy session, and minimize the involvement of therapists as far as possible, without compromising patient safety.

While there have been individual economic studies on robotic rehabilitation,[26,40,53-55] no economic systematic reviews were found during our literature review. This leads us to believe that the economic systematic review that has been conducted as part of the

thesis is the first such economic review on robotic rehabilitation. Since publishing our review report, there has been a number of requests from researchers based in Germany, Switzerland and France for our report. In this respect, we believe that our economic systematic review has generated new knowledge in terms of which patient sub-group would benefit from robotic training and the key sensitivity factors that impact the economic cost of robotics.

Adoption of robotic rehabilitation

Although robotic rehabilitation devices for adult stroke patients have been in use since year 2000,[37,38] there is a lack of deeper research into the adoption and integration of robotic stroke rehabilitation in clinical settings. During our literature search, an article discussing factors that influence adoption was found, which identified that the successful usage of these robotic rehabilitation devices depends on several factors, such as clinical effectiveness, economic viability, human behavioral and organizational variables.[41] However no detailed information was provided in the article about these aspects, and there was no direct research conducted with users of robotic devices to gain their insights into these aspects. Hence, we believe that our qualitative adoption study assists to address this information gap. The adoption study uncovered original insights from therapists who work directly with robotics in clinical settings, detailing their motivations, benefits and attitudes towards robotic training, and understanding the barriers to adoption.

The qualitative adoption study included semi-structured interviews with eight therapists from various countries (Australia, Taiwan, Switzerland and the United States).[56] The methodology of qualitative descriptive analysis was applied for this study as it allowed us to understand the actual nature of the situations faced by those involved, thereby giving us a sharper resolution of the events that were being encountered on the ground, without any loss of details or contextual meaning,[36] which then enabled the identification of specific adoption findings. Through our study, it was found that a structured plan addressing various aspects (such as staff capacity, patient flow and transport, funding mechanism, location and physical space of the robotic devices) was important to the successful adoption of robotic rehabilitation in a multi-discipline hospital setting. It was also found that therapists and patients generally had positive attitudes towards robotic training, and coupled with the benefits offered by the robotic devices, motivated them to use the devices. Ultimately, the adoption of robotic rehabilitation depends on the motivation of therapists to use the robotic devices, which in turn flows from their attitudes towards robotic devices and the benefits that robotics can offer. Therefore, it would be

worthwhile for healthcare providers who plan to introduce robotic rehabilitation to have an adoption plan that actively generated positive attitudes and expounded the benefits of robotic training. Such an adoption plan would also need to seamlessly integrate into existing settings in order to sustain the motivations of therapists on a daily work basis.

Therapists also need to be convinced of the benefits that robotics bring, not just the direct benefits to themselves (e.g. less physical strain) but also witnessing the benefits that their patients can gain. The use of 'lived' experience as a training approach has been shown to be useful and effective.[57,58] That this consideration has also been similarly uncovered by our study helps to validate our findings.

These organizational, user, and benefit-related factors that have been identified in our study are similarly discussed and considered in studies on the adoption of generic healthcare technologies.[59-61] In one of these studies,[60] the authors presented a technology implementation model, which mapped out components influencing adoption, such as users (individuals who are impacted by the technology use: patients, clinicians, administrators), workflow (the steps of accomplishing a patient care task), interfacing systems (supplementary systems that interfaces or communicates with the new technology to be adopted), communication (strategies that influence adoption: education programs, change champions, audits), leadership (the roles of executives and managers to promote technology adoption), and economic environment (determinants such as government funding, political environment, business competition). Our study has also uncovered similar considerations, with many of our findings mirroring the components of users, workflow, interfacing systems, and communication. In the area of users, we uncovered the relationships and interconnections between the two main user groups of robotic devices: therapists and patients. That there is an interplay between them and the robotic devices which is influenced by their attitudes towards robotic devices and the benefits that they gain from using robotics. Eventually, this culminates in their motivations to use the devices, which would then reinforce their attitudes and benefits, thus creating a positive strengthening cycle. The findings on organisational aspects such as staff capacity, patient flow and transport, location and physical space of the robotic devices, and the need to integrate into existing settings reflect the components of workflow and interfacing systems. The need to convince therapists of the benefits of robotic rehabilitation in order to facilitate adoption mirrors principles of the communication component.

Overall, that our study findings corroborate with these published studies on generic

technology adoption provides a measure of confidence to our analysis. Furthermore, our findings contribute to a deeper understanding regarding the specific technology adoption of robotic rehabilitation for stroke patients.

Summary

The over-arching aim of this thesis was to investigate the usefulness of robotic rehabilitation for adult stroke patients. Based on the findings of our research, we are judiciously confident to say that robotic rehabilitation is useful, that it is not only clinically effective but also economically cost effective, and especially for severely impaired lower limb patients robotic therapy provides better outcomes. While the clinical effect and economic cost aspects were reported in the systematic reviews (i.e. Chapters 2 and 4), the adoption study represents the more context-based dimensions, in that it sought to understand the usage of these robotic devices in daily clinical settings. The findings of this adoption study complement the effect and economic review studies, in the sense that it bridges the gap between evidence and translation into clinical practice. Such a bridge is important in order to fully realise, in a tangible and meaningful way at the coalface, the benefits that robotic rehabilitation can offer to users. Without this perspective, it will result in a gap between research evidence and the delivery of evidence-based care in routine practice.[62,63] The adoption study uncovered a multitude of factors that need to be taken into consideration when introducing robotic rehabilitation into practice. These factors involve not just simply user training for these devices, but also aspects such as workflow processes, interfacing systems, communication strategies to influence adoption, perceived benefits, and attitudes and motivations of users. These host of considerations would need to be addressed when translating evidence into practice.

Conceptual framework

We have discussed the findings and implications of our studies on effectiveness, economic cost and adoption of robotic rehabilitation, which distilled the essence of the knowledge and understanding that have been gained through the thesis research. The three studies have each shed some light on the topic of robotic stroke rehabilitation. In an attempt to combine the knowledge from each of these studies into a coherent spectrum that is both practical and useful for evidence translation, a conceptual framework of implementing robotic rehabilitation was developed. Figure 1 illustrates the context and components of the framework.

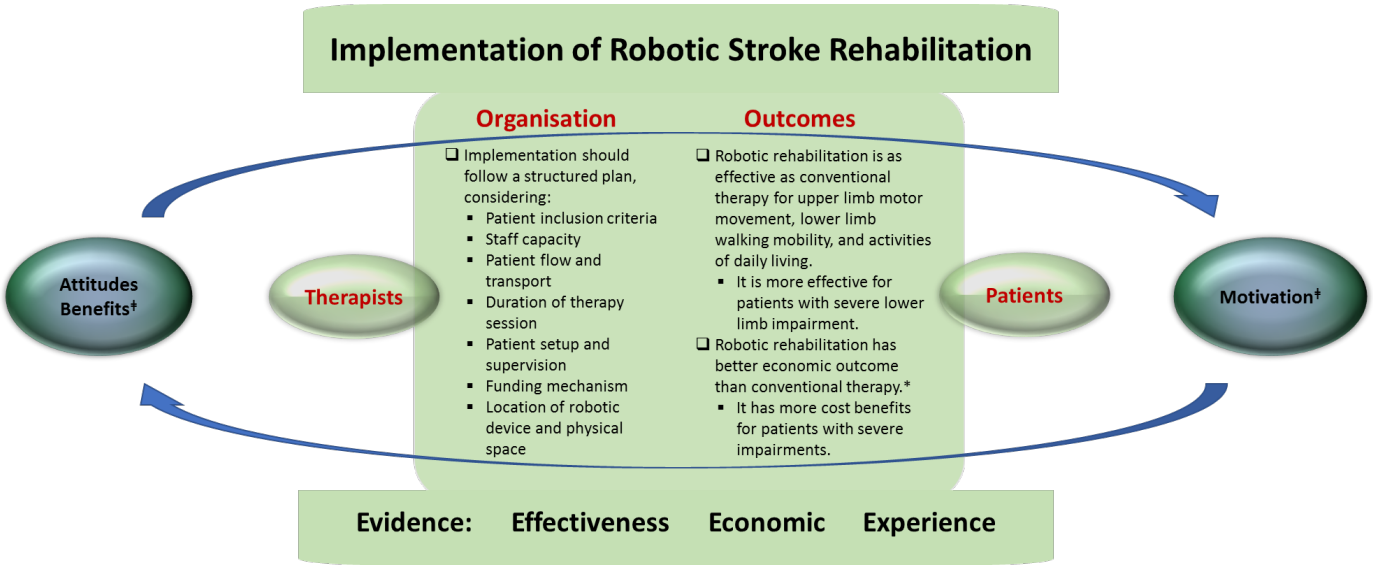

Figure 1: Conceptual framework to aid in the planning for robotic rehabilitation

* Economic cost-sensitivity factors: number of patients treated per robotic session, and time involvement of therapist per robotic session

‡ The adoption of robotic rehabilitation depends on the motivations of therapists and patients to use the robotic devices, which flows from their attitudes towards robotic devices and the benefits that these devices offer. An adoption plan that actively generates positive attitudes and benefits of robotic training, and which integrates seamlessly into organisational settings would sustainably motivate users.

The framework may assist administrators, managers and clinicians who are planning or managing the implementation of robotic rehabilitation into clinical services. It shows the various actors and concepts to consider; and illustrates the inter-connections and dependencies among these actor and concept elements.

The framework is informed by the Joanna Briggs Institute conceptual model of Evidence-Based Healthcare, which states that best practice occurs where current evidence is considered in conjunction with patient perspectives and local context.[64,65] The integration of the three studies reported in this thesis, represents the bringing together of current evidence and stakeholder perspectives and thus demonstrates congruity with the JBI Model of Evidence-Based Healthcare.

The “Evidence” block (Figure 1) informs the rest of the framework, particularly the actors who are critical for the planning and implementation of robotic rehabilitation, namely “Patients”, “Therapists” and “Organisation”. Encompassed within the “Evidence” block are the systematic review findings from the effectiveness and economic cost reviews, and the experiential findings from the qualitative adoption study with therapists who work

with robotic devices. From these findings, the evidence generated informs the context for the middle blocks of “Organisation” and “Outcomes”.

In line with the JBI Model of Evidence-Based Healthcare (which states that healthcare practices is to be informed by the best available evidence, the context in which the care is delivered, the individual patient, and the professional judgment and expertise of the health professional), we grouped our findings into similar co-related blocks. To facilitate an easier-to-understand representation of the conceptual framework, we had chosen to group the findings into the two blocks of “Organisation” and “Outcomes”. “Organisation” encapsulates our findings that mirror the JBI Model of expertise and perspectives of stakeholders (i.e. patient and professional staff), and the local context of care delivery. The stakeholder and local context are closely intertwined to the healthcare organisation, in the sense that it is the organisation which employs the professional therapist staff and is also the physical location where patients receive treatments. The organisation is also the location where both therapists and patients interact with the robotic devices, and through these interactions a cascade of events follow based upon the nature and quality of the experience. Thus, organisation defines the context where rehabilitation care is delivered. Given the close links that these various factors had in connection with organisational attributes, these findings were grouped together under “Organisation”. “Outcomes” mirrors the best available evidence of the JBI Model. In our conceptual framework, “Outcomes” conveys the practice implications of the effectiveness and economic systematic reviews that had been conducted in this thesis. It presents the evidence base that seeks to inform healthcare professionals about the clinical practices of conducting robotic rehabilitation. In the following sections, further context about the two middle blocks are elaborated.

In terms of “Organisation”, implementation considerations from this thesis pertaining to the organisational aspects of robotic rehabilitation indicate that robotic devices do not work alone but are part of a wider eco-system that involves linkages between various clinical departments (e.g. inpatient wards, outpatients, and other rehabilitation units such as pool therapy, group therapy), and also to other organisational domains such as patient transport, staff capacity and treatment protocols. This thesis found that both intra-coordination within the rehabilitation unit and inter-coordination with other clinical disciplines are needed in order to have a smooth integration into practice. For example, patient scheduling, patient transport and location of the robotic devices would need to be addressed in order to bring patients to their treatment session on time, which would, in turn, affect the utilisation rate of the robotic devices. These findings are similar to the

concepts of workflow and interfacing systems that have been discussed earlier. Likewise, as one therapist commented in the adoption study, many organisational aspects need to be considered when adopting robotic rehabilitation.

> “All of them (i.e. adoption models) probably need to take into account the space and design of the layout, of where you position your device and the flow of getting patients on and off and how do you, depending on which model you choose, how do you best utilize that design, so that you're maximizing the efficiency of time. Whichever model you choose, basically, maintaining patient safety. If you want to take into account staff satisfaction, and obviously cost efficiency and things like that.” [Physiotherapist F]

> “But because of the historical way of working on the wards, this has not fitted in very well to those models. I think whilst the model for robotics can get looked at, I think, the model for inpatient therapy could get looked at, to better utilize the two things together and work out the best way to maximize both.” [Physiotherapist F]

Other organisational aspects relating to staff capacity, staff training, robotic treatment protocols and funding mechanism (as elaborated in the adoption study) are also equally important. Clinical managers need to adequately educate their clinical staff about the evidence base of robotic training in order to gain their acceptance of robotic training. This approach is important as studies have shown that the use of evidence in training enables changes in knowledge, skills, attitudes, and behaviour, which leads to the uptake of new practices that benefit patients.[66,67] Managers also need to recognise the differing capacities of staff to adopt new technologies, that some therapists would find it easier to pick up new technologies than others.

> “It would be very different if we were trying to ask our therapists, all of our therapists, to be efficient with it; especially it's like having somebody learn a new computer program if they already have difficulty with technology. Certain therapists aren't necessary going to pick up on some of the…are going to feel comfortable with learning and using some of the new technology. Change can be difficult sometimes.” [Physiotherapist B]

How a robotic therapy session is structured is also an important consideration. The therapy training model affects the attitudes of therapists in terms of patient responsibility and ownership, therapists' ability to exercise clinical judgement, and personal fulfilment when patient recovers. It also affects the clinical skills of therapists, that while therapists appreciate learning new robotic skills, they do not wish to lose their conventional therapy skills. For example, it was found from the adoption study that a stand-alone training model where in- and out-patients were referred to for robotic training resulted in the robotic therapist feeling like a technician, isolated from other therapists, and without clinical responsibility or job fulfilment.

> "You become a technician and we're not technicians, we're clinicians who use our clinical reasoning. We assess, we set goals and we come up with intervention." [Physiotherapist E]

> "From a goal's perspective and from a fulfillment perspective, you feel very much like a robotic technician. I'm just putting them on and setting their parameters, I'm just putting them on and setting their parameters." [Physiotherapist F]

Under "Outcomes" are the findings from the systematic reviews on clinical effectiveness and economic cost effectiveness, which seeks to inform therapists about the clinical aspects of implementing robotic rehabilitation. Based on our review findings, although robotic therapy is as effective as conventional stroke therapy, it particularly benefits patients with severe lower limb impairments. Economically, robotic therapy has better cost outcomes than conventional therapy and most benefits severely impaired patients. The identified economic sensitivity factors (i.e. number of patients per robotic therapy session, and the time spent by therapists for a robotic session) also serve to inform clinicians to structure their robotic therapy sessions while maximising the economic benefits of robotic rehabilitation. The review findings imply that robotic training would be more beneficial for inpatients who are usually more severely impaired having survived a recent stroke incident.[68] As such, severe inpatients could be prioritised for robotic training. At the same time, clinical managers could also consider how robotic training is to be optimally conducted, in view of the economic sensitivity factors.

On the same plane as "Organisation" and "Outcomes", two other important actors include: "Therapists" and "Patients". These were identified as critical to the model by virtue of their centrality to both implementation of robotics, and the direct relationship

between care delivery and patient outcomes. Associated with these two actors are the domains of “Attitudes/Benefits” and “Motivation”. From our adoption study, we found that the interactions of therapists and patients with the robotic devices shaped their attitudes and the benefits that they experienced from using the devices. The “Attitudes/Benefits” and “Motivation” icons were also influenced in part by “Organisation” and “Outcomes”. The organisation context (in terms of workflow, interfacing systems, and communication) would determine the work environment, which would then influence how attitudes are formulated, and how benefits are perceived and interpreted. As an example of the role that organisation context plays, from the adoption study, it was found that certain organisational problems (e.g. lack of internal coordination) led to frontline therapists feeling overwhelmed as they had to sort out by themselves the daily operational challenges of transporting patients on time to and from robotic rehabilitation sessions. This then negatively influenced their attitudes towards robotic therapy and the level of perceived benefits that these devices offer.

> “I've faced a lot of the challenges for, against the ward not, systems, not against people but systems of making sure patients are ready, on time, toileted, dressed and getting here. Essentially, I have done the running around to do that and driven myself crazy doing that. Because those systems aren't in place and it's very intensive.” [Physiotherapist F]

The appropriate use of the evidence under “Outcomes” to guide robotic rehabilitation practices determines the effectiveness and utility of robotic training, which also subsequently influences the attitudes of users and the nature of benefits they receive.

> “They showed the clinicians the medical evidence to talk about how the robotic works and what kind of effects, benefits that both patients and therapists will get.” [Physiotherapist H]

> “If you don't see the benefit of using the device, you're not necessarily gonna make the effort to put your patients on there either. If you used the device enough, you can kind of see that patients can gain a lot from it and therefore you feel more motivated to put your patients, make sure they get on the device.” [Physiotherapist F]

Hence to show the inter-dependencies among all these elements, the icons of “Attitudes/Benefits” and “Motivation” are overlaid across the plane of “Organisation” and “Outcomes”.

The inter-connection between “Attitudes/Benefits” and “Motivation” of therapists and patients is best illustrated by the interplay that is found between attitudes, benefits and motivation from the findings of our adoption study. One of the main benefits experienced by patients was the ability to do more training repetitions in a stimulating environment, which was facilitated by the interactive games and score keeping integrated with certain robotic devices. That the robotic devices are able to keep score of each individual patient generates a positive attitude, which drives patients to beat their previous scores and thereby motivating them to exercise more. This, in turn, helps them to recover their motor movements and reduce their impairment levels. For therapists, one of the benefits is that the devices enable higher training repetitions while reducing the physical load on therapist. This is especially so for rehabilitation of lower limb patients where the robotic devices would take over the task of moving and supporting the lower limbs and cycle patients through the stepping motions. Another benefit was that the ease of adjusting the training parameters (e.g. limb guidance force, body weight support, speed, etc) allowed therapists to adapt robotic training to suit the individual abilities of patients at different stages of recovery. This enabled therapists to safely and continuously challenge patients to their training limits, which leads to better recovery of their motor movements. Seeing these benefits, therapists are predisposed to use the devices more. Overall, the attitudes/benefits of therapists and patients determine their motivation level to use the robotic devices. When there are positive attitudes and benefits, this leads to higher motivation. And when motivation is high, it creates a positive feedback loop, in which therapists and patients experience further benefits from using the robotic devices and have better attitudes towards robotic rehabilitation, which then reinforces their motivation to use robotic devices. Hence it is important for an implementation plan to actively generate positive attitudes and benefits in order to motivate users.

Taken altogether, the inter-play between the various domains of “Evidence”, “Organisation”, “Outcomes”, “Therapists”, “Patients”, “Attitudes/Benefits” and “Motivation” represent the key planning blocks that should be taken into account when planning to implement robotic rehabilitation. The evidence from this thesis suggests that integration of these domains would generate a positive momentum that funnels upwards towards supporting a successful implementation of robotic rehabilitation for stroke patients.

Limitations of framework

Small number of studies in economic systematic review

While the effectiveness review included 51 studies and provided robust evidence, the economic review only included five studies. The limited number of economic studies and that most of these studies had a relatively small sample sizes does not lend confidence to our economic findings. With inclusion of economic studies with larger sample sizes, there would be sufficient sampling data to ensure that resource variations can be adequately powered to detect cost differences and give a more definitive result.[69]

Clinical setting

In the qualitative adoption study, the interviewed therapists were from five hospitals and, except for one hospital, all four hospitals were relatively large hospitals with multidisciplinary rehabilitation departments, and all hospitals were located in metropolitan areas of higher socio-economic countries. This has an effect on the way hospitals are organized and funded, which in turn, may influence how robotic rehabilitation is adopted, such as the quantity and range of robotic devices, therapy access for which patient group, and the availability and competency of staff resources. Hence, our organisational findings are most relevant for larger hospitals in urban settings with established rehabilitation units. Having acknowledged the limitations of the settings in terms of wider applicability, the number of participants sampled in qualitative research is not considered a key characteristic for credibility or dependability of the data obtained.[70] In addition, the therapists interviewed were all very experienced in robotic rehabilitation and thus had higher information power, which states that a study can have less extensive sample participants when these participants have characteristics that are highly relevant and specific for the study aim.[71] While acknowledging the limitations of the clinical settings, we believe the findings of this study still have applicability in similar contexts.

Lack of direct insights from patients

The adoption study involved only therapists and no patients were interviewed. While patient experiences were referred to by therapists, there was no direct data from patients. Hence the framework might not be reflective of the viewpoints of patients. Nevertheless, given the professional therapeutic relationships that the interviewed therapists had with their patients, we believe that the therapists provided relevant

feedback about the experiences of their patients.

Significance of thesis

The thesis has reported on important and critical facets of robotic rehabilitation for stroke patients, such as clinical effectiveness, economic feasibility, and adoption into practice. In an attempt to integrate all these various facets during the research, a conceptual framework illustrating the various actors, concepts and interdependencies that need to be considered and addressed when implementing robotic rehabilitation was created. We believe that the combination of research methods applied to the questions in this thesis research offers a novel approach to robotic stroke rehabilitation and facilitate a holistic understanding of the topic.

The various studies conducted under the thesis have also made a meaningful contribution to knowledge on robotic stroke rehabilitation, including identifying future directions and practice recommendations for robotic stroke rehabilitation. The effectiveness systematic review has corroborated published findings that robotic training produced better outcomes for severely impaired lower limb patients, while the economic systematic review and the qualitative adoption study have generated new knowledge and assisted to address the evidence gap. As mentioned in prior sections, the economic review, since its publication, has garnered considerable interest from other researchers.

In terms of future areas of research, both the previously identified economic sensitivity factors, and insights obtained from the adoption study could potentially serve as starting points for further investigation. In view of the economic finding that patient numbers should be maximised per robotic training session, and that some therapists commented that there was no need for continuous patient monitoring by a therapist during robotic training, trials could be conducted to investigate if treatment protocols, especially during the patient supervision phase, could be modified for robotic rehabilitation. Some of the research questions could be to explore the actual need for continuous monitoring of patients by therapists while patients are training on robotic devices, the possibility of partial monitoring in view that the robotic devices are largely automated and have safety controls built in, and the option of leveraging on robotic automation for therapists to conduct both robotic and conventional training at the same time. These questions could be the starting points to investigate the optimisation of treatment protocols for robotic rehabilitation in order to determine its economic feasibility while taking into account patient outcomes, safety, and operational efficiencies.

Finally, as discussed in this chapter, the amalgamated conceptual framework of robotic rehabilitation is (as far as we know) the first such structured, evidence-informed framework proposed for implementing robotic stroke rehabilitation. This conceptual framework would facilitate planning by administrators, managers and clinicians when preparing to introduce robotic rehabilitation into their clinical practices. The framework covers aspects of clinical effectiveness, economic cost and adoption considerations, which we believe would offer clinicians a holistic and comprehensive planning aid.

Concluding remarks

The research conducted to address the questions in this thesis required the author to adopt a breadth of methodologies and analysis approaches that are both quantitative and qualitative in nature. Besides the need to examine the clinical effects of robotic stroke rehabilitation via meta-analysis (which involved a sizeable 51 studies), the author also has to understand economic cost aspects, which entails branching into understanding the limitations of meta-analysis for economic reviews,[50,72] and the alternate use of hierarchical decision matrix,[51,73] cost effectiveness plane,[74] and incremental cost effectiveness ratio.[75,76] The diverse study designs of the included economic studies also presented difficulties in extracting and analysing comparable data. In addition, to gain further insights into the economic benefits, the author extended the hierarchical decision matrix to incorporate a ranking score in order to have a deeper analysis of the economic benefits.[77] For the qualitative adoption study, to gain a broad and more comprehensive perspective, the author interviewed therapists who worked not only in Australia but also in various countries across Asia, Western Europe and Northern America. This was a challenging exercise in terms of participant recruitment and the logistics to conduct interviews with participants from different time zones. Analysis of the large amount of data from the interviews also required significant time and discussions with supervisors to identify and organise the codes and themes. Despite these challenges, the author hopes that the thesis research would contribute to the base of knowledge and evidence regarding robotic stroke rehabilitation, and be able to benefit users of robotic devices. Ultimately, it is hoped that stroke patients can gain better rehabilitation outcomes from the thesis research.

Bibliography

References

1. Tong RK, Ng MF, Li LS. Effectiveness of gait training using an electromechanical gait trainer, with and without functional electric stimulation, in subacute stroke: A randomized controlled trial. Arch Phys Med Rehabil. 2006;87(10):1298-304.

2. Rudd A, Wolfe C. Aetiology and Pathology of Stroke. Hospital Pharmacist. 2002;9:32-6.

3. National Stroke Foundation, Australia. Facts and figures about stroke [Internet]. [cited 2019 22 April]. Available from: https://strokefoundation.org.au/About-Stroke/Facts-and-figures-about-stroke.

4. Goldberg MP, Choi DW. Combined oxygen and glucose deprivation in cortical cell culture: calcium-dependent and calcium-independent mechanisms of neuronal injury. J Neurosci. 1993;13(8):3510-24.

5. National Stroke Foundation, Australia. Types of stroke; [Internet]. [cited 2018 August 12]. Available from: https://strokefoundation.com.au/about-stroke/types-of-stroke.

6. Intercollegiate Stroke Working Party. National Clinical Guideline for Stroke. 4th ed. London: Royal College of Physicians; 2012.

7. National Stroke Association, USA. Hemiparesis; [Internet]. [cited 2018 August 12]. Available from: http://www.stroke.org/we-can-help/survivors/stroke-recovery/post-stroke-conditions/physical/hemiparesis.

8. Mayo Clinic. Fibromuscular dysplasia [cited 2018 19 August]. Available from: https://www.mayoclinic.org/diseases-conditions/fibromuscular-dysplasia/symptoms-causes/syc-20352144.

9. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al. Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2016;47(6):e98-e169.

10. Intercollegiate Stroke Working Party. National Clinical Guideline for Stroke. 5th ed. London: Royal College of Physicians; 2016.

11. Sall J, Eapen BC, Tran JE, Bowles AO, Bursaw A, Rodgers ME. The Management of Stroke Rehabilitation: A Synopsis of the 2019 U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline. Ann Intern Med. 2019;171(12):916-24.

12. Hebert D, Lindsay MP, McIntyre A, Kirton A, Rumney PG, Bagg S, et al. Canadian stroke best practice recommendations: Stroke rehabilitation practice guidelines, update 2015. Int J Stroke. 2016;11(4):459-84.

13. Pollack MRP, Disler PB. Rehabilitation of patients after stroke. Medical Journal Australia. 2002;177.

14. Gresham GE, Alexander D, Bishop DS, Giuliani C, Goldberg G, Holland A, et al. Rehabilitation. Stroke. 1997;28(7):1522-6.

15. Stroke Foundation. Clinical Guidelines for Stroke Management 2017 https://app.magicapp.org/app#/guideline/3973 [cited 2020 26 January].

16. Dobkin BH. Rehabilitation after Stroke. N Engl J Med. 2005;352(16):1677-84.

17. Billinger SA, Arena R, Bernhardt J, Eng JJ, Franklin BA, Johnson CM, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(8):2532-53.

18. Takeuchi N, Izumi S. Rehabilitation with poststroke motor recovery: a review with a focus on neural plasticity. Stroke research and treatment. 2013;2013:13.

19. Kleim JA, Barbay S, Nudo RJ. Functional Reorganization of the Rat Motor Cortex Following Motor Skill Learning. J Neurophysiol. 1998;80(6):3321-5.

20. Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural Substrates for the Effects of Rehabilitative Training on Motor Recovery After Ischemic Infarct. Science. 1996;272(5269):1791-4.

21. Whitall J. Stroke Rehabilitation Research: Time to Answer More Specific Questions? Neurorehabil Neural Repair. 2004;18(1):3-11.

22. Yakub F, Md Khudzari AZ, Mori Y. Recent trends for practical rehabilitation robotics, current challenges and the future. Int J Rehabil Res. 2014;37(1):9-21.

23. Masiero S, Poli P, Rosati G, Zanotto D, Iosa M, Paolucci S, et al. The value of robotic systems in stroke rehabilitation. Expert Rev Med Devices. 2014;11(2):187-98.

24. Fazekas G. Robotics in rehabilitation: successes and expectations. Int J Rehabil Res. 2013;36(2):95-6.

25. Chang WH, Kim MS, Huh JP, Lee PK, Kim YH. Effects of robot-assisted gait training on cardiopulmonary fitness in subacute stroke patients: a randomized controlled study. Neurorehabil Neural Repair. 2012;26(4):318-24.

26. McCabe J, Monkiewicz M, Holcomb J, Pundik S, Daly JJ. Comparison of robotics, functional electrical stimulation, and motor learning methods for treatment of persistent upper extremity dysfunction after stroke: a randomized controlled trial. Arch Phys Med Rehabil. 2015;96(6):981-90.

27. Lo AC, Guarino PD, Richards LG, Haselkorn JK, Wittenberg GF, Federman DG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. N Engl J Med. 2010;362(19):1772-83.

28. Hidler J, Nichols D, Pelliccio M, Brady K, Campbell DD, Kahn JH, et al. Multicenter randomized clinical trial evaluating the effectiveness of the Lokomat in subacute stroke. Neurorehabil Neural Repair. 2009;23(1):5-13.

29. Krebs HI, Hogan N. Robotic Therapy: The Tipping Point. American journal of physical medicine & rehabilitation / Association of Academic Physiatrists. 2012;91(11 0 3):S290-S7.

30. Husemann B, Muller F, Krewer C, Heller S, Koenig E. Effects of locomotion training with assistance of a robot-driven gait orthosis in hemiparetic patients after stroke: a randomized controlled pilot study. Stroke. 2007;38(2):349-54.

31. Rosati G. The place of robotics in post-stroke rehabilitation. Expert Rev Med Devices. 2010;7(6):753-8.

32. Askie L, Offringa M. Systematic reviews and meta-analysis. Semin Fetal Neonatal Med. 2015;20(6):403-9.

33. Mulrow CD. Rationale for systematic reviews. BMJ. 1994;309(6954):597-9.

34. Oxman AD, Guyatt GH. The science of reviewing research. Ann N Y Acad Sci. 1993;703:125-33; discussion 33-4.

35. Yuan Y, Hunt RH. Systematic reviews: the good, the bad, and the ugly. Am J Gastroenterol. 2009;104(5):1086-92.

36. Sandelowski M. Whatever happened to qualitative description? Res Nurs Health. 2000(23):334–40.

37. Lum PS, Burgar CG, Shor PC, Majmundar M, Van der Loos M. Robot-assisted movement training compared with conventional therapy techniques for the rehabilitation of upper-limb motor function after stroke. Arch Phys Med Rehabil. 2002;83(7):952-9.

38. Volpe BT, Krebs HI, Hogan N, Edelstein OL, Diels C, Aisen M. A novel approach to stroke rehabilitation: robot-aided sensorimotor stimulation. Neurology. 2000;54(10):1938-44.

39. Mehrholz J, Pohl M, Platz T, Kugler J, Elsner B. Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke. Cochrane Database Syst Rev. 2018;9:Cd006876.

40. Wagner TH, Lo AC, Peduzzi P, Bravata DM, Huang GD, Krebs HI, et al. An economic analysis of robot-assisted therapy for long-term upper-limb impairment after stroke. Stroke. 2011;42(9):2630-2.

41. Turchetti G, Vitiello N, Trieste L, Romiti S, Geisler E, Micera S. Why effectiveness of robot-mediated neurorehabilitation does not necessarily influence its adoption. IEEE reviews in biomedical engineering. 2014;7:143-53.

42. Lo K, Stephenson M, Lockwood C. Effectiveness of robotic assisted rehabilitation for mobility and functional ability in adult stroke patients: a systematic review. JBI Database System Rev Implement Rep. 2017;15(12):3049-91.

43. The Joanna Briggs Institute, The University of Adelaide. Joanna Briggs Institute Reviewers' Manual: 2014 edition. Australia: Joanna Briggs Institute. 2014.

44. Mehrholz J, Thomas S, Werner C, Kugler J, Pohl M, Elsner B. Electromechanical-Assisted Training for Walking After Stroke: A Major Update of the Evidence. Stroke. 2017.

45. Mehrholz J, Werner C, Kugler J, Pohl M, Elsner B. Electromechanical-assisted training for walking after stroke. What is the evidence so far? What have we learnt? Physiotherapy (United Kingdom). 2015;101:eS990-eS1.

46. Mehrholz J, Elsner B, Werner C, Kugler J, Pohl M. Electromechanical-assisted training for walking after stroke (Review). Cochrane Database Syst Rev. 2013(7):Cd006185.

47. Prange GB, Jannink MJA, Groothuis-Oudshoorn CGM, Hermens HJ, Ijzerman MJ. Systematic review of the effect of robot-aided therapy on recovery of the hemiparetic arm after stroke. J Rehabil Res Dev. 2006;43(2):171-84.

48. Ang KK, Guan C, Phua KS, Wang C, Zhou L, Tang KY, et al. Brain-computer interface-based robotic end effector system for wrist and hand rehabilitation: results of a three-armed randomized controlled trial for chronic stroke. Front Neuroeng. 2014;7:30.

49. Lo K, Stephenson M, Lockwood C. The economic cost of robotic rehabilitation for adult stroke patients: a systematic review. JBI Database System Rev Implement Rep. 2019;17(4):520-47.

50. Gomersall J, Jadotte Y, Xue Y, Lockwood S, Riddle D, Preda A. Conducting systematic reviews of economic evaluations. . Int J Evid Based Healthc. 2015;13:170–8.

51. Gomersall J, Jadotte Y, Xue Y, Lockwood S, Riddle D, Preda A. Chapter 6: Systematic reviews of economic evidence. In: Aromataris E, Munn Z, editors. Joanna Briggs Institute Reviewer's Manual [Internet]. Adelaide: Joanna Briggs Institute, 2014.Available from: https://reviewersmanual.joannabriggs.org/.

52. Poli P, Morone G, Rosati G, Masiero S. Robotic technologies and rehabilitation: new tools for stroke patients' therapy. BioMed research international. 2013;2013:153872.

53. Hesse S, Hess A, Werner CC, Kabbert N, Buschfort R. Effect on arm function and cost of robot-assisted group therapy in subacute patients with stroke and a moderately to severely affected arm: a randomized controlled trial. Clin Rehabil. 2014;28(7):637-47.

54. Bustamante Valles K, Montes S, Madrigal Mde J, Burciaga A, Martinez ME, Johnson MJ. Technology-assisted stroke rehabilitation in Mexico: a pilot randomized trial comparing traditional therapy to circuit training in a Robot/technology-assisted therapy gym. J Neuroeng Rehabil. 2016;13(1):83.

55. Vanoglio F, Bernocchi P, Mule C, Garofali F, Mora C, Taveggia G, et al. Feasibility and efficacy of a robotic device for hand rehabilitation in hemiplegic stroke patients: A randomized pilot controlled study. Clin Rehabil. 2016;31(3):351-60.

56. Lo K, Stephenson M, Lockwood C. Adoption of robotic stroke rehabilitation into clinical settings: a qualitative descriptive analysis. 2019;Under Peer Review.

57. Roussy V, Thomacos N, Rudd A, Crockett B. Enhancing health-care workers' understanding and thinking about people living with co-occurring mental health and substance use issues through consumer-led training. Health Expect. 2015;18(5):1567-81.

58. Happell B, Bennetts W, Harris S, Platania-Phung C, Tohotoa J, Byrne L, et al. Lived experience in teaching mental health nursing: issues of fear and power. Int J Ment Health Nurs. 2015;24(1):19-27.

59. Varabyova Y, Blankart CR, Greer AL, Schreyogg J. The determinants of medical technology adoption in different decisional systems: A systematic literature review. Health Policy. 2017;121(3):230-42.

60. Schoville RR, Titler MG. Guiding healthcare technology implementation: a new integrated technology implementation model. Comput Inform Nurs. 2015;33(3):99-107; quiz E1.

61. Gücin NÖ, Berk ÖS. Technology Acceptance in Health Care: An Integrative Review of Predictive Factors and Intervention Programs. Procedia - Social and Behavioral Sciences. 2015;195:1698-704.

62. Reed JE, Howe C, Doyle C, Bell D. Simple rules for evidence translation in complex systems: A qualitative study. BMC Med. 2018;16(1):92.

63. Milat AJ, Li B. Narrative review of frameworks for translating research evidence into policy and practice. Public health research & practice. 2017;27(1).

64. Jordan Z, Lockwood C, Munn Z, Aromataris E. Redeveloping the JBI Model of Evidence Based Healthcare. International journal of evidence-based healthcare. 2018;16(4):227-41.

65. Jordan Z, Lockwood C, Munn Z, Aromataris E. The updated Joanna Briggs Institute Model of Evidence-Based Healthcare. International journal of evidence-based healthcare. 2019;17(1):58-71.

66. Dizon JM, Grimmer-Somers KA, Kumar S. Current evidence on evidence-based practice training in allied health: a systematic review of the literature. International journal of evidence-based healthcare. 2012;10(4):347-60.

67. Coomarasamy A, Khan KS. What is the evidence that postgraduate teaching in evidence based medicine changes anything? A systematic review. BMJ. 2004;329(7473):1017.

68. Masiero S, Armani M, Ferlini G, Rosati G, Rossi A. Randomized Trial of a Robotic Assistive Device for the Upper Extremity During Early Inpatient Stroke Rehabilitation. Neurorehabil Neural Repair. 2014;28(4):377-86.

69. Briggs A. Economic evaluation and clinical trials: size matters. BMJ. 2000;321(7273):1362-3.

70. Patton MQ. Qualitative research and evaluation methods (4th ed.). Thousand Oaks, CA: Sage. 2014(Module 30 Purposeful sampling and case selection: Overview of strategies and options; Module 40 Sample size for qualitative designs).

71. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. Qual Health Res. 2016;26(13):1753-60.

72. Briggs AH, Gray AM. Power and sample size calculations for stochastic cost-effectiveness analysis. Med Decis Making. 1998;18(2 Suppl):S81-92.

73. Nixon J, Khan KS, Kleijnen J. Summarising economic evaluations in systematic reviews: a new approach. BMJ. 2001;322(7302):1596-8.

74. Black WC. The CE plane: a graphic representation of cost-effectiveness. Med Decis Making. 1990;10(3):212-4.

75. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves – facts, fallacies and frequently asked questions. Health Econ. 2004;13(5):405-15.

76. Briggs AH, O'Brien BJ, Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. Annu Rev Public Health. 2002;23:377-401.

77. Lo K, Stephenson M, Lockwood C. Extending the hierarchical decision matrix to incorporate a dominance ranking score for economic systematic reviews. 2019;Under Peer Review.