Exploring upper limb interventions after stroke

A thesis by

Fiona Mary Coupar, Bsc (Hons)

Submitted for the degree of PhD

To

The University of Glasgow

From

The Academic Section of Geriatric Medicine

Division of Cardiovascular and Medical Sciences

Faculty of Medicine

Abstract

Stroke is a global health concern, with a significant impact on mortality and disability. Motor impairment, including upper limb impairment is particularly common following stroke. Upper limb impairment impacts on an individual's ability to complete activities of daily living and quality of life. Effective interventions targeted at upper limb recovery are therefore important and further research, within this area, has been identified as necessary. However, challenges researching such complex interventions have been recognised. To attempt to overcome such difficulties the Medical Research Council (MRC) proposed a framework for the development and evaluation of RCTs for complex interventions.

In this thesis the MRC framework has been used, focusing on the processes of developing and feasibility/piloting, to provide information for a phase III randomised controlled trial (RCT) of a novel intervention targeted at upper limb recovery following stroke.

A systematic review and meta-analysis was undertaken to investigate and clarify any possible association between predictive variables and upper limb recovery. Observational studies of stroke patients investigating at least one predictive variable and its relationship with a defined measure of upper limb recovery at a future time point were included. For this review data analysis combined several approaches. Fifty eight studies were included and 41 predictor variables identified. Initial measures of upper limb function and impairment were found to be the most significant predictors of upper limb recovery; odds ratio (OR) 38.62 (95% confidence interval (CI) 8.40-177.55) and OR 14.84 (95% CI 9.08-24.25) respectively. Neurophysiological factors (motor evoked potentials and somatosensory evoked potentials) were also consistently identified as strongly associated with upper limb recovery; OR 11.76 (95% CI 2.73-69.05) and OR 13.73 (95% CI 2.73-69.05) respectively. Moderate evidence of association was found for global disability and lower limb impairment. Interpretation of results is complicated by methodological

factors, particularly relating to the heterogeneous nature of the included studies.

In order to identify interventions which show potential for reducing impairment and/or improving upper limb function after stroke, an overview of the available evidence was completed. This systematic review and meta-analysis included Cochrane systematic reviews, other reviews and, where necessary, additional RCTs of interventions to promote upper limb recovery. Thirteen relevant interventions were found, covered by nine Cochrane systematic reviews (bilateral training, constraint-induced movement therapy (CIMT), electromyograhphic (EMG) biofeedback, electrostimulation, hands-on therapy interventions, mental practice, repetitive task training (RTT), electromechanical/robotic devices and virtual reality) and four other reviews (neurophysiological approaches, high-intensity therapy, mirror therapy and splinting). A statistically significant result, in terms of arm recovery, was found in favour of eight of the interventions: CIMT (standardised mean difference (SMD) 0.74 95% CI 0.44-1.03), EMG biofeedback (SMD 0.41 95% CI 0.05-0.77), electrostimulation (SMD 0.40 95% CI 0.02-0.77), mental practice (SMD 1.37 95% CI 0.60-2.15), mirror therapy (SMD 0.41 95%CI 0.05-0.77), RTT (SMD 0.23 95% CI 0.06-0.41), electromechanical/robotic devices (SMD 0.30 95% CI 0.02-0.58) and virtual reality (SMD 0.52 95% CI 0.25-0.78). Two out of the eleven interventions, which investigated hand function outcomes found a positive result (CIMT SMD 0.39 95% CI 0.11-0.68 and repetitive task training SMD 0.27 95% CI 0.06-0.47). Analyses were limited by a relatively small number of RCTs, which were also generally small in size. Heterogeneity of the available data and methodological limitations further impacts on the conclusions. Despite these limitations this overview provided a concise and informative summary of the available evidence. The interventions found to be beneficial, or showing promise tend to include elements of intensive, repetitive, task-specific practice.

To build the evidence base for upper limb interventions, two Cochrane systematic reviews were undertaken. These reviews investigated the effects of bilateral training and home therapy programmes on upper limb recovery.

Both included RCTs of stroke patients. Eighteen trials were included in the bilateral review, of which 14 were included in the analyses. Most of the included trials were considered to be at high risk of bias and the evidence was further limited by heterogeneity. No statistically significant results were found for any of the primary outcomes. One study found a statistically significant result in favour of another upper limb intervention for performance in extended ADL. No statistically significant differences were found for any of the other secondary outcomes. Four RCTs were included in the home-based therapy programmes review. No statistically significant result was found for any of the outcomes. There is currently insufficient good quality evidence to determine the effects of both the interventions studied.

Following the evidence gained from the overview of interventions elements of intensive, repetitive and task-specific practice were to be included in a novel upper limb intervention. Robotic interventions, which incorporate these principles, were also found to have a positive effect on upper limb outcomes. Therefore a pilot, feasibility and acceptability study of a novel device (Armeo®Spring) that included these elements was completed. Medically stable adults with a clinical diagnosis of stroke and arm deficits admitted to an acute stroke unit were recruited. Participants were randomly allocated to experimental intervention (high or low intensity training with the Armeo®Spring arm orthosis) or usual stroke unit care. Primary outcomes were feasibility and acceptability of the experimental device recorded at post-intervention. Secondary outcomes were; safety and three efficacy outcomes recorded at post-intervention, and 3 month follow-up. Patient recruitment was challenging; over eight months 393 consecutive stroke admissions were screened and 12 participants recruited. This study demonstrated that per-protocol levels of intensity were not feasible to provide in an acute stroke unit. However, higher levels of intensity could be achieved and this novel intervention was found to be acceptable to patients. This pilot trial also found higher change scores on the three efficacy outcomes within both intervention groups, compared to the control group. Due to small sample size and other possible confounding factors, these findings must be interpreted with caution.

Using the MRC complex intervention framework as a guide I completed development and feasibility/piloting work surrounding an upper limb intervention, following stroke. Following the results of this research further development, feasibility/piloting work is suggested for the Armeo®Spring device prior to the undertaking of a phase III RCT. The information gained from this research could be used to inform phase III RCTs of other upper limb interventions.

Acknowledgements

There are a number of people who I would like to take the opportunity to thank for assisting me in completing this thesis.

Professor Peter Langhorne, Professor Philip Rowe and Dr Christopher Weir; my supervisors, for their guidance, advice and support. Particular thanks must go to my principal supervisor, Professor Peter Langhorne, who enabled me to keep a sense of humour throughout the process and who I am privileged to have worked with.

To all my colleagues and friends in the Academic Section of Geriatric Medicine and clinical section (past and present) who have provided practical support, assistance and guidance, as well as many good times and fond memories. Lynn Legg and Gillian Kerr must be given a particular mention.

The staff, notably Beverly Honderbrink and the therapists and patients of wards 17/31 and 36 at Glasgow Royal Infirmary who allowed me to conduct the pilot feasibility study.

Katie Thomson for completing the outcome assessments for the trial and David Legg for transcribing the interviews for the feasibility study.

The co-reviewers on the systematic reviews described in this thesis and the Cochrane Stroke group for all their assistance with the two Cochrane reviews.

The Chief Scientist Office for funding my post, which allowed me to complete this research.

Sandra and Mike for all the extra babysitting duties, support and continual encouragement.

Mum and dad and my sisters, Susan and Aileen for their practical help, always believing in me and for their continued unconditional support, encouragement and love.

Lastly, but most importantly to the two most important people in my life: Philip and Abby. None of this could have been achieved without Philips' encouragement to attempt it in the first place and dedication to the cause of "getting it done." He has loved and supported me through the process, and for this I am amazed and grateful! Abby has to be thanked for her ability to continually amaze and terrify me in equal measures and for reminding me that there is something more important than this thesis. It is to the two of them that this thesis is dedicated.

Table of contents

List of tables

List of figures

Authors declaration

The research described in this thesis was completed during my time as a Chief Scientist Office Research Training Fellow in the Academic Section of Geriatric Medicine, Division of Cardiovascular and Medical Sciences, Faculty of Medicine, University of Glasgow based at Glasgow Royal Infirmary.

The protocols for the research described in this thesis were designed by me with the advice and guidance of my supervisors, principally Professor Peter Langhorne, University of Glasgow.

Dr. Alex Pollock (Research Fellow, NMAHP Research Unit, Glasgow Caledonian University) and Professor Peter Langhorne were co-reviewers of the systematic reviews and meta-analyses described in Chapters 2 and 3. Alex Pollock, Dr. Frederike van Wijck (Senior Lecturer, Queen Margaret University), Dr. Jacqui Morris (Research Fellow, University of Dundee) and Professor Peter Langhorne (University of Glasgow) were co-reviewers of the systematic review and meta-analysis described in Chapter 4. Professor Paulette van Vliet (Fellow, University of Newcastle, Australia), Dr. Alex Pollock, Professor Catherine Sackley (Professor of Rehabilitation, University of Birmingham) and Lynn Legg (Research Training Fellow, University of Glasgow) were co-reviewers of the systematic review and meta-analysis described in Chapter 5. The screening of stroke patients into the stroke unit at Glasgow Royal Infirmary was completed by me, although I had assistance form the clinical staff and therapists within the unit and from Ruth Graham (Stroke Research Nurse, Glasgow Royal Infirmary). Katie Thomson (Lecturer in Occupational Therapy, Glasgow Caledonian University) completed the end of intervention and 3-month follow-up assessments for the participants in the trial described in Chapter 6. Assistance was received to transcribe the interviews undertaken during the pilot trial and Lynn Legg acted as a second reviewer when analysing qualitative data. Statistical advice regarding sample size calculation was given by Dr Christopher Weir. All other work, including data analysis was completed by me.

The idea, design, organisation, administration and writing up of this thesis were performed by me with the advice and guidance of my supervisors, particularly Professor Peter Langhorne.

The original research completed for this thesis was performed in accordance with the principles stated in the Declaration of Helsinki, and the conduct of the research accorded to the principles of good clinical practice. Consent was gained according to the requirements of the local research ethics committee. Management of all data was in compliance with the Data Protections Act.

List of abbreviations

5MWT	5 Metre Walk Test
ADL	Activities of daily living
ADM	Abductor digiti minimi
AMED	Allied and complementary medicine database
APB	Abductor pollicis brevis
ARAT	Action Research Arm Test
BBT	Box and Block Test
BI	Barthel Index
CI	Confidence interval
CINAHL	Cumulative index to nursing and allied health literature
CNS	Canadian Neurological Scale
CST	Corticospinal tract
EDC	Extensor digitorum communis
EMBASE	Excerpta medica database
EMG	Electromyography
F	Female
FA	Fractional anisotropy
FAT	Frenchay Arm Test
FDI	First dorsal interosseus
F-M	Fugl-Meyer Assessment
GCS	Glasgow Coma Scale
M	Male
MAL	Motor Activity Log
MAS	Motor Assessment Scale
MEDLINE	Medical literature analysis and retrieval system online
MEPs	Motor Evoked Potentials
MI	Motricity Index
MMSE	Mini Mental State Examination
Mos	Months
MRC	Medical Research Council
NHPT	Nine Hole Peg Test

NIHSS	National Institute for Health Stroke Scale
OCSP	Oxfordshire Community Stroke Project
OR	Odds ratio
QOM	Quality of movement
RCT	Randomised controlled trial
SD	Standard deviation
SMD	Standardised mean difference
SPD	Silent period duration
SSEP	Somatosensory evoked potential
STREAM	Stroke Rehabilitation Assessment of Movement
TMS	Transcranial Magnetic Stimulation
UEFT	Upper Extremity Function Test
UK	United Kingdom
UL	Upper limb
USA	United States of America
WMFT	Wolf Motor Function Test

List of publications

Chapter 2

Coupar F, Pollock A, Rowe P, Weir C, Langhorne P. Predictors of upper limb recovery after stroke: a systematic review and meta-analysis. Clinical Rehabilitation 2012 26(4): 291-313

Chapter 3

Langhorne P, Coupar F, Pollock A. Motor recovery after stroke: a systematic review. Lancet Neurology 2009 Aug;8(8):741-54.

Chapter 4

Coupar F, Pollock A, van Wijck F, Morris J, Langhorne P. Simultaneous bilateral training for improving arm function after stroke. Cochrane Database of Systematic Reviews 2010, Issue 4. Art. No.: CD006432. DOI: 10.1002/14651858.CD006432.pub2.

Pollock A, Morris J, Wijck F, Coupar F, Langhorne P. Response to Cauruagh J. H et al Bilateral movement training and stroke motor recovery progress. Human Movement Science 2011 Feb 30(1) 143-6; author reply 147-9.

Chapter 5

Coupar F, Pollock A, Sackley C, Legg L, van Vliet P. Home-based therapy programmes for upper limb functional recovery following stroke Cochrane Database of Systematic Reviews 2012, Issue 5. Art No.: CD006755. DOI: 10.1002/14651858.CD006755.pub2.

List of presentations

Chapter 2

Coupar F, Pollock A, Rowe P, Weir C, Langhorne P. Predictors of upper limb recovery following stroke: A systematic review. Oral presentation at UK Stroke Forum 2008. Abstract published in International Journal of Stroke.

Coupar F, Pollock A, Rowe P, Weir C, Langhorne P. Predictors of upper limb recovery following stroke: A systematic review. Poster presentation at European Stroke Conference 2008. Abstract published in Cerebrovascular Diseases.

Chapter 3

Coupar F, Pollock A, Rowe P, Weir C, Langhorne P. Effectiveness of interventions for upper limb recovery after stroke. Oral presentation at European Stroke Conference 2009. Abstract published in Cerebrovascular Diseases.

Coupar F, Pollock A, Rowe P, Weir C, Langhorne P. Effectiveness of interventions for upper limb recovery after stroke. Oral presentation at UK Stroke Forum 2009. Abstract published in International Journal of Stroke.

Chapter 4

Coupar F, van Wijck F, Morris J, Pollock A, Langhorne P. Simultaneous bilateral training for improving arm function after stroke: A Cochrane Systematic Review. Poster presentation at UK stroke forum 2007. Abstract published in International Journal of Stroke.

Chapter 5

Coupar F, Pollock A, Sackley C, Legg L, van Vliet P. Home-based therapy programmes for upper limb functional recovery following stroke: A Cochrane Systematic Review. Oral presentation at the UK Stroke Forum 2011. Abstract published in International Journal of Stroke.

Chapter 6

Coupar F, Thomson K, Weir C, Langhorne P. A randomised, feasibility study of an assistive technology intervention targeted at the upper limb. Oral presentation at the Society of Rehabilitation Research July 2012 (winner of best oral presenation).

Chapter 1

Introduction

Chapter 1 Introduction

This thesis investigates upper limb interventions following stroke. This introductory chapter will define key terms and place this investigation in appropriate context.

1.1 Stroke

1.1.1 Definition of stroke

Stroke is regularly defined as;

> "a syndrome of rapidly developing symptoms and signs of focal, and at times, global, loss of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin[1]"

This definition encompasses three pathological types of stroke; ischaemic, primary intracerebral haemorrhage and subarachnoid haemorrhage (SAH)[2]. Two systematic reviews[3;4] of population-based incidence studies reported on the prevalence of stroke type and found largely consistent results. Approximately, ischaemic stroke accounts for 80% of cases, intracerebral haemorrhage 10%, SAH 5% and uncertain cause 5%. The studies in these reviews however were largely based on white people in more developed countries and therefore the findings are not generalisable to various ethnic groups and less developed countries. A further limitation of these reviews is that not all the participants in the studies received computerised tomography (CT) or magnetic resonance imaging (MRI) scans and therefore rates of intracerebral haemorrhage may have been underestimated[5].

While the above definition has been broadly accepted for many years, a revised definition has recently been proposed. This revised definition does not include subarachnoid haemorrhage, as it is argued that the clinical features, aetiology, prognosis and treatment of SAH are quite distinct. The modified definition of stroke is therefore;

> "a clinical syndrome characterised by an acute loss of focal cerebral function with symptoms lasting more than 24 hours or leading to death, which is thought to be due to either spontaneous haemorrhage into the brain substance (haemorrhagic stroke) or inadequate cerebral blood supply to a part of the brain (ischaemic stroke) as a result of low blood flow, thrombosis or embolism associated with diseases of the blood vessels (arteries or veins), heart or blood"[5].

In addition, to account for advancing technologies and treatments, the new proposed definition adds the following section:

> "Patients who are being assessed within 24 hours of symptom onset and who still have focal neurological symptoms are temporarily classified as having a 'brain attack' (or something similar, such as an 'acute stroke syndrome' or 'unstable brain ischemia')"[5].

1.1.2 The impact of stroke on public health

Stroke is a major public health concern worldwide and places a huge burden on patients, families and wider society[2]. Globally stroke is the third most common cause of death (after coronary heart disease (CHD) and cancers) and a leading cause of permanent disability[6].

Within the United Kingdom (UK) stroke affects between 174 and 216 people per 100,000 of the population[7], with approximately 12,500 new stroke events annually[8]. Of these individuals 20-30% would be expected to die within a month[9] and nearly 50% to remain dependent after a year[2]. Therefore, it is evident that the main impact of stroke is in increased levels of chronic, permanent disability, rather than death (in contrast to CHD and cancers). Indeed in the UK stroke is reported as the most prevalent cause of severe adult disability[10]. Additionally while stroke mortality in developed countries is falling, it is argued that a large proportion of this is related to a reduction in case-fatality and other factors, rather than a reduction in incidence[5]. Further there is little evidence that the burden of stroke-related disability has fallen, adding weight to this argument[11].

Subsequently, stroke is a major source of health and social care expenditure. In the UK 6% of the National Health Service (NHS) and social service spending budget is attributable to stroke and its consequences[11]. Additionally, with an increasingly ageing population the incidence of stroke is likely to increase[12], and medical advancements are likely to further reduce case-fatality. Thus stroke-related disability and its associated costs are likely to escalate. It is predicted that disability-adjusted life years (DALYs) lost to stroke will rise from 38 million in 1990 to 51 million in 2020[6]. For all of these reasons stroke has been identified as an NHS priority area[13;14].

1.1.3 The impact of stroke on the individual

At an individual level the consequences of stroke can be devastating. Depending on the area of the brain affected and the extent of the damage, the effects can be wide-ranging[15]. Residual neurological deficits can include loss or impairment of the use of a limb (paresis), difficulties with speech (aphasia/dyspharthia), decline in mental functions (cognitive/perceptual impairments) and impaired emotional functioning[16]. These deficits can impact upon an individual's ability to move (e.g. walking), complete activities of daily living (ADL) (e.g. feeding, dressing) and reduce quality of life. Additionally a number of secondary medical problems; particularly infections and falls are common after stroke[17]. However each stroke will have a varying clinical presentation secondary to vascular anomalies and the size and extent of the lesion[18].

If the consequences of stroke are considered in terms of the World Health Organization (WHO) International Classification of Functioning, Disability and Health[19] the full impact of stroke can be recognised. Stroke can affect each aspect of an individual's life, as represented by the model; it can impair bodily functions and structures, limit activity and restrict participation.

One of the most common and obvious deficits following stroke is motor impairment[4]. Upper limb motor impairment has been estimated to affect

between 50-80% of stroke patients[20]. In the population-based Copenhagen stroke study 32% of patients were admitted with severe upper extremity paresis, and 37% with mild arm paresis[21]. It has been further suggested that, despite rehabilitation efforts, 50-75% of patients with initial upper limb impairment report persisting problems 6 months later[22].

Upper limb impairment is therefore a considerable problem following stroke and a significant contributor to stroke-related disability[23]. This is perhaps most highlighted when considering the range of activities that involve arm function in everyday life: basic activities of daily living (e.g. dressing, eating and drinking, toileting) communication; sensory activities (touch, temperature, pain); manipulation; defence and aggression and sexual activity[24]. Additionally upper limb impairment has been found to be associated with reduced quality of life and unhappiness[25].

Upper limb motor deficits can occur following damage to the motor cortex, pre-motor cortex, supplementary motor cortex or damage to the descending fibres of the corticospinal tract. Upper limb problems can be present in any of the Oxfordshire Community Stroke Project (OCSP) classifications; lacunar syndrome (LACs), total anterior circulation syndrome (TACs), posterior circulation syndromes (POCs) and partial anterior circulation syndrome (PACs)[5].

The main characteristics of upper limb impairment following stroke include changes in muscle tone and strength, abnormal reflexes, impairment of volitional movements and sensory deficits[5]. Related secondary complications e.g. shoulder subluxation, oedema, pain and shoulder hand syndrome are also common[26].

It is therefore evident that upper limb impairments are a frequent, persisting and disabling consequence of stroke[27]. Upper limb motor deficits and interventions targeted at recovery of upper limb functional movement and reduction in motor impairment will form the focus of this thesis. Before giving

further consideration to these aspects it is worth reviewing the current treatments available to stroke patients.

1.1.4 Current stroke treatments

It is beyond the scope of this thesis to discuss in any detail the range of therapies available for the treatment of stroke. It is worth however mentioning that a number of treatments (e.g. drug regimes, surgical interventions and rehabilitation) are available for the prevention and management of stroke and evidence is continually emerging on the effects of such treatments. It has been suggested that there are currently two main treatments for stroke that significantly improve outcomes – thrombolysis and stroke units[15].

Thrombolysis has been found to significantly reduce the proportion of individuals, with acute ischaemic stroke, dead or dependent at the end of follow-up (odds ratio (OR) 0.84, 95% confidence interval (CI) 0.75 to 0.95)[28]. Thrombolysis is however, restricted in use; it can only be delivered to those with ischemic stroke, admitted within four and a half hours of definite onset of symptoms and should be delivered within the context of an acute stroke unit[29]. Due to these restrictions less than 10% of stroke patients are currently eligible for thrombolytic therapy[30;31].

Stroke unit care is now widely recommended as the most appropriate method for the organisation of hospital stroke services[32-34]. The evidence for stroke units has been growing for over 10 years. The stroke unit trialists collaboration (SUTC) provide systematic review evidence that, when compared to general wards, stroke unit care is associated with a reduction in death (OR 0.86, 95% CI 0.76 to 0.98), combined outcomes of death or dependency (OR 0.82, 95% CI 0.73 to 0.92) and death or institutionalisation (OR 0.82, 95% CI 0.73 to 0.92) at the end of follow-up[35].

This review completed subgroup analyses based on patient and intervention characteristics and the conclusions (based on 31 trials) of this review are that acute stroke patients are more likely to survive, return home and regain independence if they receive organised inpatient (stroke unit) care when compared to alternative care. The subgroup analysis results indicate that the benefits of organised stroke unit care are not limited to any particular subgroup of patients (male/female, over 75/under 75, mild/moderate/severe stroke) or model of stroke unit organisation (comprehensive units, mixed assessment/rehabilitation units, rehabilitation stroke units). Therefore this treatment approach is more likely to have a beneficial effect on a greater number of individuals. However the authors of this review urge caution in respect of interpretation of these findings due to low statistical power.

Despite the evidence for the effectiveness of organised (stroke unit) care the precise mechanisms of what constitutes an effective service are difficult to define due to the complex and multi-faceted nature of this treatment. The main features of stroke unit care however have been described as: (i) a discrete unit, (ii) organisation (coordinated multidisciplinary rehabilitation, nursing integration and involvement of carers in rehabilitation process), (iii) specialist staffing (medical, nursing and therapy staff with specialist interest in stroke/rehabilitation) and (iiii) programmes of education and training[35]. Additionally, it has been found that trials which demonstrated a beneficial effect each followed a similar approach to care that incorporated: (i) assessment and monitoring procedures (medical, nursing and therapy), (ii) early management policies (e.g. avoidance of urinary catheterisation, early mobilisation, treatment of early infection and (iii) ongoing rehabilitation policies (e.g. goal-setting, early assessment for discharge)[36].

Interpretation of the stroke unit trials would therefore suggest that multidisciplinary rehabilitation is a central component of this effective treatment.

1.1.5 Stroke rehabilitation

Multidisciplinary rehabilitation is a well established and accepted element of stroke care[32-34]. While no single definition is available a clear consensus exists that rehabilitation aims to minimise the impact of stroke and prevent secondary complications. These aims are achieved using goal-setting, and a variety of problem-solving and therapeutic approaches[5;37]. The key elements of rehabilitation are; assessment, goal-setting and intervention[5;37;38].

Stroke rehabilitation tends to involve experts from a number of different disciplines. It has been suggested that the core multidisciplinary team should consist of appropriate levels of nursing, medical, physiotherapy, occupational therapy, speech and language therapy and social work staff[33]. However, perhaps the most important person in the process is the stroke patient themselves as rehabilitation requires patience, perseverance and active involvement[39].

As stated previously this research will concentrate on the problem of upper limb motor deficits following stroke and the particular focus will be on the intervention element of rehabilitation, in relation to these deficits.

In order to reduce upper limb motor impairment and subsequent disability, upper limb recovery has been identified as an important rehabilitation goal[40]. As with other rehabilitation interventions, therapy targeted at the upper limb, (provided primarily by physiotherapists and occupational therapists) focuses on reducing impairment and increasing function. Due to the impact upper limb problems can have on an individual it is essential that related interventions are effective in order to; maximise outcomes, reduce dependency and ensure appropriate use of resources. Improving upper limb outcomes however continues to present a challenge[41] due to the complexity of the area and a lack of definitive research evidence to guide practice.

1.2 Problems researching rehabilitation

Historically, research into all aspects of rehabilitation has been limited and frequently of poor quality[13]. Randomised controlled trials (RCTs) are widely accepted as the "gold-standard" for assessing the effects of interventions[42]. However, it has been acknowledged that very few well designed and reliable RCTs exist that assess the effectiveness of rehabilitation after stroke[16]. This situation has improved, however a number of inherent problems in researching such "complex interventions" still exist. Complex interventions are defined as those "built up from a number of components, which may act both independently and inter-dependently" and encompass the majority of healthcare interventions[43]. The particular difficulties of researching such interventions are identified below[44;45]:

- Small sample sizes
- Interventions poorly described or difficult to compare
- Blinding
- Difficulty testing accepted practice against placebo
- Difficulty accepting uncertainty and acknowledging requirement for RCTs
- Lack of funding, education, infrastructure and experience of research
- Learning "curve" for practices
- Patients' concerns/reluctance to participate in RCTs

Each of these elements will now be given further consideration, relating to stroke or general rehabilitation research.

Small sample sizes

A frequent criticism of rehabilitation trials is that the sample size is too small. This leads to a lack of sufficient statistical power and thus does not allow for definitive conclusions to be made[43]. Research should enable hypothesis to be answered and that this can only be achieved through appropriate trial design and adequate numbers of patients[46].

Interventions poorly described or difficult to compare

Within complex interventions it is often difficult to ascertain what the "active ingredient" actually is[43]. Difficulties often arise in assessing complex interventions as researchers have not fully defined and developed the intervention[47]. Unless the processes and mechanisms of the interventions are made clear then replication or generalisation is nearly impossible[47;48]. The expertise of the professionals involved, dosage, intensity and setting of the intervention are just some of the elements that need to be considered[43].

Blinding

In order to reduce bias the trial participants, outcome assessors and therapists providing the intervention should be unaware of group assignment[49]. Trials which do not report double-blinding have been found to yield larger estimates of effect[50]. However, due to the nature of rehabilitation trials it is often impossible to blind participants and the therapists providing the intervention. However it should almost always be possible to blind outcome assessors

When therapists/other staff are not blinded to group assignment, there is a risk of 'competitive therapy bias[51], whereby patients in the control group receive additional 'usual care' as they are prioritised by ward therapists over those receiving the additional intervention. This can inevitably impact upon the estimated study effects.

Difficulty testing accepted practice against placebo

Many aspects of rehabilitation e.g. physiotherapy and occupational therapy are an accepted and recommended part of stroke treatment. While the evidence base is growing[52;53] further RCTs are required to evaluate various aspects of stroke rehabilitation. However, it is generally considered unethical to deny patients accepted treatments. Therefore interventions are generally compared to other interventions (e.g. usual care) rather than placebo, limiting statistical power.

Difficulty accepting uncertainty and acknowledging requirement for RCTs

Traditionally, rehabilitation interventions have been developed from an intuitive belief about what may be effective, rather than from research evidence[43]. Additionally there is evidence that firmly held clinical beliefs can be unfounded; illuminating the importance of well-designed randomised controlled trials[54].

Lack of funding, education, infrastructure and experience of research

Within the stroke arena significant progress is being made. Nevertheless rehabilitation research still has a long way to go. Indeed the potential of allied health professionals (AHPs) as researchers is not yet fully realised and continued support is needed to enable them to become fully research-aware, research-active and evidence-based professions[55].

Learning "curve" for practices

Rehabilitation interventions are complex in nature and quality in delivery improves with repetition and over time. Therefore randomising between a familiar and unfamiliar intervention could introduce bias against the latter[44].

In addition to the above difficulties there is also issues relating to economic evaluataion of rehabiltiaiton interventions. To date very few rehabilitation trials have incorporated economic evaluation. This is probably due to those undertaking rehabilitation research having limited knowledge and expertise in this area and researchers tending to focus on the efficacy of interventions. Economic evaluation requires specialist health economist input, and requires analysis of many elements; however economic evaluation should be considered as part of rehabilitation trials, particularly larger studies to investigate if interventions are economically feasible as well as effective.

Additional difficulties are particular to stroke rehabilitation research; spontaneous improvement, variety of outcome measures and heterogeneity of patients.

Spontaneous improvement

Most stroke patients have some degree of spontaneous recovery which compounds the difficulties in stroke rehabilitation research[16]. By employing a randomised controlled trial methodology this should no longer be a factor. However if the sample size is not large enough disparity between groups may occur.

Variety of outcome measures

Difficulties with outcome measures in rehabilitation research include; lack of reliability, validity and/or sensitivity and difficulty ascertaining what particular aspect is being measured. It has been argued that while rehabilitation studies have tended to assess the effectiveness of interventions using "higher level" outcome measures e.g. global ADL measures this approach should be re-considered and impairment outcome measures be considered, in the first instance, to assess if the intervention has an impact at the level at which it is aimed[54]. The number of outcome measures available also causes difficulties as combining and comparing trials where different measures have been used, is problematic[16].

Heterogeneity of patients

As outlined previously, stroke can affect people in a number of different ways. Frequently stroke rehabilitation trials have relatively broad inclusion criteria, which may generate less useful information about the types of patients who may benefit (or not) from a specific intervention[56]. In terms of upper limb rehabilitation, there are no clear guidelines on best practice and it has been argued that this is primarily due to uncertainty regarding who benefits from treatment and in what way[57].

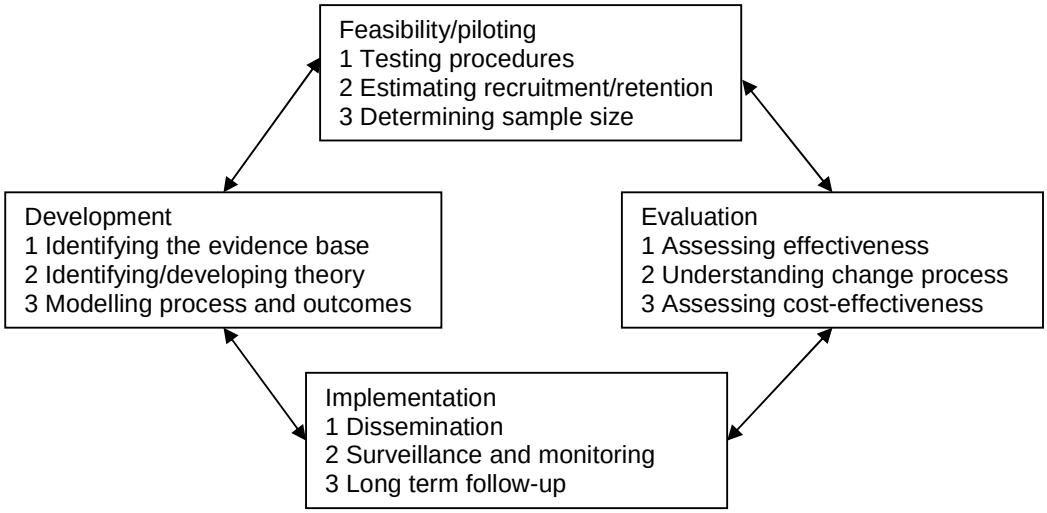
Within stroke rehabilitation research there is also the question of 'faster' or 'better' levels of recovery. Often within stroke rehabilitation research, particularly trials completed in the acute stages, it is unclear if the intervention under investigation improves levels of recovery, or simply hastens the process of recovery. For such reasons it is important to include a range of outcome measures, i.e. it is important to include outcomes

covering a wide range of spectrums (ADL, motor impairment, functional movement) and it is also important to have outcomes measured over a period of time. Stroke rehabilitation trials have tended to have short term follow-up (e.g. end of intervention, 3 month), probably principally due to practical issues such as funding and feasibility of completing longer term follow-up. However this means it is often unclear if effects of interventions are maintained in the longer-term (6 months, 12 months and beyond). Therefore, when designing studies longer-term outcomes should be incorporated if at all possible. If interventions are only effective in the short-term and have no impact on outcomes in the longer-term the suitability of the intervention may be questioned, particularly in times of limited resources.

1.2.2 Framework for researching complex interventions

To overcome the difficulties posed by complex interventions, a framework for the development and evaluation of RCTs for complex interventions was initially proposed in 2000 by the Medical Research Council (MRC)[43]. This framework consisted of 5 phases (pre-clinical, modelling, exploratory trial, definitive RCT and long term implementation) each with a separate purpose and set of suggested tasks[43;47;58]. This guidance was updated and extended in 2008[59]. The updated framework places emphasis on the processes of development, feasibility/piloting, evaluation and implementation of complex interventions. In contrast to the original guidance the updated framework is less linear and provides a more flexible approach. The process of investigating complex interventions is represented in the figure below[59;60].

Figure 1-1 - Graphical representation of MRC framework of the key elements of the development and evaluation process



The key components of each part of the process are indicated in the above figure. The components that are most relevant to this thesis are development and feasibility/piloting.

Development

This part of the process is essential as it is imperative to develop the intervention to the point where it can be reasonably expected to have a worthwhile effect[59;60].

Feasibility/Piloting

There is evidence to suggest that the feasibility/piloting part of the process is often not completed, which can lead to problems of acceptability, compliance, delivery of the intervention, recruitment and retention and smaller than expected effect sizes at the evaluation stage[59;60].

The evaluation of complex interventions poses a number of challenges and requires a substantial investment of time. However, only thorough consideration of the processes and mechanisms of the problem, the intervention and evaluation can an adequate and cost-effective proposal for a randomised controlled trial be developed[47].

1.3 Conclusion

From this introductory chapter it is clear that stroke is an important global health concern, and one that is likely to escalate with an increasing ageing population. Thus, it is imperative that effective strategies for the prevention, treatment, and rehabilitation of this disease are investigated.

Organised inpatient (stroke unit) care has been identified as the most effective intervention in the treatment of patients with stroke. While the essential components of stroke unit care are still not clear, multidisciplinary rehabilitation is accepted as a core component.

Multidisciplinary stroke rehabilitation involves a number of processes and interventions, which aim to reduce impairment and disability and improve function. The evidence for some aspects of stroke rehabilitation is still relatively limited or unclear. Therefore, in order to ensure improved outcomes for patients, further research is crucial.

Difficulties with researching complex interventions, such as aspects of rehabilitation, have been identified; however, to overcome such complexities a framework has been suggested.

My research will use this complex intervention framework as a guide to identify and evaluate a novel intervention for upper limb recovery following stroke. Upper limb recovery has been identified as an area of concern and an important area for research due to its prevalence and impact on an individual's ability to complete activities of daily living.

1.4 Research aims

This thesis will investigate a number of issues related to upper limb recovery following stroke in order to provide information for a phase III randomised controlled trial that is; theoretically-defensible, reproducible and adequately controlled, with appropriate statistical power.

1.4.1 Research objectives

1. To identify predictive variables of upper limb recovery after stroke
2. To identify interventions that show potential for reducing impairment and/or improving upper limb function after stroke
3. To identify a novel, evidence-based intervention to reduce upper limb impairment/improve function
4. To complete a pilot trial and provide information for a phase III randomised controlled trial of a novel upper limb intervention

To meet these stated aims a programme of work will be completed and for each stage of the programme the appropriate research method to answer the research questions will be utilised.

In Chapter 2 the background to investigating predictive variables will be discussed and the mechanisms and results of a systematic review of this area will be presented.

In Chapter 3 the background to investigating upper limb interventions will be examined and the mechanisms and results of a systematic review and meta-analysis of this area will be described.

In Chapters 4 and 5 investigations into the effects of particular upper limb interventions will be presented.

In Chapter 6 the design, methods and subsequent results of a pilot trial of a novel upper limb intervention will be described.

In Chapter 7 conclusions will be drawn. Limitations of the work will also be discussed and how the information gained could inform other phase III trials will be proposed.

Chapter 2

Predictors of upper limb recovery after stroke: a systematic review and meta-analysis

Chapter 2 Predictors of upper limb recovery after stroke: a systematic review and meta-analysis

2.1 Introduction

2.1.1 Upper limb deficits

As reported in Chapter 1 upper limb deficits are one of the most common impairments to affect individuals following stroke. In addition the upper limbs are of special concern because of the significant impact these impairments have on disability, health and quality of life[61] and due to the relatively limited attention this area has received[62].

2.1.2 Variability of outcome of upper limb following stroke

It is acknowledged in the literature that there is variability across individuals in the nature and extent of upper limb outcome[63]. While several studies have been conducted to examine the recovery of the hemiplegic arm, discrepancies in terms of reported rates of recovery are evident. Rates of no functional recovery have been reported as 13% (n=491)[21] and 60% (n=92)[64]. Complete functional recovery has been reported as occurring in between 12% (n=102)[65] and 20% of patients (n=491)[21]. The discrepancies between these studies could be attributable to differing choice of outcome measure, variations in the time to measurement of recovery and/or slight differences in case selection. Despite the variations it is clear that some patients will have little or no functional improvement, some partial recovery and others complete recovery.

As a result of these differing levels of recovery individual patients will have different rehabilitation needs. However the literature currently lacks methods for stratification and individualisation of rehabilitation programmes for the

upper limb[57]. A systematic review of exercise therapy for arm function concluded that identification of patients who would be most likely to benefit from particular interventions was not possible[66]. In addition it has been proposed that the lack of positive findings in the stroke rehabilitation literature could be attributed to the heterogeneity of study populations[67].

Therefore to optimise rehabilitation, clarify outcomes and effects of therapy, identify appropriate interventions, stratify patients within trials and accurately inform patients of likely outcomes, there is a need to identify variables, which may allow early and reliable prediction of upper limb outcome[65;68;69]. This information would be useful to both clinicians and researchers[70]. I wanted to gain a better understanding of upper limb problems and enable a better characterisation of clinical presentation[54] and likelihood of recovery. This was achieved through completion of a systematic review of predictor studies. The purposes of prognostic/predictive studies are identified below:

- To guide clinical decision making, including treatment selection and patient counselling
- To improve understanding of the disease process
- To improve the design and analysis of clinical trials (for example, risk stratification)
- To assist in comparing outcome between treatment groups in non-randomised studies by allowing adjustment for case mix
- To define risk groups based on prognosis
- To predict disease outcome more accurately or parsimoniously

For the reasons outlined above and to allow appropriate stratification and analysis in my planned trial, an investigation into variables which predict upper limb outcome was deemed appropriate. Due to the potential difficulties of establishing and using complex prediction models[71;72] and in order to highlight easily used and potentially clinically relevant variables I decided to focus on the identification of individual (univariate) predictor variables.

A brief review of the literature established that a number of variables have been investigated in terms of their predictive value for upper limb recovery, including presence of evoked potentials[73], initial motor deficit of the arm[74], age[70], ability to shrug the shoulder[75] and cognitive impairment[76]. Inconsistency was evident between studies regarding the usefulness of such individual predictive variables. Therefore a formal investigation to clarify associations between predictive variables and upper limb recovery was deemed appropriate. This was achieved through the completion of a systematic review.

A similar analysis[77], published during conduct of this review, reported that neurophysiological measures and initial sensoriomotor abilities were the best predictors of voluntary arm movement after stroke. This review focused on categorising the predictive variables and associated outcome measures in terms of the International Classification of Functioning, Disability and Health[19]. In contrast, I intended to provide a more wide-ranging and comprehensive summary of reported predictive variables and their association with upper limb recovery. A further review of prediction of motor recovery[78] considered only the predictive value of motor impairment scores, neuroimaging and neurophysiological assessment. The aim of the current review was to systematically review and summarise the current, available literature regarding prognostic variables relating to upper limb recovery following stroke.

2.1.3 Systematic reviews

Systematic reviews have become essential tools to allow individuals to keep up to date with ever-accumulating evidence, in their field of interest[79]. A systematic review is defined as;

> "an overview of primary studies which contains an explicit statement of objectives, materials and methods and has been conducted according to explicit and reproducible methodology[80]"

Where appropriate and sensible to do so, systematic reviews may include a meta-analysis, which is a statistical technique used to synthesise the results from independent studies. It is important to distinguish between systematic review and meta-analysis because whilst it is always desirable to systematically review a body of data on some occasions it may be inappropriate or even misleading, to pool results from separate studies[79]. It is therefore crucial that the limitations of meta-analysis and the importance of exploring sources of heterogeneity (inconsistency of results across studies) and bias are understood.

Systematic review and meta-analysis methodology are most commonly associated with reviews of randomised controlled trials, and this will be discussed further in subsequent chapters. However, this methodology are applicable to all types of research design, including prognostic/predictive studies[71]. Indeed as multiple studies investigating prediction of a particular outcome accumulate it becomes increasingly important to identify and evaluate all of the relevant studies to develop a more reliable overall assessment.

For prognostic/predictive studies the process of systematic review is not straightforward and a number of particular difficulties have been identified, as follows[71]:

- Difficulty identifying all studies
- Negative (non-significant) results may not be reported (publication bias)
- Inadequate reporting of methods
- Variation in study design
- Most studies are retrospective
- Variation in inclusion criteria
- Lack of recognised criteria for quality assessment
- Variation in methods of analysis
- Differing methods of handling of continuous variables (some dependent on data)

- Different statistical methods of adjustment
- Adjustment for different sets of variables
- Inadequate reporting of quantitative information on outcome
- Variation in presentation of results (e.g. survival at different time points) and inconsistency in terms of outcome measures used

Due to the presence of serious methodological limitations, it is often difficult to carry out sensible meta-analysis. However, application of the principals of systematic review is desirable and advocated for predictive studies. I therefore carried out a systematic review that followed the standard process of; statement of objectives, identification of eligibility criteria, identification of appropriate literature, data extraction, assessment of methodological quality, and data-analysis. The aim of the review was to systematically review and summarise the current literature regarding prognostic variables relating to upper limb recovery following stroke.

2.2 Objectives

- To review which variables have been studied in relation to upper limb recovery
- To identify which, if any variables independently predict upper limb recovery

2.3 Methods

The MOOSE (Meta-analysis of observational studies in epidemiology) guidelines for Meta-Analyses and Systematic Reviews of Observational Studies were used, for guidance to complete and report this review[81].

2.3.1 Eligibility criteria

Types of studies

Observational studies, regardless of specific study design. A study must have investigated at least one variable (explanatory variable); measured at baseline or another pre-determined point and its relationship with a measure of upper limb recovery (response variable), measured at a future time point. Only studies with extractable data of independent predictors were included i.e. studies with only multivariate analysis were not included in this review.

Studies were included regardless of the nature of rehabilitation undertaken, although where available this information was documented.

Subgroup analyses, completed within randomised controlled trials (RCTs) of specific interventions were not included in this review. Entire cohorts of patients participating in RCTs were included.

Types of participants

The study population of interest were individuals with upper limb impairment following a clinical diagnosis of stroke. If studies included a small percentage of individuals without upper limb impairment, where possible these individuals were excluded from any analysis.

Types of outcome measures

The outcome of interest (response variable) was upper limb recovery. For the purposes of this review any outcome measures related to upper limb recovery, which fell into one of three categories were included:

1. Upper limb function (measures of upper limb functional ability). Measures include; upper limb subsections of Barthel Index (BI)[82], Rankin Scale[83] and Functional Independence Measure (FIM)[84]. Global measures of function (i.e. full measure not just upper limb subsections) were excluded.

2. Upper limb functional movement (measures of general functional movement, dexterity, manipulation, grasp/grip/pinch). Measures include; Action Research Arm Test (ARAT)[85], Motor Assessment Scale (MAS)[86] and Box and Block Test (BBT)[87].
3. Upper limb motor impairment (measures of general upper limb impairment, muscle strength). Measures include; Fugl-Meyer (F-M) assessment scale (upper limb section)[88] and muscle testing. Outcomes related to specific impairments e.g. pain, spasticity, contractures were excluded from this review.

All end points in each study were recorded. Where more than one measure of upper limb recovery was used within a study the three categories were used in a priority order hierarchy i.e. if a study reported a measure of upper limb function and a measure of upper limb impairment, the exploratory variable was assessed in relation to the measure of upper limb function, for use in the primary analysis. Secondary analysis was undertaken to assess the association between predictive variables and measures of upper limb function/functional movement and measures of motor impairment. If more than one outcome measurement was available within a category, the decision about which outcome to include was made by consensus.

Timing of measurement of outcomes was recorded, as reported in the studies. Where more than one measurement was taken i.e. 3, 6 and 12 months the data from the 6 month outcome measurement was used in the analysis, as most motor recovery will be achieved by 6 months[89]. If outcomes were not measured at 6 months or were not presented in a suitable format for use in the analysis, the data from the last outcome measurement or the data that was the most complete and suitable for inclusion was used.

Where both change and outcome scores were available, outcome scores were used in the analysis. If only change scores were available and could be incorporated, these were used.

2.3.2 Search methods for identification of studies

To identify relevant studies the following databases, with associated time periods were searched:

- MEDLINE (1950 - November 2010)
- EMBASE (1980 - November 2010)
- AMED (1985 –November 2010)
- CINHAL (1982 – November 2010)
- Cochrane CENTRAL (September 2007)
- Follow-up references from relevant papers

The search strategy (outlined below) was generated following consultation with a medical librarian, consideration of appropriate literature[71], and using search terms developed by the Cochrane Stroke Group[90]. The searches were not limited to English. This review was restricted to published articles. Only published data was used. No attempt was made to contact authors for clarification.

Search Strategy

1. exp cohort studies/
2. incidence.sh.
3. exp mortality/
4. follow-up studies.sh.
5. prognos$.tw.
6. predict$.tw.
7. course$.tw.
8. predictor$.tw.
9. exp models, statistical/
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or cerebrovascular accident/ or exp brain infarction/ or exp cerebrovascular trauma/ or exp hypoxia-ischemia, brain/ or exp

intracranial arterial diseases/ or intracranial arteriovenous malformations/ or exp "Intracranial Embolism and Thrombosis"/ or exp intracranial hemorrhages/ or vasospasm, intracranial/ or vertebral artery dissection/

12. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
13. hemiplegia/ or exp paresis/
14. (hemipleg$ or hemipar$ or paresis or paretic).tw.
15. 11 or 12 or 13 or 14
16. exp Upper Extremity/
17. (upper adj3 (limb$ or extremity)).tw.
18. (arm or shoulder or elbow or forearm or hand or wrist or finger or fingers).tw.
19. 16 or 17 or 18
20. 10 and 15 and 19

This search strategy was modified to suit different databases.

2.3.3 Identification of relevant studies

Initially I reviewed all the titles identified by the searches, removed all the duplicate titles between the databases and then deleted any obviously irrelevant titles. Two independent reviewers then ranked abstracts as “relevant, possibly relevant or definitely irrelevant.” The full text of studies categorised by at least one reviewer as “relevant or possibly relevant” were retrieved and eligibility of the study was again assessed by two review authors. Where disagreement existed, consensus was reached through discussion.

2.3.4 Data extraction

Two reviewers independently extracted data. Any differences between reviewer’s results were resolved by returning to the relevant study and

through discussion. Where possible the following information was documented:

1. Study setting (e.g. hospital, community, out-patients)
2. Participant details (age, gender, type of stroke, time since stroke, initial upper limb impairment)
3. Inclusion and exclusion criteria
4. Rehabilitation received
5. Predictive variables investigated
6. Duration of follow up
7. Outcomes investigated
8. Data on associations between exploratory and dependent variables (when possible, the odds ratio (OR) was used, or calculated). Otherwise, other measures of associations (hazard ratio, correlations) or values for statistical significance (*P* value) of the reported association were extracted).

2.3.5 Documentation of methodological quality

The variation of the methodological quality of observational studies may influence the results and conclusions of a systematic review. Therefore, the quality of each individual study was assessed.

Assessing the quality of observational studies is more difficult and problematic than assessing the quality of randomised controlled trials and other types of experimental studies. For this reason quality assessment methods for observational studies have not been formalised and although several checklists are available, none have been fully validated. One commonly used checklist for assessing the quality of observational studies is the Newcastle-Ottawa Scale[91]. This checklist is quite comprehensive and has been partly validated. This was considered by the review team as a method of assessing the quality of the included studies; however this scale was not felt to be compatible with the nature of the studies included in this review. Previously proposed criteria[79] for assessing the validity of studies

related to prognosis was considered to be more relevant to the studies included in this review. Therefore a checklist was developed, based on this criterion and following suggestions in previous reviews of predictor studies[92;93]

Two reviewers independently rated the quality of the included studies. Any disagreements were resolved through discussion. The methodological criteria included questions relating to:

1. Sample of patients
2. Follow-up
3. Prognostic variable
4. Outcome measurement
5. Treatment
6. Analysis

2.3.6 Data analysis

Due to the exploratory nature of this review and the expected variations in the available evidence, data analysis was undertaken using a combination of approaches.

Initially data were analysed using a vote counting methodology. For this analysis the number of studies investigating a particular explanatory variable was identified and the number of these studies that reported a statistically significant association between the specific variable and upper limb recovery was recorded.

Based on the information gained from the vote counting analysis a best evidence synthesis was used to summarise the data. This was assessed by defining four levels of evidence,[42;94] illustrated in Table 2-1.

Table 2-1 - Levels of evidence

Strong	Consistent findings (≥80%) in at least 2 high quality cohorts

Moderate	One high quality cohort and consistent findings (≥80%) in one or more low more low quality cohorts
Limited	Findings of one cohort or consistent findings in one or more low quality cohorts
Inconclusive	Inconsistent findings regardless of study quality

To give an overview of the collected data and a graphical representation of the studies, statistical pooling was performed and forest plots generated. This was completed using, where available, odds ratios (ORs) presented in the original papers. Where odds ratios were not presented but sufficient data was available, the association between each predictive variable(s) (explanatory variable) and measures of upper limb recovery (response variable) in terms of odds ratio with 95% confidence intervals was calculated. Cut-offs used to calculate the odds ratios were determined by those used in other studies and/or the data available. Odds ratios were calculated in order to ascertain the strength of association with better upper limb outcomes. This also involved inverting some odds ratios which were presented in the reciprocal format in the original papers. In order to combine presented and calculated odds ratio the inverse variance analysis was used. Due to suspected heterogeneity between the studies, analyses were completed using a random effects model. All analyses was undertaken using the Cochrane software package RevMan 4.2[95].

As a final analysis a consensus approach to categorising the evidence, based on the strength and consistency of the evidence was undertaken. This took into account the outcomes of both the vote counting and statistical methodologies.

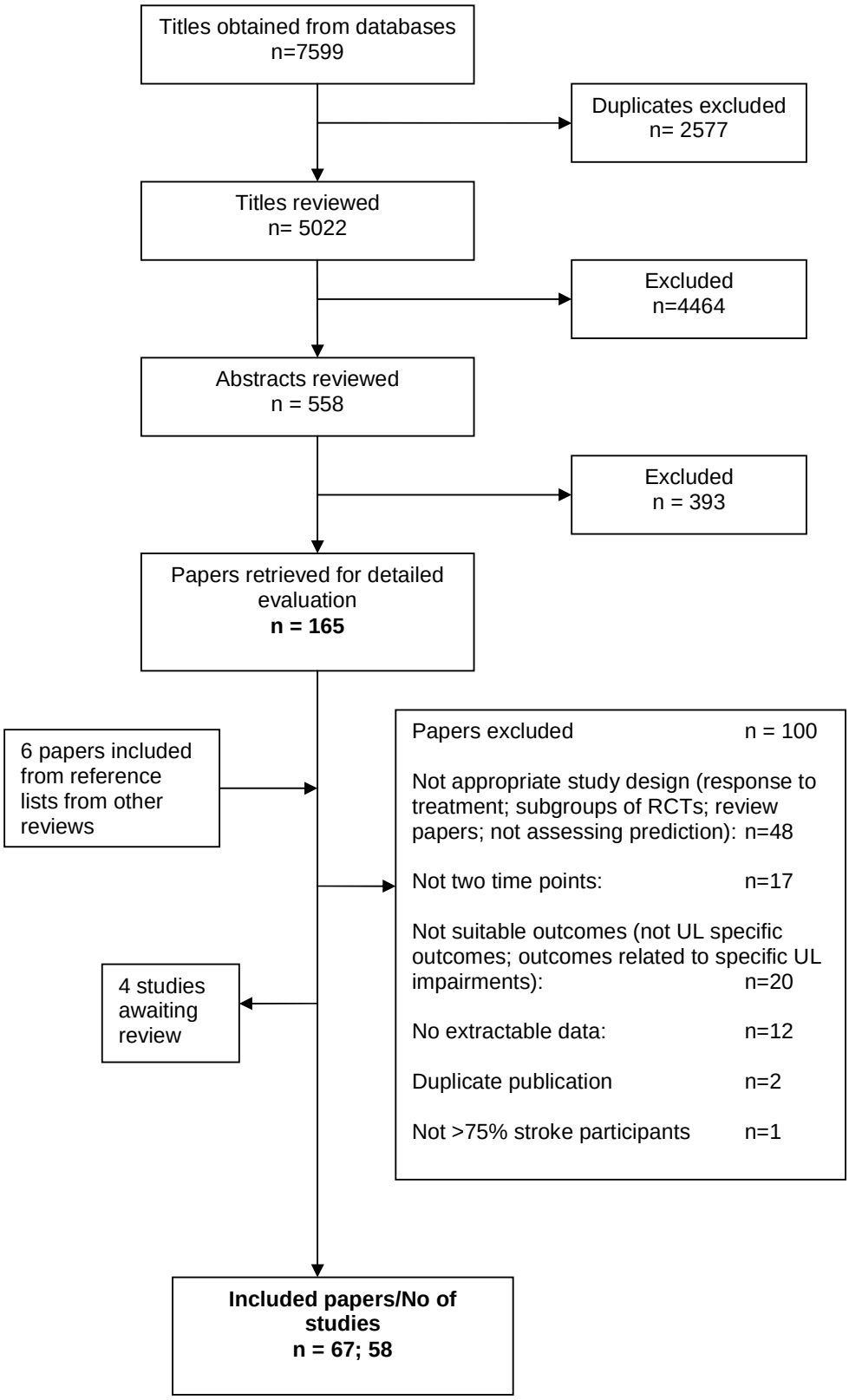
2.4 Results

2.4.1 Results of the search

The initial and updated searches identified a total of 7599 non-duplicate titles. After the first screening, 558 abstracts were selected and reviewed, following which 165 full papers were retrieved. One hundred papers were

excluded, reasons for which are summarised in Figure 2-1. Three studies were in languages other than English, and I have been unable to access a further study. Therefore four studies were identified that have not been included as they could not be fully reviewed. An additional six papers were included from reference lists from other reviews. Sixty seven papers reporting on 58 studies were included in this review. The flow chart of the study selection is shown in Figure 2-1. To avoid duplication of counting of participants, where it was assessed that participants were included in more than one publication, such papers were counted as one study. However, pertinent information from as many publications as relevant was used. The most comprehensive publication was used to describe the study.

Figure 2-1 - Study selection flow diagram



2.4.2 Included studies

A brief overview of the included studies is presented below. Table 2-2 outlines the pertinent information of the included studies; number of participants, predictor variables and outcomes used in the analysis of this review.

Table 2-2 - Characteristics of included studies

Study	Number of participants	Explanatory variables investigated	Outcomes used (Cut-off used) Timing of outcome(s) used
Alagona 2001[96] Delaux 2003[97]	N=25 N=22 (6 mos) N=16 (12 mos) for UL impairment	Age (≤55/>55), sex (M/F), global disability (NIH; <11/≥11), TMS variables (MEP; FDI muscle of the hand, present/absent), side of stroke (L/R), UL impairment (MRC scale 0-5; ≥2/<2)	(1) Barthel Motor (≥20/<20) (2) MRC (FDI muscle) (≥4/<4) 6 months (12 months for analysis of UL impairment)
Al-Rawi 2009[98]	N=22	UL impairment (MRC scale), SSEP	MRC scale 3 months
Au-Yeung 2009[99]	N=70 N=57 (follow-up)	UL impairment (MI), side of stroke, stroke location (lacunar or no obvious lesion, cortical, subcortical or combined subcortical and cortical lesions), overall disability (NIHSS), cognition and perceptual (neurobehavioural cognitive status examination), UL sensation (two point discrimination)	ARAT (0-57) (≥35/<35) 6 months
Barreca 1999[76]	N=16	UL functional movement (UEFT score), cognition and perception (Halstead Category test score), time post stroke, UL impairment (Chedoke McMaster stroke assessment arm and hand subscore)	UEFT (0-100) Last week of rehabilitation (average length of rehabilitation 77 days)
Beebe 2009[100]	N=33 N=28 (3 mos)	UL impairment (NIHSS motor arm score; (≤2/>2)	(1) ARAT (0-57) (≥40/<40) (2) Grip (kg) (≥14/<14) 3 months post-stroke
Binkofski 2001[101]	N=52 N=15 (6 mos) Analyses based on n=52	UL functional movement (arm and hand function score 0-32; ≤16/>16), lesion size, lesion localisation (subcortical/ cortical)	Multifactorial score for arm and hand function (0-32; inverted scale, ≤16/>16) 180 days after admission
Canning 2004[102]	N=22	Upper limb functional movement (MAS), UL impairment (strength; torques)	MAS (item 6 – upper arm function; 0-6) 27 weeks post-stroke
*Catano 1995[103]	N=40	TMS (MEP responses; FDI and ADM muscles; present/absent)	MRC (FDI and ADM muscle) 90 days post-stroke
*Catano 1997[104]	N=49	TMS (EMG silence – silent period following MEP; SPD stable/ SPD reduced by increasing facilitation)	MRC (FDI muscle) (≥4/<4) 90 days post-stroke

Cho 2007[105]	N=55	Diffusion tensor tractography (integrity of corticospinal tract)	Modified Brunnstrom classification 6 months after onset
Cruz-Martinez 1999[106]	N=15 (with UL deficit)	TMS variables (MEPs; thenar muscles, present/absent), age (≤55/>55), sex, size of lesion (1-3cm/>3cm), side of lesion (L/R), UL impairment (CNS distal arm score; 1.0/<1.0)	CNS (distal arm score; 0-1.5) (≥1.0/<1.0) 6 months post-stroke
Dachy 2003[107]	N=56 N=48 (76±17 days)	TMS variables; (MEPs; ADM muscle, present/absent), side of lesion	MI (UL; 0-100) Late stage of rehabilitation mean 76±17 days post-stroke
De Souza 1980[108]	N=14	UL impairment (arm, trunk and hand movement; >50%/<50%)	Assessment of arm, trunk and hand movement (>80%/<80%) 32 weeks post-stroke
De Weerdt 1987[109]	N=111 N=58 (6 mos)	Age, sex, pre-stroke ability, pre-stroke mental status, duration for stroke to develop, handedness, global impairment, speech disorders, side of lesion (side of hemiplegia), number of previous strokes, visual disorders (visual field loss), seventh cranial nerve, pain in arm (spontaneous arm pain), shoulder complications, UL impairments (F-M), UL functional movement (ARAT), sensation (light touch), cognition and perception (post-stroke mental status)	(1) ARAT (0-57) (2) F-M (0-66) 6 months
Escudero 1998[110]	N=50 N=39 (6 mos) Analyses based on n=50	UL impairment (MRC abductor pollicis brevis), Global disability (Barthel Index), TMS variables (MEPs APB muscle present/absent)	MRC scale (APB muscle) 6 months
Feys 2000[70] Feys 2000[111] Feys 2000[112]	N=100 N=96 (6 mos) For stroke location analysis; n=45 For MEPs and SEPs analysis; n=48	Global disability (BI), TMS variables (MEPs; APB muscle present/absent), SSEPs; median nerves at the wrist, present/absent, infarction location, age, sex, UL impairment (F-M UL section), side of hemiparesis, UL sensation (tactile), visual disorders (hemianopia; not occurring/occurring) cognition and perceptual (MMSE; no deficit ≥ 24/deficit <24), speech disorders (not occurring/occurring), mood (Hospital Anxiety and Depression Scale; no deficit >10/ deficit ≤10), shoulder complications (shoulder pain; absent/present)	F-M (UL section; 0-66) 6 months

Gowland 1982[113]	N=229 N=223 (discharge) Nos in analyses not always n=223 due to missing or excluded data	Age (≤55/>55), UL sensation (normal sensation/sensory involvement), perception (no deficit/deficit), global impairment (hemiparesis/hemiplegia), time since stroke (onset <12 weeks/ >12 weeks), side of stroke (side of hemiplegia R/L)	Brunnstrom stages of arm motor recovery (1-6) (≥1/0 stages of improvement) Discharge from rehabilitation centre (median 7 (range 1-23) weeks)
Hatakenaka 2007[114]	N=34	Sex, UL impairment (F-M UL section), distribution of upper extremity paresis (proximal /distal), TMS variables (MEPs; biceps brachii potentials presence/absence), size of lesion	Functional category of upper extremity (A-D) (A-B/D) End of inpatient rehabilitation (108±17 days)
Heald 1993[115]	N=118 N=76 (12 mos)	TMS variables (central motor conduction time; normal, delayed or absent)	(1) NHPT (2) MI 12 months
Hendricks 1997[116] Hendricks 1994[117]	N=29 N=20 (follow-up 1-4 yrs) Analyses based on n=29	MEPs (abductor digiti quinti muscle, present/absent), SEPs (median nerve stimulation; present/absent)	Motor recovery (voluntary motor action) (Presence/absence of motor recovery) 1-4 years post-stroke (mean 2.4 years)
Hendricks 2003[118]	N=43 N=40 (26 weeks)	TMS variables (MEPs; biceps brachii muscle, present/absent)	F-M (arm score; 0-30; arm motor recovery yes/ no) 26 weeks post-stroke
Higgins 2005[119]	N=56 N=55 (5 weeks)	Age, sex, UL functional movement (FAT), UL impairment (strength; Jamar), general motor impairment (STREAM), lower limb impairment (gait speed; 5MWT), number of co morbid conditions, type of stroke, side of lesion	BBT (number of blocks in one minute) 5 weeks post-stroke
Jang 2010[120]	N=53	TMS variable (MEP; abductor pollics brevis, present/absent), Diffusion tenor tractography imaging (CST integrity, +/-)	MI (>62/<62) 6 months post-stroke
Jorgensen 1999[89] Nakayama 1994[21]	N=826 UL impariment N=619 (6 mos)	Upper limb impairment (Scandinavian Stroke Scale sub-scores for arm and hand; mild or moderate/severe)	BI (subscores for feeding and grooming; full or partial function/ no function) 6 months

Katrak 1990[75]	N=29 (initial UL deficits and followed-up)	UL impairment (hand movement scale, 1-6; >2/≤2 and shoulder shrug; present/absent)	(1)MAS; Hand movement section Discharge from hospital (mean 125 days post-stroke) (2) Hand movement scale (0-6; ≥4/<4) Final discharge (average 223 days post-stroke)
Katrak 1998[121]	N=57 N=46 (3 mos)	Age, sex, UL impairment (hand movement scale, 1-6; 1/2 or 3),UL sensation (incorporating light touch, sensory inattention and proprioception), side of stroke (side of hemiparesis)	(1)Hand function test (1-4) – "Good" hand function – able to complete one of the tasks. (2) Hand movement scale (1-6) (≥4 "Good" hand movements/<4) 3 months
Keren 1993[122] Keren 1995[**123**]	N=19	SEPs (median nerve, present/absent)	(1) Rancho Los Amigos (17 UL activities) (2) MI (0-100) Approximately 10 weeks after first evaluation (71±14.6 days)
Kwakkel 2003[65]	N=102 N=100 (6 mos)	Age (<70/ ≥70), sex, UL impairment (MI (arm), 0-100; ≥11/<11), urinary incontinence (BI subsection; absent/present), type of stroke (OCSP), side of stroke (L/R), time since stroke, cognition and perception (MMSE; no deficit/deficit), consciousness during initial 24 hours (GCS), sitting balance (Trunk Control Test; no deficit/ deficit), global disability (Barthel), UL sensation (Thumb finding test), visual deficits (hemianopia; no/yes), social support (present/absent), lower limb impairment (F-M leg; ≥25/<25)	ARAT (0-57) (≥10/≤9) 6 months
La Joie 1982[124]	N=68	SSEPs evoked potentials (median nerve; present/absent), UL function at admission (present/absent)	UL functional return (self-care activity; functional return/no functional return) Discharge (mean 84 (range 44-205) days)
Lin 2009[125]	N=57	Age, sex, side of stroke, time since stroke, global disability (NIHSS), UL impairment (F-M distal section)	(1) MAL (QOM scale) (2) F-M (UL section) End of intervention period (3 weeks)

Loewen 1990[126]	N=57 N=50 (discharge)	Age, sitting balance (Modified MAS component), sit to stand (Modified MAS component), UL functional movement (Modified MAS; combined arm score), bowel function (BI component), urinary incontinence/ bladder function (BI component)	Modified MAS (combined arm score; sum of scores on upper arm function, hand movements and advanced hand movement sections) Discharge
Loubinoux 2003[127]	N=9	Global disability (NIHSS, <11/ ≥11), UL impairment (MI; UL section, 0-100; ≥11/<11), UL functional movement (NHPT; able to complete/ unable to complete), global impairment (MI; ≥66/<66)	MI (UL section, 0-100; ≥66/<66) 28 days after first assessment (11±6 days)
Meldrum 2004[57] Meldrum 2000[128]	N=114 N=108 (6 mos)	Age (<65/65-74/ ≥75), type of stroke (OCSP), UL sensation (normal/ impaired/absent or unable to assess), UL impairment (Rivermead arm score), global disability (Orpington Prognostic score)	Rivermead arm score (0-15; 5-15/ 0-4/death) 6 months
Nagao 1992[129]	N=13	Age(≤55 >55), sex, side of stroke (L/R), TMS variables (MEP; thenar muscles, present/absent), UL impairment (Manual Motor Test, 0-5; >2/≤2), time since stroke (Day 0/ ≥Day 1)	Manual Motor Test (0-5; ≥2 (fair and good/<2 (poor) 3 months after initial testing
Nascimbeni 2006[69]	N=19	TMS (MEP; first dorsal interosseous muscle, present/ absent), UL impairment (Motricity Index, upper limb subscale; ≥11/<11), global disability (NIHSS, <11/≥11)	MRC scale (hand, 0-5; ≥2/<2) 4 months post stroke
Nijland 2010[130]	N=188 N=156 (6 mos)	Age (<70/ ≥70), sex, side of stroke (L/R), type of stroke (OCSP), time since stroke, comorbidities (≥1/0), cognition and perception (present/absent), visual deficits (hemianopia; no/yes), sensation (absent/present), urinary incontinence (BI subsection; absent/present), lower limb impairment (MI leg; ≥25/<25), sitting balance (present/absent), UL impairment (F-M finger extension <1/≥1)	ARAT (0-57) (≥10/≤9) 6 months
Olsen 1990[131]	N=66	UL impairment (MRC scale, 0-5; >2/≤2), global disability (BI, ≥60/<60)	BI (UL sections; prepare tray and feed self and dress upper body; 0-11, ≥9/<9) Discharge
Paci 2007[132]	N=121 N=107 (completed)	Age, sex, side of stroke, length of stay, time since onset of stroke, UL impairment (motricity sub-score of F-M; UL), UL sensation (F-M; UL sensory score), shoulder complications (shoulder pain; absence/presence)	F-M (Upper limb score) Follow-up (30-40 days) after discharge from rehabilitation
Park 2008[133]	N=222	UL motor impairment (F-M), age, sex, side of stroke, global disability (Functional level), sensation (F-M light touch), UL functional measures (WMFT functional ability scale), time after stroke, type of stroke, cognition and perception (impaired visual perception)	MAL (QOM) scale(≥3/<3) 12 months post-treatment

Parker 1986[27]	N=266 initial Ul deficits N=152 (3 mos)	UL impairment (MI, 0-100; ≥33 (mild or moderate)/<33 (severe)	(1) FAT (0-5; ≥4/<4) (2) MI (0-100; ≥66/<66) 3 months
Pennisi 1999[134]	N=15	Age(≤55/>55), sex, infarction location (subcortical or cortico-subcortical), lesion size, side of stroke, global disability (NIHSS, <11/ ≥11)	Scale derived from MRC (0-5) (≥2/<2) Day 365
Pizzi 2009[135]	N=52 N=38 (follow-up)	TMS (MEP; EDC present/absent), UL impairment (MRC scale EDC ≥2/<2)	FAT (0-5; ≥2/<2) MRC scale (≥4/<4) 12 months
Prabhakaran 2008[136]	N=41	Age, sex, UL impairment (F-M UL), lesion location, lesion volume, time to reassessment	F-M UL change score (0-66) 3 months post-infarct
Putman 2007[63]	N=532 N-419	Socioeconomic status	Rivermead motor assessment (arm section; 0-5/6-10/11-15) Discharge
Rapisarda 1996[137]	N=26	TMS (MEP; hand muscles, present/absent), global disability (NIH, <11/≥11)	Scale derived from MRC scale (hand; 0-5) (≥2/<2) Day 14
Renner 2009[138]	N=16	UL impairment (hand grip)	(1) ARAT (2) Hand grip 6 weeks after enrolment
Roy 1995[139]	N=76	Shoulder complications (shoulder pain; absence/presence), cognition, UL sensation (touch sensation absent/present) and urinary incontinence (absent/present)	(1) FAT (2) MI 12 weeks
Shelton 2001a[74] Shelton 2001b[68]	N=171 N=41 used for analysis of global disability	Age, sex, UL impairment (F-M; UL motor section), cognition (MMSE), type/class of stroke (hemiparetic motor deficits, hemiparetic motor plus hemisensory deficit or hemianopic visual deficits, motor plus hemisensory plus hemianopic visual deficits or other combinations of deficits), lower limb impairment (F-M; lower limb motor section), global impairment (F-M), lesion location (cortical/ subcortical/ mixed), handedness (right/left/ambidextrous), side of stroke, time since stroke (interval from stroke to admission; < 2 weeks/ 2-4 weeks/ >4 weeks), global disability (FIM)	F-M (UL 0-58) Recorded at discharge (38±17days)
Smania 2007[140]	N=48 N=37 (6 mos)	UL impairment (hand movement scale, 1-6; >3/≤3)	(1) NHPT (2) MI (UL section) 180 days after stroke

Stinear 2007[141]	N=21 N=17 (30 days)	Age (≤55/>55), sex, side of stroke (hemisphere affected (L/ R)), time since stroke <29 mos/> 29 mos), hand grip asymmetry (force transducer), TMS variables (MEPs; extensor carpi radialis, present/ absent), global disability (NIHSS, ≤4/>4), UL impairment (F-M UL movement section, 0-32; ≥11/<11), infarction location (motor cortex damage), UL sensation (cutaneous sensation; no sensation loss/sensation loss)	F-M (UL movement section; 0-32) (≥2/<2 points of improvement) End of motor practice (30 days)
Sunderland 1989[142]	N=38 N=31 (6 mos)	UL impairment (MI, 0-100; >18/<18), UL functional movement (FAT; >0/0)	FAT (>0/0) 6 months (193±16 days) post-stroke
Trompetto 2000[143]	N=21 N=14 (6 mos)	TMS variables (MEPs; thenar muscles, present/ absent), age (<70/≥70), sex, side of stroke (L/R), global disability (Scandinavian stroke scale 0-58; >29/≤29), UL impairment (Scandinavian stroke scale hand motor score, 0-6; 0/ ≥1)	Scandinavian Stroke Scale (subscore for hand motor function; 0-6) (≥4/<4) 6 months after stroke
Turton 1996[144]	N=21	UL impairment (Motricity Index upper limb section; >11/≤11), age (≤55/>55), sex (M/F), side of stroke (L/R), TMS (MEPs response/no response)	(1) NHPT (able/unable to complete). Only available for TMS variable 6 weeks (2) MI (UL section 0-100; ≥66/<66) 6 months
Tzvetanov 2005[145] Tzvetanov 2004[146]	N=102 N=94 (6 mos) N=22 for analyses of age, sex and side of stroke	SSEPs (median nerve, normal/absent/amplitude ratio <0.5 but >0), age, UL impairment (MRC scale), sex, side of stroke.	MRC scale (0-5) 6 months after stroke
Van Kuijk 2009[147]	N=39 N=35 (follow-up)	UL impairment (F-M ; presence/absence of any motor recovery of the UL), TMS (MEPs; present/absent), lower limb impairment (F-M lower limb section; presence/absence of motor recovery)	F-M; hand section (0-14; (>3/≤3) 6 months after stroke
Wagner 2007[148]	N=39	UL impairments (composite active range of motion), shoulder complications (shoulder pain), UL sensation (composite light touch sensation)	Accuracy of reaching 108.7±16.6 days
Yagura 2003[149]	N=947	Time since stroke, upper limb functional movement (category B-D)	Upper extremity functional category (A-D, reaching independence (category A)) Discharge (length of stay 101.18±27.3 days)
Yoshioka 2008[150]	N=17	Diffusion-tensor tractography imaging data (FA ratio, ((>0.75/≤0.75), age (≤55/>55), gender, stroke location, stroke volume (<15/>15ml), UL impairment (MMT >2/≤2), lower limb impairment (>2/≤2)	Manual Motor Test (0-5) (≥3/<3) 3 months after stroke onset

Footnotes
Those in bold represent the main study (if more than one publication)
Unless otherwise stated (mean±SD)
* - These studies were considered unique studies but at least some overlap of participants is possible

Abbreviations used in Table:

ADM – Abductor digiti minimi
APB – Abductor pollicis brevis
ARAT - Action Research Arm Test
BI – Barthel Index
BBT – Box and Block Test
CNS – Canadian Neurological Scale
CST – Corticospinal tract
EMG – Electromyography
EDC - Extensor digitorum communis
FAT – Frenchay Arm Test
F – Female
FDI – First dorsal interosseus
FA - Fractional anisotropy
F-M – Fugl-Meyer
GCS – Glasgow Coma Scale
M – Male
MMSE – Mini Mental State Examination
MAL – Motor Activity Log
MAS – Motor Assessment Scale
MEPs – Motor Evoked Potentials
MI – Motricity Index
MRC – Medical Research Council
Mos - Months
NIHSS – National Institute for Health Stroke Scale
NHPT – Nine Hole Peg Test
OCSP – Oxfordshire Community Stroke Project
QOM – Quality of movement
SPD – Silent period duration
SSEP – Somatosensory evoked potential
STREAM – Stroke Rehabilitation Assessment of Movement
TMS – Transcranial Magnetic Stimulation
WMFT – Wolf Motor Function Test
UEFT – Upper Extremity Function Test
UL – Upper limb
5MWT – 5 Metre Walk Test

Study design

The type of study design was often not reported. All studies were categorised as some form of cohort study, with the exception of eight[98;102;104;105;132;138;139;150]. These studies were reported as a longitudinal descriptive study[102], case-control[132], multiple baseline experiment[138], prospective observational study[139] and case series[150] respectively. Three studies were clearly convenience sample studies[98;104;105]. Six studies were reported as cohorts embedded within randomised controlled trials[65;70;119;133;142;148]. Twenty nine studies[27;57;63;65;70;74-76;89;100;101;103;109;110;113;116;118-121;126;131;135;136;139;140;142;143;147] explicitly reported or were assessed to have screened consecutive admissions.

Setting

Of the 58 studies, six were each carried out in Netherlands[65;100;116;118;130;147]; United Kingdom (UK)[27;108;109;115;142;144] and USA[74;124;131;133;136;148]. Five were carried out in Italy[69;132;135;140;143]; four were completed in Canada[76;113;119;126], Belgium[96;103;104;107] and Japan[114;129;149;150]; three were completed in Australia[75;102;121]; two in New Zealand[139;141], Germany[101;138], Spain[106;110] and Republic of Korea[105;120] and one in China[99], France[127], Israel[122], Denmark[89], Ireland[57], Iraq[98] and Bulgaria[145] respectively. One study[63] was completed between four countries (UK, Belgium, Switzerland and Germany) and one study[70] was completed between two countries (Belgium and Switzerland). It was unclear if two studies were completed in Italy or Belgium[134;137] and if one study[125] was undertaken in Taiwan or USA.

All studies explicitly stated or were assessed to have recruited hospital inpatients (either from acute general wards, stroke units or rehabilitation units), with the exception of four studies. Three studies[108;125;133] recruited outpatients; another study[141] was assumed to be a mixed inpatient and outpatient population.

Sample size

The sample sizes reported within the included studies ranged from 9[127] to 1197[89] Twenty nine studies[69;75;76;96;98;100;102-104;106;108;114;116;118;122;127;129;134;136-

[138;140-144;147;148;150] included 50 participants or less and only 15 studies[27;57;63;65;70;74;89;109;113;115;130;132;133;145;149] had an initial sample size of 100 or more participants. Therefore the remaining 14 studies[99;101;105;107;110;119-121;124-126;131;135;139] had an initial sample size of between 51 and 99 participants.

Participants

The 58 studies initially recruited a total of 6404 participants, of which 5443 demographic details were reported and 5741 were considered to have some form of initial upper limb impairment. Where it was clear from the publication, only participants with initial upper limb impairment were included in the analyses. In the analyses 5051 participants were included.

Of the studies that reported loss to follow-up (n=31), the percentage of participants lost to follow up varied between 2%[65] and 48%[109].

All except two studies[63;109] reported information on gender of included participants. The remaining 56 studies included both genders, with 54% of participants being male.

All of the included studies, with one exception[109] reported information relating to the age of the included participants. The mean (or median) ranged from 53[101] to 74.39[140] years. In 12 studies[96;100;101;105;106;120;122;127;129;136;141;147] participants had a mean (or median) age of less than 60 and in ten studies[27;63;89;110;115;132;139-141;143] the mean age was 70 or over.

Time since stroke

The mean time since stroke was reported in a variety of ways across the 58 studies. The mean (or median) time since stroke ranged from within 24 hours (or admission to acute hospital)[89;101;119;134;137;140] to 29 months[141].

Thirty-six studies[27;57;65;69;89;96;98;99;101;103;104;106;109;110;115;116;118-121;126;127;129;130;134;136;137;139;140;142-145;147;148;150] reported, or were assumed to have recruited the majority of participants within 14 days of stroke onset.

Twelve studies[63;70;74;100;102;105;107;108;122;131;132;138] reported mean time of stroke of participants to be within one month. A further five studies[75;113;114;124;135] recruited within 3 months of stroke and two studies recruited patients between 3 months and 6 months[76;149]. One study[133] recruited patients between 3 and 9 months poststroke (mean 182.5 days) and in another study[125] participants were a mean of 12 months post-stroke (0.7-88 months).

Type of stroke

The type of stroke of participants in the studies was recorded; however this was reported inconsistently across the included studies. Twenty-three studies[57;65;69;74;96;99;101;103-107;110;116;122;127;130;134;136-138;140;147] reported that participants only had ischaemic stroke, three studies haemorrhagic stroke only[120;129;150], 15 studies[70;89;98;100;114;119;126;131;133;135;143-145;148;149] reported participants with both types of stroke and within 17 studies[27;63;75;76;102;108;109;113;115;118;121;124;125;132;139;141;142] it was not reported or was unclear. Further stroke classifications were either not reported or reported inconsistently.

Initial upper limb impairment

A wide variety of measures were used to assess initial upper limb impairment and therefore close comparability of the studies, in terms of initial upper limb impairment was difficult to obtain. Thirty-six studies[63;65;69;70;75;96;99-106;108;110;113;116;118;120;121;125;127;130;131;133-137;141-144;147;148] explicitly reported some form of upper limb impairment at onset as an inclusion criterion; however, the definitions of such ranged considerably e.g. hemiplegia or hemiparesis or below a score on a certain clinical test (e.g. Fugl-Meyer upper limb section). Fifty-two studies[27;57;63;65;69;70;75;76;89;96;98-108;110;113;115;116;118-121;124;125;127;129-131;133-145;147-150] provided details on initial upper limb impairment in terms of a mean score on a clinical measure e.g. Motricity Index (arm), Rivermead Motor Assessment (arm section) or by using general descriptions such as hemiplegia or paresis. Six studies[74;109;114;122;126;132] did not report any details on initial upper limb impairment.

2.4.3 Predictor variables

The variables assessed for prognostic ability of upper limb outcomes, varied between the studies. Details of the variables used in the data analyses (including cut-offs used, where appropriate) are presented in Table 2-2. Some studies reported using additional variables, however then did not report the association of these variables with a measure of upper limb recovery, therefore only those variables available for use in this review are presented.

To allow for increased statistical pooling and ease of reporting, predictor variables of similar constructs were linked together e.g. measures of cognition and perception. This process identified 41 groups of variables, which are listed below in order of the number of studies reporting each and where appropriate, with a brief description of what were included in the categories.

1. upper limb impairment measures (n=39). Measures of upper limb impairment, muscle strength, muscle tone, individual movements.
2. age (n=23). Various cut-offs used for defining younger/older participants.
3. side of stroke (n=21). Incorporating hemisphere affected and side of hemiparesis – left or right sided stroke.
4. sex (n=21). Male/Female.
5. motor evoked potentials (n=20). Presence/absence of a motor evoked potential in an upper limb muscle following transcranial magnetic stimulation (TMS).
6. global disability (n=16). Measures of functional ability.
7. upper limb sensation (n=11). Different measures of upper limb sensation.
8. upper limb functional measures (n=10). Any measures/scales of upper limb functional movement i.e. scales that look at arm movement in a functional manner.

9. time since stroke (n=11). Different cut-offs were used for defining less/more time since stroke.
10. cognition and perception (n=10). Measures of cognitive and perceptual abilities.
11. stroke location (n=8). Different locations of stroke e.g. cortical vs. subcortical.
12. type/class of stroke (n=7). Measures indicating global severity of stroke or particular stroke classifications e.g. OSCP classification.
13. lower limb motor impairment (n=6). Measures of lower limb impairment.
14. somatosensory evoked potentials (SSEPs) (n=6). Presence/absence of SSEPs in upper limb nerve following stimulation.
15. global motor impairment (n=5). Measures of complete motor impairment e.g. measuring arm and leg impairment (e.g. Fugl-Meyer).
16. shoulder complications (n=5). Measures of shoulder pain or subluxation.
17. infarction volume/size of lesion (n=5). Different cut-offs used to assess size/volume of lesion.
18. visual disorders (n=4). Presence/absence of homonymous hemianopia or other type of visual disorder.
19. urinary incontinence/bladder function (n=4). Presence/absence of urinary incontinence.
20. sitting balance (n=3). No deficit/deficit on a measure of sitting balance.
21. diffusion tensor tractography (n=3). Integrity of cerebrospinal tract.
22. speech disorders (n=2). Absence/presence of any speech disorders.
23. handedness (n=2). Right or left handed.
24. sensation (n=2). No deficit/deficit of sensation.
25. no. of comorbid conditions (n=2). Less/more comorbid conditions.
26. pre-stroke ability (n=1)
27. pre-stroke mental status (n=1)
28. bowel function (n=1)
29. distribution of paresis (n=1). Proximal or distal paresis.
30. no of previous strokes (n=1)

31. sit to stand ability (n=1)
32. pain in arm (n=1)
33. 7th cranial nerve lesion (n=1)
34. duration for stroke to develop (n=1)
35. mood (n=1)
36. social support (n=1)
37. length of stay (n=1)
38. socioeconomic status (n=1)
39. level of consciousness at onset (n=1)
40. hand grip asymmetry (n=1)
41. recombinant tissue plasminogen activator (Rt-PA) (n=1)

Of these 41 predictor groups, 25 were reported by more than one study.

As it was impossible to anticipate the full range of predictor variables that had been studied, the process of categorising the predictor variables into the above groups was undertaken by consensus, following data extraction but prior to analysis.

Some studies reported more than one predictor variable, within a categorised group. The decision on which variable to include was agreed by consensus between reviewers. This decision took into account the following factors; availability of information for inclusion in data analysis, consistency between the studies and the most comprehensive measure (e.g. Fugl-Meyer upper limb scores chosen as a predictor of upper limb impairment over a measure of muscle strength). The predictor variable chosen (where more than one variable available in a grouping) is presented in the table of included studies (Table 2-2). Where more than one predictor was available within a category and a different association (e.g. non-significant instead of a significant result was found) with the measure of upper limb recovery, this is highlighted as footnotes in Appendix A and Appendix B. Some predictor variables identified in the studies were not available for inclusion in the analysis due to lack of extractable data or lack of information within the papers.

To allow for ease of presentation of results predictor variables were further categorised into headings of comparable variables. These headings were agreed between two reviewers and reflected the nature of the variables. The headings are (i) Demographic variables (ii) Severity of stroke – global factors (iii) Severity of stroke – focal factors (iv) Co-factors (associated with severity) (v) Neurophysiological factors and (vi) Pre-morbid function.

2.4.4 Outcome measures

The 58 included studies used a wide range of different outcome measures, time intervals for follow-up and statistical analysis. The outcome measures and the timing of these measures used in the analyses are presented in Table 2-2. Within the included studies 28 different outcome measures were reported and included in the analyses.

Upper limb function

Three studies[89;96;131] reported an upper limb function outcome. Measures in this category were: Barthel feeding, personal toilet and dressing, Barthel feeding and grooming and Barthel feeding and dressing upper limb subsections respectively.

Upper limb functional movement

Twenty six studies[27;65;75;76;99-102;109;114;115;119;121;122;124-126;130;133;135;138-140;142;144;149]reported an upper limb functional movement outcome. Measures in this category were: ARAT (6 studies), Frenchay Arm Test (4 studies), Nine Hole Peg Test (3 studies), Motor Assessment scale (of some form; 3 studies), Functional category of upper extremity (2 studies), Motor Activity Log (Quality of movement) scale (2 studies), a multifactorial score designed for examining hand and arm function, Upper Extremity Function Test, Rancho Los Amigos, Box and Block Test, Hand function grade and ability to use upper extremity for some aspect of self-care.

Upper limb impairment

Forty-three studies[27;57;63;69;70;74;75;96;98;100;103-110;113;115;116;118;120-122;125;127;129;132;134-141;143-145;147;148;150] reported an outcome, classified as an impairment outcome. Measures in this category were: Motricity Index (upper limb section) (9 studies), Fugl-Meyer (upper limb section) (8 studies), Rivermead Motor Assessment (arm score) (2 studies), MRC scale (8 studies), scale derived from MRC scale (2 studies), Grip strength (2 studies), hand movement scale (2 studies), Brunnstrom classification (2 studies), Manual Motor Test (2 studies), Canadian neurological scale (distal arm score), arm, trunk and hand movement score, any voluntary motor action, accuracy of reaching, Scandinavian Stroke Scale (hand motor power), and Fugl-Meyer hand subset were all reported by one study.

Fourteen studies[27;75;96;100;109;115;121;122;125;135;136;139;140;144] reported more than one category of outcome measure. All except one study[96] reported a functional movement and an impairment measure. This study[96] reported an upper limb function and an upper limb impairment outcome.

Seven studies[27;100;105;120;126;140;148] reported more than one outcome measure within a category, the outcome measure used in this review is indicated in Table 2-2 (Characteristics of included studies).

Within the included studies a variety of different statistical analyses were used to determine association between a certain variable and a measure of upper limb recovery. From the data presented in 26 studies[27;69;75;89;96;100;101;104;106;108;113;118;120;124;127;129;131;134;135;137;141-144;147;150] odds ratios with 95% confidence intervals were calculated for at least one of the variables and its association with a measure of upper limb recovery. A further six studies[65;99;114;116;121;130] presented odds ratios which were used in the analysis.

The shortest follow-up period was 2 weeks[137] and the longest between 1-4 years (mean 2.4 years)[116].

2.4.5 Methodological quality of included studies

The methodological quality of the included studies varied considerably. The results of the quality assessment are presented in Table 2-3.

Table 2-3 - Methodological quality of included studies

Potential bias	Studies adequately assessing bias	Domains addressed	Studies assessing domain
The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation)	13/58 22%	1. Sampling frame and recruitment adequately described? 2. Inclusion/exclusion adequately described? 3. Clinical and demographic characteristics described? 4. Were participants recruited at within 2 weeks of stroke onset? 5. Was sample size adequate in relation to number of variable(K exceeds 10:1)?	21/58 36% 43/58 74% 42/58 72% 32/58 55% 44/58 76%
Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e. the study data adequately represent the sample (study attrition)	31/58 53%	1. Was follow-up ≥3 months? 2. Was the data collected prospectively? 3. Was the response rate (i.e. proportion of study sample completing the study and providing outcome data) adequate (>80%)? 4. Were reasons for loss to follow-up provided?	41/58 71% 50/58 86% 46/58 79% 51/58 88%
The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (prognostic factor measurement)	54/58 93%	1. Was a clear definition or description of the predictive variable provided, including method of measurement, if relevant? 2. Were the variables measured in a valid and reliable way? 3. Was there adequate proportion of the study sample with complete data for variables?	56/58 97% 47/58 81% 56/58 97%

The outcomes of interest are adequately measured in study participants to sufficiently limit potential bias (outcome measurement)	15/58 26%	1. Was a clear definition of the outcome of interest provided? 2. Was the outcome of interest appropriate/clinically relevant? 3. Were the outcomes used standardised or tested for reliability and validity (or references made to other studies) 4. Was the outcome assessor blinded? 5. Was the data presented for most important outcome measures?	53/58 91% 56/58 97% 41/58 71% 14/58 24% 55/58 95%
Treatment given to cohort (possible confounding)	27/58 47%	1. Is the treatment given to the cohort described? 2. Is the treatment provided to the cohort standardised/randomised?	29/58 50% 28/58 45%
The statistical analysis is appropriate for the design of the study, limiting potential for presentation of results (analysis)	26/58 45%	1. Were continuous variables analysed appropriately? 2. Is there sufficient presentation of the data to assess the adequacy of the analysis? 3. Is the relationship between dependent and independent variables tested for statistical significance?	31/58 53% 34/58 59% 44/58 76%

As is evident from Table 2-3 only measurement and reporting of the prognostic variable was consistently reported.

Due to poor reporting within the studies some assumptions and/or a number of subjective decisions had to be made. Where disagreement between authors occurred, this was resolved by discussion.

2.4.6 Primary analysis

Each identified predictive variable and its relationship with a measure of upper limb recovery (as defined in the outcomes section above) was analysed. The results for the primary analysis (any outcome of the upper limb recovery) are outlined in Table 2-4 and Figure 2-2. For subsequent secondary analyses (ii) functional measures (incorporating UL function and functional measures) and (iii) impairment measures the results are displayed graphically in Figure 2-3 and Figure 2-4 respectively and the main points of

the results are discussed. Full details of these analyses are tabulated in Appendix A and B. The data is presented according to the headings of; (i) Demographics (ii) Severity of stroke – global factors (iii) Severity of stroke – focal factors (iv) Co-factors (relating to stroke impairment) (v) Neurophysiological factors and (vi) Pre-morbid function, as discussed previously.

Table 2-4 - Primary analysis: Results of association of predictor variables and measure of upper limb recovery

Variable	Total no. of studies (participants)	Vote counting (significant association)	Strength of evidence analysis	Statistical analysis. No. of studies (participants) Pooled odds ratio (95% CI)	Statistical conclusion	Combined assessment of evidence.
Demographic factors						
Age (younger vs. older)	23[57;65;70;74;96;106;109;113;119;121;125;126;129;130;132-134;136;141;143;144;146;150] (n=1695)	2[57;125] (n=265)	Strong evidence of no association	11[65;96;106;113;129;130;134;141;143;144;150] (n=590) 1.54 (1.06 - 2.25)	Significant association	**Inconclusive evidence.** Suggestion that younger people are more likely to have better upper limb recovery.
Sex (male vs. female)	21[65;70;74;96;106;109;114;119;121;125;129;130;132-134;136;141;143;144;146;150] (n=1371)	0	Strong evidence of no association	11[65;96;106;114;129;130;134;141;143;144;150] (n=424) 1.61 (1.11 – 2.33)	Significant association	**Inconclusive evidence.** Suggestion that males are more likely to have better upper limb recovery.
Time since stroke (less vs. more time)	11[65;74;76;113;125;129;130;132;133;141;149] (n=2006)	5[65;125;133;141;149] (n=1343)	Inconclusive evidence	5[65;113;129;130;141] (n=486) 1.13 (0.90 – 1.40)	No significant association	**Inconclusive evidence.**
Socioeconomic status	1[63] (n=419)	1	Limited evidence of assosication	0	NA	**Limited evidence** of association between socioeconomic status and upper limb recovery.
Social support (yes/no)	1[65] (n=100)	0	Limited evidence of no association	1[65] (n=100) 1.41 (0.84 – 2.38)	NA	**Limited evidence of no association** between level of social support and upper limb recovery.
Severity of stroke – global factors						

Global disability (less vs. more disability)	16[57;65;68-70;96;99;110;125;127;131;133;134;137;141;143] (n=919)	9[57;65;70;99;110;125;131;133;134] (n=771)	Inconclusive evidence	9[65;69;96;127;131;134;137;141;143] (n=288) 3.64 (1.63 - 8.10) I^2=52%	Significant association	**Moderate evidence of association.** Those with less initial disability more likely to have better upper limb recovery.
Type/Class of stroke (less vs. more severe)	7[57;65;74;110;119;130;133] (n=862)	4[57;65;74;130] (n=535)	Inconclusive evidence	2[65;130] (n=256) 3.54 (0.46 – 27.34) I^2=95%	No significant association	**Inconclusive evidence of association** between severity of stroke and upper limb recovery.
Global impairment (less vs. more impairment)	5[74;109;113;119;127] (n=493)	3[74;109;119] (n=284)	Inconclusive evidence	2[113;127] (n=209) 2.19 (0.35 - 13.90)	No significant association	**Inconclusive evidence of association** between global impairment and upper limb recovery.
Lesion size/volume (smaller vs. larger)	5[101;106;114;134;150] (n=132)	0	Limited evidence of no association	3[106;114;150] (n=65) 1.32 (0.74 - 2.38)	No significant association	**Limited evidence of no association** between infarction size/volume and upper limb recovery.
Urinary incontinence (absent vs. present)	4[65;126;130;139] (n=382)	2[65;130] (n=256)	Inconclusive evidence	2[65;130] (n=256) 4.12 (1.82 – 9.32) I^2=55.2%	Significant association	**Inconclusive evidence** relating to the association between urinary incontinence and upper limb recovery.
Level of consciousness at onset (GCS)	1[65] (n=100)	1[65] (n=100)	Limited evidence of association	1 (n=100) 1.03 (1.01 – 1.06)	Significant association	**Limited evidence of association** between level of consciousness at onset and upper limb recovery.

7th Cranial nerve	1[109] (n=58)	1 (n=58)	Limited evidence of association	0	NA	**Limited evidence of association** between 7th cranial nerve involvement and upper limb recovery.
Bowel function	1[126] (n=50)	0	Limited evidence of no association	0	NA	**Limited evidence of no association** between bowel function and upper limb recovery.
Severity of stroke – focal factors						
UL baseline impairment measures (less vs. more impairment)*	39[27;57;65;69;70;74-76;89;97-100;102;106;108-110;114;119;121;125;127;129-133;135;138;140-145;147;148;150] (n=2715)	25[27;57;65;70;74-76;89;98;99;109;114;125;127;129-133;135;142;144;145;147;148] (n=2349)	Strong evidence of association	20[27;65;69;89;97;100;106;108;121;127;129-131;135;141-144;147;150] (n=1425) 14.84 (9.08 – 24.25)	Significant association	**Strong evidence of association.** Those with less initial UL impairment are more likely to have better upper limb recovery.
UL baseline functional measures (more vs. less function)	10[101;102;109;119;124;126;127;133;142;149] (n=1512)	9[101;102;109;119;124;126;133;142;149] (n=1503)	Strong evidence of association	4[101;124;127;142] (n=158) 38.62 (8.40 – 177.53)	Significant association	**Strong evidence of association.** Those with more initial upper limb function are more likely to have better upper limb recovery.
Lower limb impairment (less vs. more impairment)	6[65;74;119;130;147;150] (n=534)	5[65;74;119;130;147] (n=517)	Moderate evidence of association	4[65;130;147;150] (n=308) 11.83 (6.53 – 21.42)	Significant association	**Moderate evidence of association.** Those with less leg impairment more likely to have better upper limb recovery.

Hand grip asymmetry	1[141] (n=17)	0	Limited evidence of no association	0	NA	**Limited evidence of no association** between hand grip asymmetry and upper limb recovery.
Co-factors (associated with stroke severity)						
Side of stroke (left vs. right)	21[65;70;74;96;99;106;107;109;113;119;121;125;129;130;132-134;141;143;144;146] (n=1506)	2[65;130] (n=256)	Strong evidence of no association	11[65;96;99;106;113;129;130;134;141;143;144] (n=624) 1.47 (1.07 – 2.01)	Significant association	**Inconclusive evidence.** Suggestion that left hemisphere stroke may be associated with better upper limb recovery.
UL sensation (no deficit vs. deficit)	11[57;65;70;99;109;113;121;132;139;141;148] (n=859)	6[57;65;99;109;113;132] (n=584)	Inconclusive evidence	3[65;113;141] (n=271) 1.92 (1.41 – 2.61)	Significant association	**Inconclusive evidence.** Suggestion that absence of sensory deficit is associated with better upper limb recovery.
Cognition and perception (no deficit vs. deficit)	10[65;70;74;76;99;109;113;130;133;139] (n=1101)	4[74;76;109;130] (n=401)	Inconclusive evidence	4[65;99;113;130] (n=462) 1.86 (0.91 – 3.78) I^2=89.4%	No significant association	**Inconclusive evidence** relating to the association between cognition and perception and upper limb recovery.
Stroke location	8[74;99;101;111;134;136;141;150] (n=415)	3[74;99;101] (n=280)	Inconclusive evidence	Unable to pool data together in statistical analysis	Unable to pool data	**Inconclusive evidence.** Unable to combine data.
Shoulder complications (absent vs. present)	5[70;109;132;139;148] (n=376)	2[109;139] (n=134)	Inconclusive evidence	0	NA	**Inconclusive evidence** regarding association between shoulder complications and upper limb recovery.

Visual disorders (absent vs. present)	4[65;70;109;130] (n=410)	3[65;109;130] (n=314)	Moderate evidence of association	2[65;130] (n=256) 5.22 (2.40 – 11.36)	Significant association	**Moderate evidence of association.** Those with absence of a visual disorder more likely to have better upper limb recovery.
Sitting balance (no deficit vs. deficit)	3[65;126;130] (n=306)	1[130] (n=156)	Inconclusive evidence	2[65;130] (n=256) 4.75 (0.28 – 80.53) I^2=96.8%	No significant association	**Inconclusive evidence.** Suggestion of no association between sitting balance and upper limb recovery.
Speech disorders (absent vs. present)	2[70;109] (n=154)	1[109] (n=58)	Inconclusive evidence	0	NA	**Inconclusive evidence** relating to association between speech disorders and upper limb recovery.
Handedness (right vs. left vs. ambidextrous)	2[74;109] (n=229)	0	Limited evidence of no association	0	NA	**Limited evidence of no association** between handedness and upper limb recovery.
Sensation (no deficit vs. deficit)	2[130;133] (n=378)	1[130] (n=156)	Inconclusive evidence	1[130] (n=156) 9.15 (3.36 – 24.89)	Significant association	**Inconclusive evidence** relating to association between sensation and upper limb functional recovery.
No. of comorbid conditions (less vs. more)	2[119;130] (n=211)	0	Limited evidence of no association	1[130] (n=156) 1.96 (0.96 – 3.98)	No significant association	**Limited evidence of no association** between no. of comorbid conditions and upper limb functional recovery.

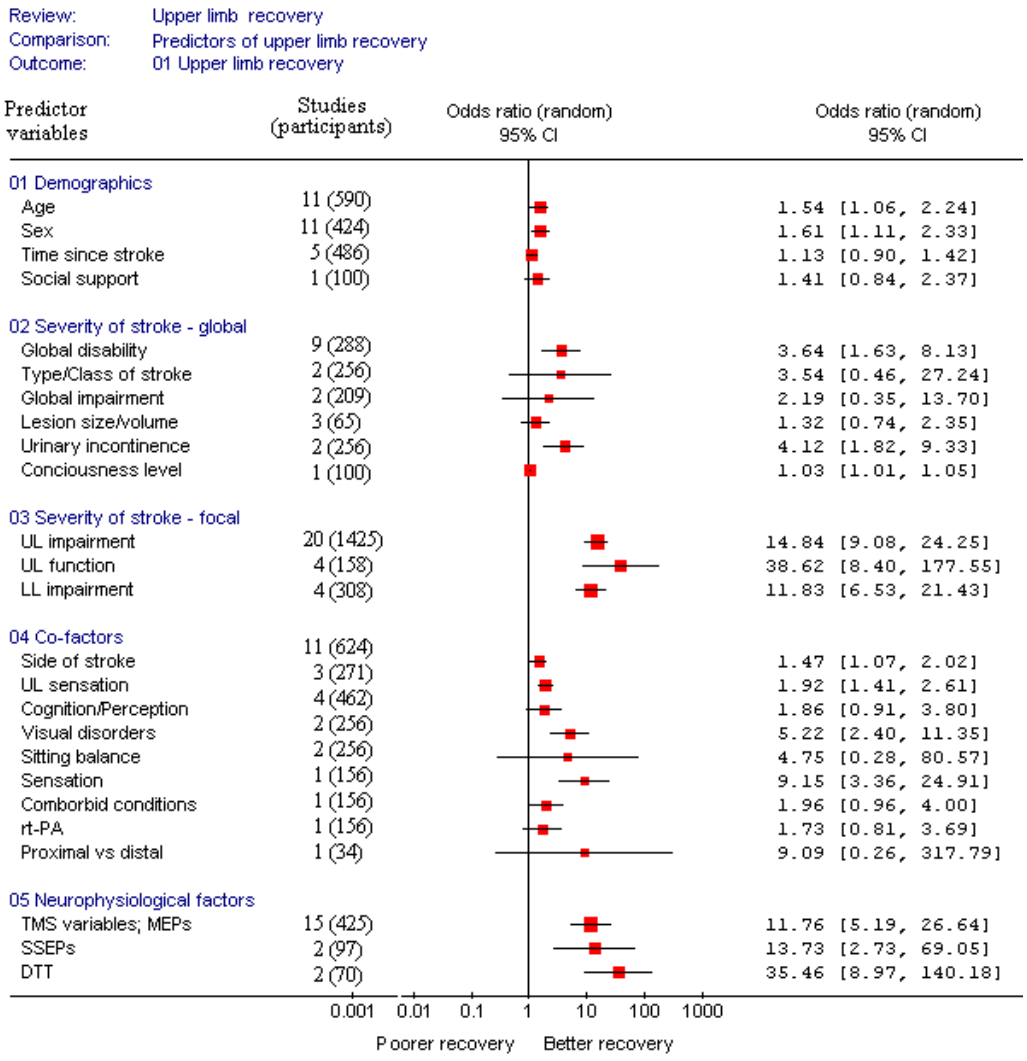
Rt-PA (yes/no)	1[130] (n=156)	0	Limited evidence of no association	1[130] (n=156) 1.73 (0.81 – 3.73)	No significant association	**Limited evidence of no association** between Rt-PA and upper limb functional recovery.
Length of stay	1[132] (n=107)	0	Limited evidence of no association	0	NA	**Limited evidence of no association** between length of stay and upper limb recovery.
Mood	1[70] (n=96)	0	Limited evidence of no association	0	NA	**Limited evidence of no association** between mood and upper limb recovery.
No. of previous strokes	1[109] (n=58)	1[109] (n=58)	Limited evidence of association	0	NA	**Limited evidence of association** between number of previous strokes and upper limb recovery.
Duration for stroke to develop	1[109] (n=58)	1[109] (n=58)	Limited evidence of association	0	NA	**Limited evidence of association** between duration for stroke to develop and upper limb recovery.
Pain in arm	1[109] (n=58)	1[109] (n=58)	Limited evidence of association	0	NA	**Limited evidence of association** between pain in arm and upper limb recovery.
Sit to stand	1[126] (n=50)	0	Limited evidence of no association	0	NA	**Limited evidence of no association** between sit to stand and upper limb recovery.

Proximal/Distal paresis	1[114] (n=34)	0	Limited evidence of no association	1 (n=34) 9.09 (0.26 – 333.33)	No significant association	**Limited evidence of no association** between distribution of paresis and upper limb recovery.
Neurophysiological factors						
Motor evoked potentials (present vs. absent)	20[69;96;103;104;106;107;110;112;114-116;118;120;129;135;137;141;143;144;147] (n=687)	15[69;96;103;107;110;112;115-117;120;129;135;137;143;147] (n=551)	Strong evidence of association	15[69;96;104;106;114;116;118;120;129;135;137;141;143;144;147] (n=425) 11.76 (5.19 – 26.65)	Significant association	**Strong evidence of association.** Those with present MEPs are more likely to have better upper limb recovery.
Somatosensory evoked potentials (present vs. absent)	6[98;112;116;122;124;145] (n=280)	6[98;112;116;122;124;145] (n=280)	Strong evidence of association	2[116;124] (n=97) 13.73 (2.73 – 69.10)	Significant association	**Strong evidence of association.** Those with present SSEPs are more likely to have better upper limb recovery.
Diffusion tensor tractography (DTT) (preserved corticospinal tract or not)	3[105;120;150] (n=125)	3[105;120;150] (n=125)	Limited evidence of association	2[120;150] (n=70) 35.46 (8.97 – 140.10)	Significant association	**Limited evidence of association.** Those with preserved corticospinal tract (determined by DTT) more likely to have better upper limb recovery.
Pre-morbid function						
Pre-stroke ability	1[109] (n=58)	0	Limited evidence of no association	0	NA	**Limited evidence of no association** between pre-stroke ability and upper limb recovery.

Pre-stroke mental status	1[109] (n=58)	0	Limited evidence of no association	0	NA	**Limited evidence of no association** between pre-stroke mental status and upper limb recovery.

Footnotes:
0 – no studies able to be included in statistical analysis
NA – no conclusions could be drawn from statistical analysis as no studies were available for inclusion in meta-analysis
Unable to pool data – due to differences in way data presented unable to sensibly combine in a meta-analysis
I^2 data only given if I^2>50%

Figure 2-2 – Meta-analysis of primary analysis: Predictor variables and association with upper limb recovery



Demographic factors

Within the main analysis (better upper limb recovery in terms of functional or impairment measures), combined evidence conclusions for the variables of age and sex were inconclusive due to inconsistencies between data analysis methods. Vote counting analysis did not identify any association with either of these variables and upper limb recovery, however a statistically significant result was found in both cases (OR 1.54 (95% CI 1.06 -2.25) and OR 1.61 (95% CI (1.11 – 2.33) respectively). These statistical analyses suggested

younger people and males respectively are more likely to have better upper limb recovery.

Severity of stroke – global factors

Inconclusive evidence was identified in the vote counting analysis for the variable of global disability. However, a statistically significant result was found in the statistical analysis of nine studies (n=288) suggesting that those with less disability are more likely to have better upper limb recovery. Inconclusive evidence was found for global motor impairment, urinary incontinence and type/class of stroke and limited evidence of no association for lesion size/volume and bowel function; in terms of upper limb recovery.

Severity of stroke – focal factors

The most commonly investigated variable was a baseline measure of upper limb impairment. The overall qualitative conclusion was that there was strong evidence that a lesser degree of impairment is associated with better upper limb recovery. Although this was due to only 25 of the 39 studies reporting a significant association, this did encompass 87% of the included participants. Strong evidence of association was found for baseline upper limb functional measures and moderate evidence for baseline lower limb impairment.

Co-factors (related to stroke impairment)

In terms of side of stroke only two of 21 studies reported an association; however, statistical analysis suggests that left hemisphere stroke is significantly associated with better upper limb recovery. The evidence was inconclusive for cognition and perception, stroke location, shoulder complications, sitting balance, speech disorders and sensation. Evidence was also inconclusive for an association between upper limb sensory deficits and upper limb recovery.

Neurophysiological factors

Consistent results were found between studies indicating strong evidence for the association between the presence of evoked potentials (both motor and

somatosensory) and better upper limb recovery. Limited evidence was found for an association between preserved corticospinal tract (determined by diffusion tensor tractography) and better upper limb recovery.

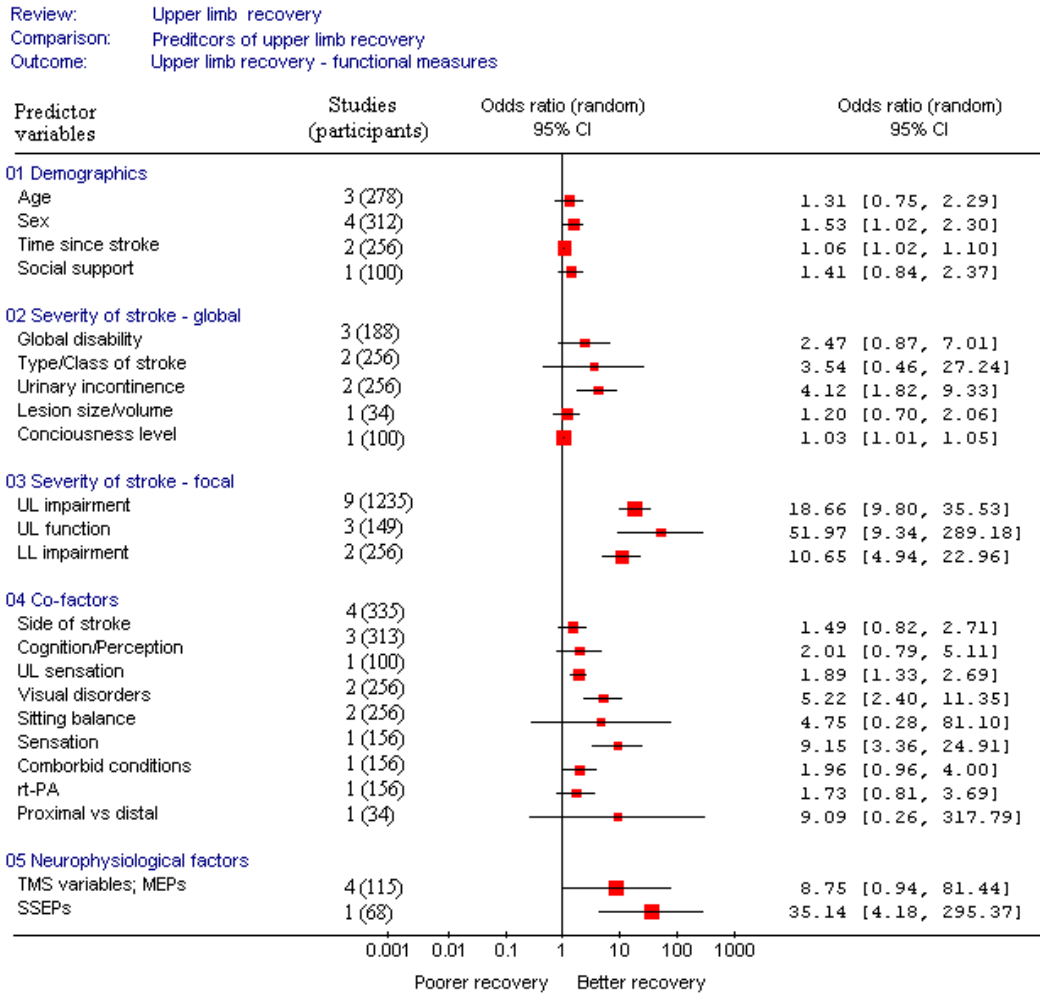
Pre-morbid function

Limited evidence of no association was found for the pre-morbid function variables of pre-stroke ability and pre-stroke mental status.

Therefore in this main analysis strong evidence was found for an association between initial upper limb impairment and functional measures, presence of motor and somatosensory evoked potentials and better upper limb recovery.

2.4.7 Secondary analysis

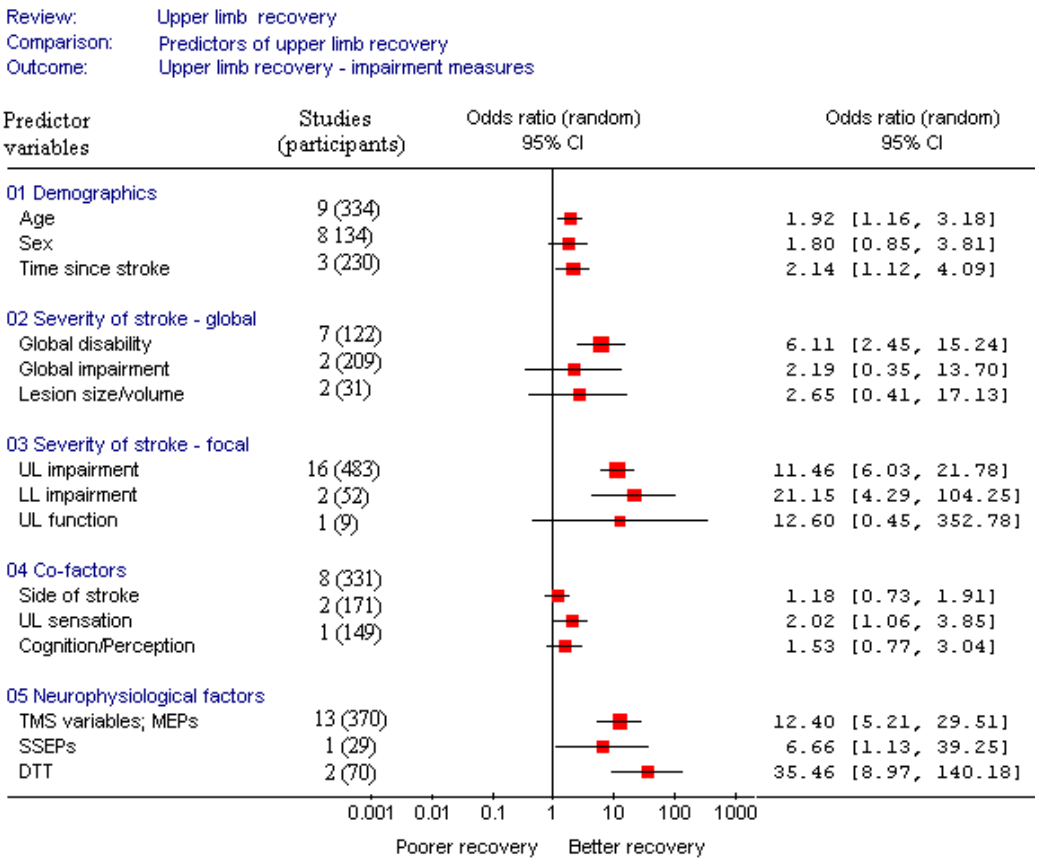
Figure 2-3 – Meta-analysis of secondary analysis (1): Predictor variables and association with measures of upper limb functional recovery



Consistent with the main analysis, initial measures of upper limb impairment and upper limb function were found to be strongly associated with better upper limb functional outcomes. However, some inconsistencies in the considered judgements between this secondary and the main analysis were identified. Inconclusive evidence of association for the variable of age was found in the main analysis. However, in this secondary analysis there was strong evidence of no association. This is likely to be related to the fact that 11 studies were included in the main statistical analysis and only three studies were included in this secondary analysis. A further discrepancy was

identified for the variables of motor evoked potentials and somatosensory evoked potentials. Strong evidence of association was found for these variables in the main analysis, however in this analysis inconclusive and limited evidence of association respectively was found. This again is probably related to a greater number of studies being included in the main analysis.

Figure 2-4 - Meta-analysis of secondary analysis (2): Predictor variables and association with measures of upper limb impairment



Consistent with the main analysis, initial measures of upper limb impairment and evoked potentials (motor and somatosensory) were found to be strongly associated with upper limb recovery, in terms of impairment. Discrepancies however were again evident. In the main analysis inconclusive evidence was found for the variable of sex, however in this analysis there was strong evidence of no association. For side of stroke the evidence in the main

analysis was inconclusive, and yet in this analysis the evidence strongly suggested no association.

For ease of presentation Table 2-5 indicates the combined assessment of evidence conclusions for each of the analysis. Only those variables investigated by more than one study have been included.

Table 2-5 - Overall evidence conclusions for each of the three analyses

Variable	Main analysis conclusion	Functional outcome analysis conclusion	Impairment outcome analysis conclusion
Age	Inconclusive evidence	Strong evidence of no association	Inconclusive evidence
Sex	Inconclusive evidence	Inconclusive evidence	Strong evidence of no association
Time	Inconclusive evidence	Moderate evidence of association	Inconclusive evidence
Global disability	Moderate evidence of association	Inconclusive evidence	Moderate evidence of association
Type/class of stroke	Inconclusive evidence	Inconclusive evidence	Limited evidence of association
Global impairment	Inconclusive evidence	Limited evidence of association	Inconclusive evidence
Lesion size/volume	Limited evidence of no association	Limited evidence of no association	Limited evidence of no association
Urinary incontinence	Inconclusive evidence	Inconclusive evidence	Limited evidence of no association
UL baseline impairment measures	Strong evidence of association	Strong evidence of association	Strong evidence of association
UL baseline functional measures	Strong evidence of association	Strong evidence of association	Limited evidence of no association
Lower limb impairment	Moderate evidence of association	Moderate evidence of association	Limited evidence of association
Side of stroke	Inconclusive evidence	Moderate evidence of no association	Strong evidence of no association
UL sensation	Inconclusive evidence	Inconclusive evidence	Inconclusive evidence
Cognition and perception	Inconclusive evidence	Inconclusive evidence	Inconclusive evidence
Stroke location	Inconclusive evidence	Limited evidence of association	Moderate evidence of no association
Shoulder complications	Inconclusive evidence	Limited evidence of association	Inconclusive evidence
Visual disorders	Moderate evidence of association	Moderate evidence of association	Inconclusive evidence
Sitting balance	Inconclusive evidence	Inconclusive evidence	NA
Speech disorders	Inconclusive evidence	Limited evidence of association	Inconclusive evidence
Handedness	Limited evidence of no association	Limited evidence of no association	Limited evidence of no association
Sensation	Inconclusive evidence	Inconclusive evidence	NA
Motor evoked potentials	Strong evidence of association	Inconclusive evidence	Strong evidence of association
Somatosensory evoked potentials	Strong evidence of association	Limited evidence of association	Strong evidence of association

Diffusion-tensor tractography (DTT) (preserved corticospinal tract or not)	Limited evidence of association	NA	Limited evidence of association

Footnote:
NA – no studies identified to include in this analysis i.e. no studies investigated that variable in association with any relevant outcomes in that category.

2.5 Discussion

2.5.1 Summary of findings

This review identified and summarised the results of 58 studies that reported on the predictive value of a number of variables for upper limb recovery following stroke. A wide range of variables and outcome measures have been considered within the literature. However, despite a number of variables being investigated, only baseline upper limb functional and impairment measures and neurophysiological factors (motor evoked potentials and somatosensory evoked potentials) were consistently identified as being strongly associated with upper limb recovery following stroke. Motor evoked potentials and somatosensory evoked potentials (neurophysiological factors) provide assessment of the integrity of cortico-spinal and somatosensory pathways. Therefore it is perhaps unsurprising that they provide an objective and useful insight into prediction of recovery following stroke.

Moderate evidence that less disability and lower limb impairment were associated with better upper limb recovery was also identified. No predictive value was found for lesion size. The findings of this review are largely consistent with the other previous reviews in this area[77;78], despite these other reviews having different objectives and using different methods of data analysis. The first of these reviews[77] also used a systematic approach to reviewing the evidence, however, in contrast, a best evidence synthesis was used and therefore only evidence from studies considered to be of higher methodological quality was reported. No meta-analysis was undertaken in this review. The other review[78] was a narrative type of review with no clear systematic methodology, and focused on the predictive value of motor impairment scores and neuroimaging, rather than the range of predictor variables.

For this review the decision was taken to have the broad concept of upper limb recovery as the main outcome. It could be argued that a more focused approach to outcomes would have been better. However, secondary analysis by functional and impairment outcomes was also undertaken and it is evident that the findings were largely consistent across the analyses. Any discrepancies can be related to the differences in the quantity of evidence available. The consistency of results adds weight to the findings of this review.

2.5.2 Limitations of the review and the included studies

Many of the limitations of this review relate to the problems of systematic reviews of prognostic studies[71], referred to in the introduction of this chapter. Those most relevant to this review will now be considered.

Difficulty identifying all studies

Despite a rigorous and thorough search strategy, it is acknowledged that relevant studies may have been missed.

Negative (non-significant) results may not be reported (publication bias)

Publication bias is a concern with this type of review. Studies with significant results are more likely to be published, have more than one associated publication and also are more likely to be identified through the searching process[151]. This was addressed through a rigorous searching process. It is reassuring that the completed search for this review identified a very similar group of studies to the other recent reviews of this area[77;78].

Inadequate reporting of methods

Limitations in reporting of methods were evident throughout a number of studies. Therefore a number of subjective decisions and assumptions had to be made throughout the review process, which could have potentially introduced bias.

Variation in study design

The included studies were heterogeneous in many aspects, and this was the main limitation of this review. Some included studies were clearly prospective cohorts set up to investigate predictors of upper limb recovery, whereas other studies were randomised controlled trials which also investigated predictive variables. The variation in length of follow-up (2 weeks to 1-4 years) will have had a substantial impact on the interpretation of the results, and is evidence of one of the main variations between the studies.

Variation in inclusion criteria

This was evident throughout the studies; some studies had very clear and explicitly stated inclusion and exclusion criteria, whereas others had only limited reporting of inclusion criteria. Also variations between participants included and excluded were evident, adding to the heterogeneous nature of the included studies.

Lack of recognised criteria for quality assessment

The quality assessment criteria used within this review were based on sound theoretical considerations. The decision was taken not to use an established quality criteria checklist, such as the Newcastle-Ottawa scale[91] but rather to consider the studies in terms of quality criteria[71]. However, consensus between the reviewers was difficult to obtain as a number of subjective decisions had to be made due to frequent poor reporting of methodological aspects. For this reason the methodological quality of the studies was not used to exclude studies. It should be recognised that conclusions with moderate evidence of association could potentially be overturned by more methodologically robust studies.

Variation in methods of analysis

This was encountered within this review. Some studies used correlation coefficients to assess association, others odds ratios and others just reported if significant or not. This made combining studies difficult.

Differing methods of handling of continuous variables (some dependent on data)

In order to analyse continuous variables some studies did dichotomise predictor and outcome variables. From examination of these studies it was clear that most did try and make a decision on the cut-off based on clinical significance or following further analysis, however, it is acknowledged that some cut-offs may have been data dependent. This problem was further compounded by the fact that in order to include as many relevant studies as possible within the statistical analysis a decision was taken to ascribe cut-offs to predictor variables and outcomes of interest, to calculate odds ratios, where data allowed. The cut-offs to be used were not stipulated prior to data extraction. However, instead of being data driven, attempts were made to use cut-offs used within other studies.

Adjustment for different sets of variables

This particular issue was avoided in this review as only univariate analyses were considered.

As stated above the main limitation of this review relates to the heterogeneity of the studies. This includes the varying definitions of initial upper limb problems, differing predictive variables and measurements, outcome measures, length of follow up and data presentation. Statistical heterogeneity (I^2) was seen in a number of the studies, reflecting the differing nature of many of the studies. Ascribing arbitrary cut-offs to variables, including continuous measures, which were not consistent across the studies further adds to the potential heterogeneity.

The main focus of this review was to answer the question: Is there any evidence of association between individual variables and upper limb recovery? The approach to data analysis was suitable for answering the question. Despite this ascertain, limitations with these approaches to data analysis must be acknowledged. Vote counting is recognised as having limitations[152]. The main weaknesses of vote counting relate to the fact that no account is taken of the differential weights of each study and usually

subjective decisions have to be taken. However, as the research question was limited to looking for evidence of effect this approach was considered to be appropriate and allowed for the inclusion of the greatest number of studies. Additionally, as this approach was supplemented by quantitative analyses complete emphasis was not placed on this method of data analysis. Statistical analysis of predictive studies is also recognised as raising significant challenges[71]. The poor quality of predictive studies, variable methodological quality and often poor reporting of methodology[79] are identified as reasons for not completing meta-analysis of such studies. Differences between studies (as highlighted above) further raise questions about the suitability of undertaking meta-analysis. Despite these concerns, it was considered that statistical analysis of the studies added another dimension and reduced the subjectivity in interpreting the evidence. Therefore, while the individual approaches to data analysis used within this review have their limitations, this review was strengthened by having both types of analysis and also considered judgements about the state of the evidence, which considered not only the results of the vote counting and statistical results but also the quality of each study. Despite a few discrepancies, particularly relating to age and sex, there was a good level of consistency between the conclusions of the statistical and other analytical approaches. This adds confidence to the findings of this review.

Within this review the findings were based on information from univariate analyses. These univariate results are not adjusted for potential confounders; which is considered to be good practice in studies of predictive variables[79]. However, this review was intended to identify which predictor variables were available and their individual ability to predict upper limb recovery.

The exclusion of studies that did not report univariate results may have introduced a degree of bias into this review as some useful information may have been omitted. However only a small number of studies were excluded for this reason, as most studies that did go onto complete multi-variate analyses initially reported univariate results.

The way that individual predictor variables were grouped and the outcome measures that were chosen for inclusion in the analysis may have influenced the results of this review. However, there is no suggestion that the main conclusions would have changed had alternative groupings or outcomes been chosen.

2.5.3 Strengths of the review

The main strength of this review was that a rigorous systematic review methodology was used and that a large number of studies were included. Furthermore, a rigorous, explicit and prospective approach to identify, appraise, combine and synthesise a lot of complex data into a clear and concise format was used. The included studies showed a reasonable consistency of results, which adds to the confidence in the conclusions of the review.

2.5.4 Implications for practice

This review found evidence for variables that suggest an association with upper limb outcome. Upper limb level of impairment and function at baseline and intact motor evoked potentials or somatosensory potentials appear to be the most powerful predictors of upper limb recovery. Evoked potentials are usually only collected in the context of research trials and therefore clinical measures will be far more useful to clinicians. This information may be useful to clinicians when planning treatment programmes and discussing likely prognosis with patients.

2.5.5 Implications for research

For stratification in clinical trials researchers should consider using those measures which have been found to be strongly associated with recovery (for example, baseline Fugl-Meyer, MRC scale, Action Research Arm Test).

This review has highlighted the need for improved quality of reporting of predictive studies in this area. In addition, large high quality cohort studies would be useful to validate the strength of evidence of this systematic review. Further studies could also investigate multivariate models and their usefulness for predicting upper limb recovery. For future studies to be relevant to clinical practice and research it would be useful to establish an international consensus on a core set of relevant predictive variables and standardised outcome criteria for upper limb recovery. The COMET[153] core outcomes project is currently looking into producing datasets of core outcome measures for use in clinical trials, however, have not yet produced details of outcomes relating to stroke rehabilitation trials. These findings will be passed onto the COMET working group, and a stroke rehabilitation outcomes work stream will be proposed. The distinction between outcomes appropriate for stroke rehabilitation trials and acute stroke trials will be highlighted to the group.

2.5.6 Conclusions

This systematic review found a large number of studies which investigated the predictive value of at least one variable and its association with a measure of upper limb recovery at a future time point. This information was synthesised and combined, in order to highlight those variables which have been found to show evidence of association with upper limb recovery.

Strong evidence was found that indicated that initial measures of upper limb function and impairment and neurophysiological measures can predict upper limb recovery. Moderate evidence of association was found for the variables of global disability and lower limb impairment. Limited evidence of association or no association or inconclusive evidence was concluded for the other variables.

The results of this review must be taken in context of the limitations of this review, which particularly relate to the heterogeneous nature of the included studies.

Chapter 3

Effectiveness of interventions targeted at upper limb recovery after stroke: an overview

Chapter 3 Effectiveness of interventions targeted at upper limb recovery after stroke: an overview

3.1 Introduction

In order to plan a randomised controlled trial of an evidence-based intervention for improving upper limb recovery after stroke, examination of the current literature on the subject was considered appropriate. This chapter will focus on the current, available evidence for the treatment of upper limb motor impairment and restoration of motor function after stroke and identify which interventions have been studied and which, if any show promise of efficacy.

3.1.1 Motor impairment

As outlined previously the most common and recognisable deficit following stroke is motor impairment. Motor impairment, of some description, will affect approximately 80% of stroke patients and will present as a loss or limitation of function in muscle control or movement[154] of the face, arm and/or leg of one side of the body. For the purposes of this thesis the focus is on motor impairment of the upper limb.

3.1.2 Upper limb rehabilitation

Within stroke rehabilitation interventions targeted at reducing impairment and improving the function of the upper limb are common, and forms much of the focus of occupational therapy and physiotherapy interventions within stroke rehabilitation. Two studies illustrate this[155;156].

A small pilot study[155] of occupational therapists and physiotherapists (n=13), found that upper limb interventions were one of the most frequently recorded

aspects of physiotherapy. The other study, investigating the content of physiotherapy (PT) and occupational therapy (OT) sessions, across four European stroke centres, found that in a one hour PT session, selective movements (which included upper limb interventions) were the most frequently completed activities (median 16.03 minutes).

The ultimate goal of therapy targeted at upper limb motor impairment is to improve the function of the upper limb, as well as recovery of movement. For the purposes of this review motor impairment and its associated functional activities have been considered as part of a continuum.

Despite being a common element of stroke rehabilitation, rehabilitation of the upper limb is acknowledged as posing a particular challenge to the multidisciplinary team[157] due to poor levels of upper limb recovery and a lack of conclusive evidence to guide practice.

3.1.3 Interventions for motor recovery of the upper limb

It is clear from the rehabilitation literature over the past decade that to attempt to improve upper limb outcomes a number of interventions have been designed, many of which have been evaluated using systematic review and/or randomised controlled trial (RCT) methodology[90]. However, this area is confusing as most of these developed interventions do not explicitly target a specific pathophysiological process and have been tested using a variety of patient groups and outcome measures.

In order to identify which interventions appear to show promise I undertook a broad based systematic review of previously tested interventions. The purpose of this review was to provide a standardised summary of the available evidence for the treatment of upper limb motor impairment and restoration of motor function after stroke.

3.2 Objectives

- To summarise the available evidence of interventions which target upper limb recovery following stroke
- To identify interventions which show promise of efficacy
- To identify characteristics of interventions that show promise of efficacy
- To relate the information gained to the current guideline advice on clinical management
- To use the information gained to identify a suitable intervention to be investigated in the planned randomised controlled trial

3.3 Methods

Due to the summary nature of this review and the known variations in the available evidence base a pragmatic, empirical approach was taken to describing and reviewing the evidence.

3.3.1 Eligibility criteria

Types of studies

In order to identify relevant upper limb interventions a number of approaches had previously been completed, which included expert opinion[158], gauging the views of multidisciplinary focus groups and systematic searching of relevant texts and guidelines[159]. This was supplemented by searching the Cochrane Stroke Group list of systematic reviews and protocols[90] and the Cochrane library for additional systematic reviews.

Systematic reviews of randomised trials of interventions to promote upper limb motor recovery (recovery of impairment or related function) after stroke were considered and included in the first instance. It was decided to initially concentrate on reviewing the available systematic review evidence, as a number of such reviews have already been carried out within (or overlap)

with this area and systematic reviews are considered to be the highest level of evidence[160]. Therefore, where available, systematic reviews were sought and used, and then supplemented (where necessary) with additional information from recent RCTs.

Types of participants

The population of interest was adults with a clinical diagnosis of stroke.

Types of interventions

Any intervention aimed specifically at improving upper limb motor recovery was considered. Pharmacological and surgical interventions were excluded. Any duration or intensity of programme was included.

Types of comparisons

Comparisons of interventions against no treatment, placebo intervention or standard/usual care were included. Randomised controlled trials comparing one specific upper limb intervention to another specific upper limb intervention (for example constraint-induced movement therapy vs. robotic intervention) were excluded, wherever possible (see results for exceptions).

Types of outcome measures

The focus of this review was on the effects of interventions on recovery of upper limb movement and function. For analysis this was separated into arm and hand function. A wide range of outcome measures related to upper limb recovery were included. Priority was given to functional tests (e.g. Action Research Arm Test (ARAT)[85], Motor Assessment Scale (MAS)[86], Frenchay Arm Test (FAT)[161], Nine Hole Peg Test (NHPT)[162] before impairment scales (Fugl-Meyer (F-M) scale[88], Motricity Index (MI)[163]). However, in the first instance the outcome measures reported in the relevant systematic reviews were used. As the primary focus of this review was motor recovery of the upper limb (impairment and associated functions) outcomes relating to the recovery of impairment of specific muscles or muscle groups (such as muscle tone or muscle length), or related impairments (such as pain, spasticity or contractures) were not included.

For analysis, data recorded at the end of the intervention period was used, where possible. Otherwise data recorded at different time points (e.g. end of scheduled follow-up), as reported in the relevant systematic review was used.

3.3.2 Search methods for identification of studies

Initially the list of all systematic reviews (full reviews, protocols and titles) registered with the Cochrane Stroke Group[90] by March 2009 and then updated to September 2011 was searched to identify all relevant Cochrane systematic reviews .

If a Cochrane systematic review was identified fully covering the intervention of interest, searching for additional RCTs was only carried out past the search date of the identified review. If a Cochrane review was not available the Cochrane Library (using the terms “stroke” and intervention specific terms, such as “approaches to therapy”, “neurophysiological”, “bobath”, “bilateral training”, “constraint-induced movement therapy”, “biofeedback”, “electrostimulation” “intensity”, “mental practice” “imagery”, “mirror”, “repetitive task training”, “robotics” “splinting”, “orthosis” and “virtual reality”) was searched for “other” systematic reviews and/or RCTs relevant to the topic. This was supplemented by a MEDLINE search of key terms. Only full, published studies were considered for inclusion.

3.3.3 Identification of relevant trials

Initially I read all the identified titles and excluded any obviously irrelevant studies. Obviously relevant studies were included within the relevant intervention categories. If I was uncertain about including a study or about allocation to a particular intervention the opinion of a second reviewer was sought.

3.3.4 Data extraction

The purpose of this review was to provide an overview of the available evidence and therefore only a limited amount of information was extracted.

The following information was extracted from the systematic reviews:

1. Number of RCTs (as relevant to this review)
2. Number of participants (as relevant to this review)
3. Intervention characteristics
4. Comparison intervention(s)
5. Outcome(s)

Where additional trials were identified the following information was extracted:

1. Number of participants (as relevant to this review)
2. Intervention characteristics
3. Comparison intervention(s)
4. Outcome(s)

3.3.5 Documentation of methodological quality

The three key methodological characteristics[164] likely to influence the reliability of study conclusions were considered:

1. Allocation concealment – did the trial report describe adequate concealment of treatment allocation?
2. Blinding of outcome assessor – did the trials report that the outcome assessor was unaware of treatment allocation?
3. Intention-to-treat analysis – did the trial report the use of an intention-to-treat analysis?

Where available the assessment undertaken within the Cochrane systematic review was used, otherwise each trial was critically appraised considering the three outlined criteria.

3.3.6 Data analysis

Where possible, means and standard deviations (SD) for outcomes relating to upper limb recovery, from each group, were extracted either directly from the relevant systematic reviews or from individual trials and combined within a meta-analysis to derive a standardised mean difference (SMD) and 95% confidence intervals (CI). This expresses the difference between intervention and control groups in terms of standard deviation units.

Where additional trials to those already included within a systematic review were identified, data from these trials were added into the analysis, where possible, and new estimates of effect obtained. A number of the identified reviews presented analyses of outcomes in a different way from the global outcome of interest of this review. Where this occurred the data from the individual trials included in the review were re-analysed. In some cases trials with different comparators (e.g. placebo, control and usual care) were also grouped together to gain one estimate of intervention effect. For these reasons the summary estimates of treatment effect and conclusions of this review may vary from the previously published, identified reviews of individual interventions. Where means and standard deviations were not presented within a trial, these trials were either excluded from data analysis or, in a few cases; imputations were made for the missing data and/or calculations made to derive the required data. Where more than one subgroup was presented in a trial both were included in the analysis. If the same control group was used for both subgroups i.e. in trials which had two appropriate interventions (e.g. high and low intensity of a robotic intervention) compared to one control group, the number of participants within the control group was split between the two subgroups and the standard deviation was doubled to reduce the weight given to the two halves of the control groups. RevMan 5 software[165] was used for all analyses. Results were analysed

using the standardised mean difference with a fixed effects model. Heterogeneity was determined using the I-squared (I^2) statistic ($I^2 > 50\%$ considered substantial heterogeneity). If $I^2 > 50\%$ meta-analysis was performed using both fixed-effect and random-effects modelling to assess sensitivity to the choice of modelling approach.

Classification of the effects of an intervention

For understanding SMD in terms of clinical difference it is generally considered that a SMD of 0.2 suggests a small effect, 0.5 a moderate effect and 0.8 and over indicates a large effect[166]. To attempt to provide further clarification of the effect of each intervention a semi-quantitative Clinical Evidence classification of effectiveness[167] was also used, where each intervention was classified as 'beneficial', 'likely to be beneficial', 'trade-off between benefits and harm', 'unlikely to be beneficial', 'likely to be ineffectual or harmful' or 'unknown effectiveness'. These classification decisions were based on the results of the statistical analysis, combined with a considered judgement relating to the power of the RCTs and their heterogeneity and consistency of effect.

The most recently published Scottish Intercollegiate Guidelines Network (SIGN)[33] were searched and guidance on the use of identified interventions for upper limb recovery was also reported.

3.4 Results

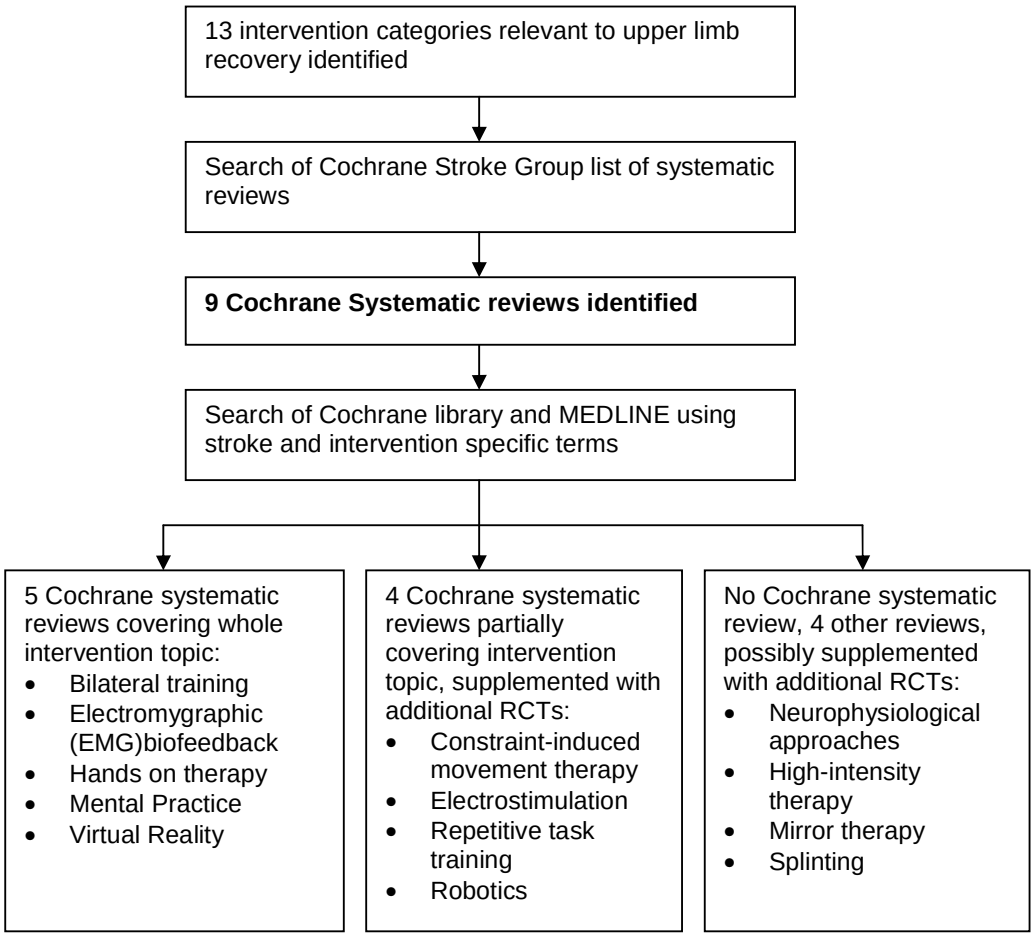
3.4.1 Results of the search

Thirteen intervention categories relevant to upper limb motor recovery after stroke were identified.

Of the 13 interventions, nine had associated Cochrane systematic reviews and four were covered by another review (Figure 3-1).

The sum of the included RCTs is 118, however seven trials were included in more than one intervention category, therefore 111 RCTs were included in this overview of interventions to improve upper limb recovery.

Figure 3-1 - Flow chart of searching process and evidence identified at each stage of searching



3.4.2 Included studies

Table 3-1 outlines the thirteen intervention categories (with an accompanying description of each intervention) and the associated sources of evidence which were identified and used in this review. Sources included the relevant Cochrane systematic review or similar high quality systematic review, the relevant trials included within that review and any additional trials identified.

For all of the included interventions a systematic review was identified (nine Cochrane reviews and four other reviews) and, in seven cases this information was supplemented with data from additional RCTs. Most of the analyses of the effects of an intervention were informed by a relatively small number of randomised trials (average of 8 trials per intervention category for outcome of arm function and 3 for outcome of hand function).

Table 3-1 - Outline of intervention categories and sources of evidence

Intervention	Description	Cochrane or other review (relevant RCTs included)	Additional RCTs identified	Total RCTs included
Approaches to therapy - Neurophysiological (Bobath)	Various therapeutic approaches based on neurophysiological knowledge and theories, most commonly the Bobath approach	Other review[168] (2 RCTs)[169;170]	3[171-173]	5
Bilateral training	Using both upper limbs to perform identical activities simultaneously but independently	CR[174] (10 RCTs)[175-184]	0	10
Constraint induced movement therapy (CIMT)	Restraint of the intact limb, in combination with a large number of repetitions of task-specific training	CR[185] (19 RCTs)[186-204]	4[178;205-207]	23
EMG biofeedback	Using instrumentation applied to muscles with external electrodes to capture motor unit electrical potentials. The instrumentation converts the potentials into audio or visual information	CR[208] (4 RCTs)[209-212]	0	4
Electrostimulation	Electrostimulation delivered to the peripheral neuromuscular system by external or internal electrodes, at a range of frequencies, intensities and patterns of delivery	CR[213] (10 RCTs)[175;214-222]	11[41;223-232]	21
Hands-on therapy interventions	Hands-on physical interventions (manual therapy techniques)	CR[233] (3 RCTs)[234-236]	0	3
High-intensity therapy	Increased amount of focused	Other review[237] (4 RCTs)[51;238-	0	4

	therapy/interventions	[240]		
Mental practice/Imagery	Cognitive rehearsal of a physical action.	CR[241] (6 RCTs)[242-247]	0	6
Mirror therapy	Mirror is placed in the patient's midsagittal plane, presenting the patient the mirror image of their non-affected arm	Other review[248] (4 RCTs)[249-252]	1[253]	5
Repetitive task training	Active motor sequence performed repetitively within a single training session, aimed towards a clear functional goal.	CR [254] (8 RCTs)[62;170;173;238;255-258]	1[259]	9
Electromechanical/ Robotics	Devices which allow for high-intensity, repetitive, task-specific and interactive treatment of the upper limb	CR[260] (10 RCTs)[181;261-269]	6[270-275]	16
Splinting/orthosis	External, removable devices that are used to meet a number of clinical aims	Other review[276] (2 RCTs)[277;278]	1[279]	3
Virtual reality	An advanced form of human-computer interface that allows the user to 'interact' with and become 'immersed' in a computer-generated environment in a naturalistic fashion.	CR[280] (9 RCTs)[272;281-288]	0	9

Additional details extracted from all of the included trials, taken from Cochrane systematic reviews where possible, or from the individual trials (numbers of participants, intervention undertaken, comparison group and outcome measure(s) used in this review) are outlined in (Appendix C) and briefly reported below.

Participants

Only basic information i.e. number of participants within each study at recruitment (as relevant to this review) and then at outcome was recorded. If a trial reported more than one control group only one control group was chosen for inclusion and only these participants were included. Despite only basic information being extracted and presented it was clear from the literature that a heterogeneous group of patients' i.e. differing populations across and within the different intervention categories had been studied. In terms of numbers it was clear that most of the included trials only recruited

relatively small numbers of participants, as relevant to this review (average of 36 participants; median 27 per trial). Only seven[51;173;182;201;239;240;259] of the included trials recruited more than 100 participants, which were relevant to this review.

Interventions

It was clear that even within the intervention categories there were variations in the interventions delivered. This was evident in terms of intensity, duration and types of intervention delivered (e.g. type of constraint-induced movement therapy, electromechanical/robotic device used).

Comparators

Differences in the comparator interventions were also evident. As far as possible I aimed to only include RCTs which compared the intervention of interest to usual care, placebo or no treatment. However this was not always possible (as evident in Appendix C). In some cases increased intensity of usual care was also evident.

Outcome measures

A range of measures of upper limb motor recovery (arm and hand function/impairment) were reported. The outcome measures reported by the included Cochrane systematic reviews were used in this analysis. Therefore on occasions an outcome relating to motor impairment (e.g. Fugl-Meyer Scale) was included over a measure of motor function (e.g. Action Research Arm Test). For trials that were identified, in addition to those included in the Cochrane reviews, functional measures were chosen over motor impairment measures. The most commonly used outcome measures in this review were the ARAT, MAS, F-M scale and BBT. For hand function the most common measures of hand function were various peg tests, particularly the NHPT.

3.4.3 Methodological quality of the included studies

Table 3-2 outlines the key design features of the included trials within each intervention category, in relation to the three main features that are likely to

affect the reliability of the trials conclusions; whether there was adequate allocation concealment; whether the outcome assessor was blinded to treatment allocation; and whether an intention-to-treat analysis was used.

Table 3-2 - Key design features of the included trials

Intervention category	Number of included RCTs	Allocation concealment Adequate/Unclear /Not adequate	Blinded assessor	Intention-to-treat analysis
Approaches to therapy – Neurophysiological (Bobath)	5	2 / 3 / 0	3	1
Bilateral training	10	3 / 4 / 3	8	0
Constraint-induced movement therapy	23	4 / 19 / 0	20	2
EMG biofeedback	4	1 / 1 / 2	2	0
Electrostimulation	21	3 / 16 / 2	11	4
Hands-on therapy interventions	3	1 / 2 / 0	0	0
High-intensity therapy	4	3 / 1 / 0	4	1
Mental practice/imagery	6	0 / 6 / 0	5	0
Mirror therapy	5	3 / 2 / 0	5	1
Repetitive task training	9	6 / 2 / 1	6	2
Electromechanical/Robotic devices	16	3 / 10 / 3	12	2
Splinting/orthotics	3	2 / 1 / 0	3	2
Virtual reality	9	5 / 3 / 1	6	3

Quality of the included trials was variable. Adequate allocation concealment was reported in only 30% of trials (although only 10% had clearly inadequate allocation concealment), blinding of outcome assessment was reported in 72%, and an intention-to-treat analysis was only clearly reported as completed in 15% of trials; although this may, in part be attributable to poor reporting. Additionally many of the trials did not report any dropouts.

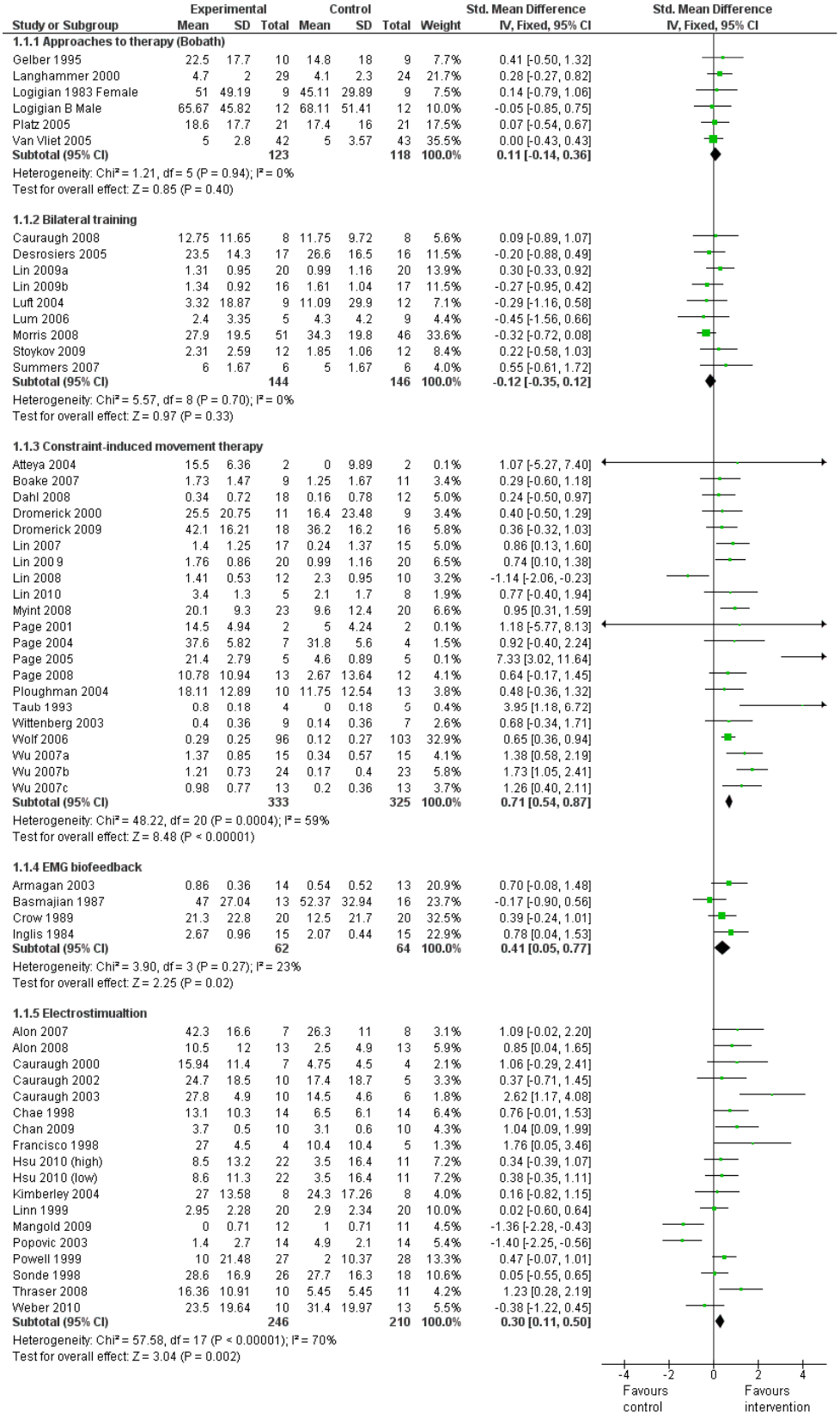
3.4.4 Evidence for effects of interventions: Arm function

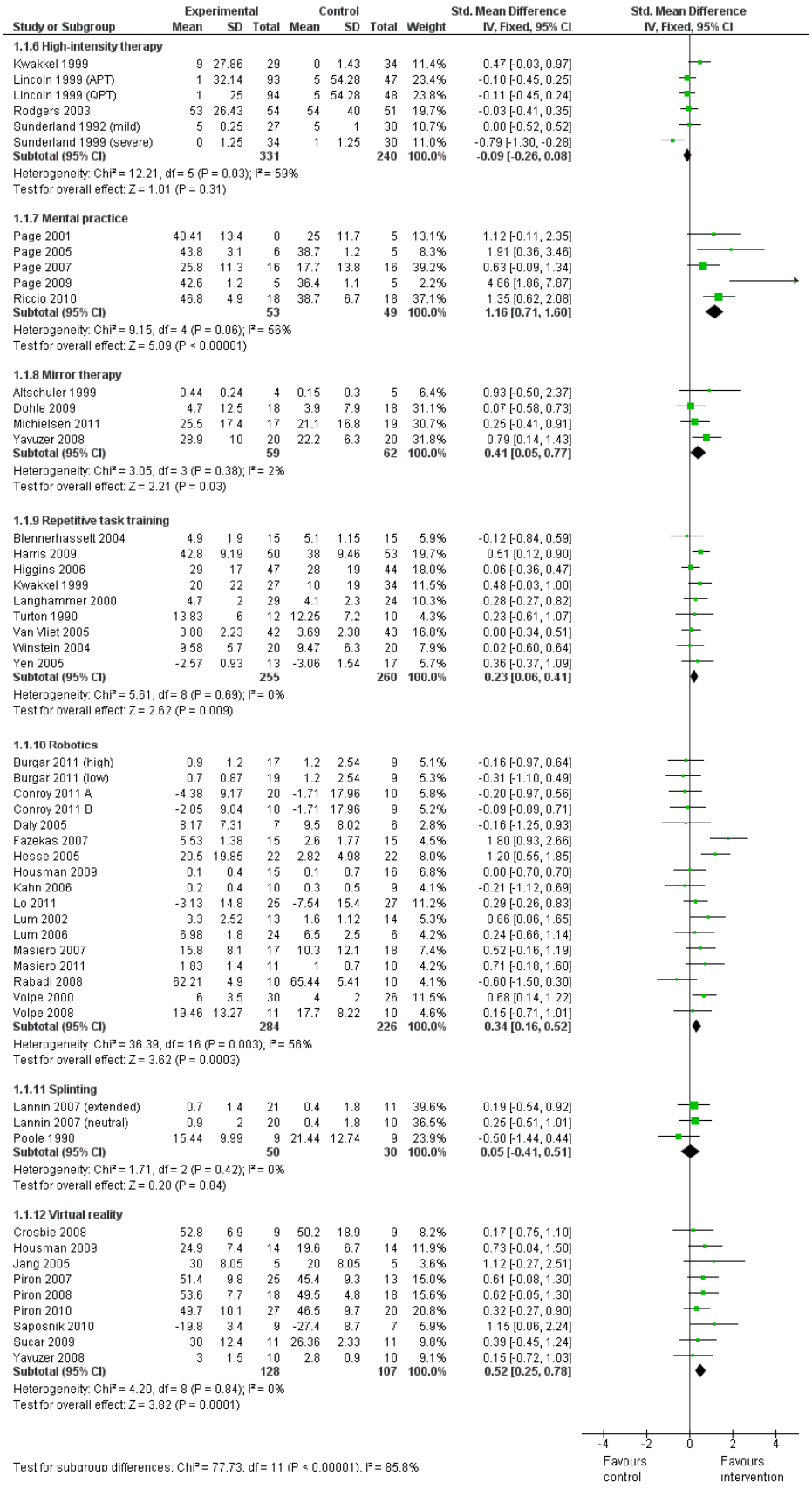
Figure 3-2 and Table 3-3 summarise the results of the meta-analysis for the effect of the identified upper-limb interventions on measures of motor recovery (impairment/function) of the arm. Figure 3-2 is presented over two

pages. A range of measures of arm function were reported and included in this analysis. The most common were the ARAT, MAS and F-M scale.

The results indicate that several interventions have a potential effect on arm function. Eight interventions were found to have a statistically significant result: constraint-induced movement therapy (SMD 0.71 95% CI 0.54-0.87), EMG biofeedback (SMD 0.41 95% CI 0.05-0.77), electrostimulation (SMD 0.30 95% CI 0.11-0.50), mental practice (SMD 1.16 95% CI 0.71-1.60), mirror therapy (SMD 0.41 95% CI 0.05-0.77), repetitive task training (SMD 0.23 95% CI 0.06-0.41), electromechanical/robotics (SMD 0.34 95% CI 0.16-0.52) and virtual reality (SMD 0.52 95% CI 0.25-0.78). One intervention category; hands-on therapy interventions only included three trials and was not included in any meta-analyses, as the authors of this included systematic review deemed the interventions too heterogeneous. The four other interventions (approaches to therapy, bilateral training, high-intensity therapy and splinting) had a non significant result for arm recovery.

Figure 3-2 - Forest plot of 13 interventions targeted at arm recovery compared to control group




Experimental
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
1.1.6 High-intensity therapy
Kwakkel 1999 9 27.86 29 0 1.43 34 11.4% 0.47 [-0.03, 0.97]
Lincoln 1999 (APT) 1 32.14 93 5 54.28 47 23.4% -0.10 [-0.45, 0.25]
Lincoln 1999 (QPT) 1 25 94 5 54.28 48 23.8% -0.11 [-0.45, 0.24]
Rodgers 2003 53 26.43 54 54 40 51 19.7% -0.03 [-0.41, 0.35]
Sunderland 1992 (mild) 5 0.25 27 5 1 30 10.7% 0.00 [-0.52, 0.52]
Sunderland 1999 (severe) 0 1.25 34 1 1.25 30 11.0% -0.79 [-1.30, -0.28]
Subtotal (95% CI) 331 240 100.0% -0.09 [-0.26, 0.08]
Heterogeneity: Chi² = 12.21, df = 5 (P = 0.03); I² = 59%
Test for overall effect: Z = 1.01 (P = 0.31)
1.1.7 Mental practice
Page 2001 40.41 13.4 8 25 11.7 5 13.1% 1.12 [-0.11, 2.35]
Page 2005 43.8 3.1 6 38.7 1.2 5 8.3% 1.91 [0.36, 3.46]
Page 2007 25.8 11.3 16 17.7 13.8 16 39.2% 0.63 [-0.09, 1.34]
Page 2009 42.6 1.2 5 36.4 1.1 5 2.2% 4.86 [1.86, 7.87]
Riccio 2010 46.8 4.9 18 38.7 6.7 18 37.1% 1.35 [0.62, 2.08]
Subtotal (95% CI) 53 49 100.0% 1.16 [0.71, 1.60]
Heterogeneity: Chi² = 9.15, df = 4 (P = 0.06); I² = 56%
Test for overall effect: Z = 5.09 (P < 0.00001)
1.1.8 Mirror therapy
Altschuler 1999 0.44 0.24 4 0.15 0.3 5 6.4% 0.93 [-0.50, 2.37]
Dohle 2009 4.7 12.5 18 3.9 7.9 18 31.1% 0.07 [-0.58, 0.73]
Michielsen 2011 25.5 17.4 17 21.1 16.8 19 30.7% 0.25 [-0.41, 0.91]
Yavuzer 2008 28.9 10 20 22.2 6.3 20 31.8% 0.79 [0.14, 1.43]
Subtotal (95% CI) 59 62 100.0% 0.41 [0.05, 0.77]
Heterogeneity: Chi² = 3.05, df = 3 (P = 0.38); I² = 2%
Test for overall effect: Z = 2.21 (P = 0.03)
1.1.9 Repetitive task training
Blennerhassett 2004 4.9 1.9 15 5.1 1.15 15 5.9% -0.12 [-0.84, 0.59]
Harris 2009 42.8 9.19 50 38 9.46 53 19.7% 0.51 [0.12, 0.90]
Higgins 2006 29 17 47 28 19 44 18.0% 0.06 [-0.36, 0.47]
Kwakkel 1999 20 22 27 10 19 34 11.5% 0.48 [-0.03, 1.00]
Langhammer 2000 4.7 2 29 4.1 2.3 24 10.3% 0.28 [-0.27, 0.82]
Turton 1990 13.83 6 12 12.25 7.2 10 4.3% 0.23 [-0.61, 1.07]
Van Vliet 2005 3.88 2.23 42 3.69 2.38 43 16.8% 0.08 [-0.34, 0.51]
Winstein 2004 9.58 5.7 20 9.47 6.3 20 7.9% 0.02 [-0.60, 0.64]
Yen 2005 -2.57 0.93 13 -3.06 1.54 17 5.7% 0.36 [-0.37, 1.09]
Subtotal (95% CI) 255 260 100.0% 0.23 [0.06, 0.41]
Heterogeneity: Chi² = 5.61, df = 8 (P = 0.69); I² = 0%
Test for overall effect: Z = 2.62 (P = 0.009)
1.1.10 Robotics
Burgar 2011 (high) 0.9 1.2 17 1.2 2.54 9 5.1% -0.16 [-0.97, 0.64]
Burgar 2011 (low) 0.7 0.87 19 1.2 2.54 9 5.3% -0.31 [-1.10, 0.49]
Conroy 2011 A -4.38 9.17 20 -1.71 17.96 10 5.8% -0.20 [-0.97, 0.56]
Conroy 2011 B -2.85 9.04 18 -1.71 17.96 9 5.2% -0.09 [-0.89, 0.71]
Daly 2005 8.17 7.31 7 9.5 8.02 6 2.8% -0.16 [-1.25, 0.93]
Fazekas 2007 5.53 1.38 15 2.6 1.77 15 4.5% 1.80 [0.93, 2.66]
Hesse 2005 20.5 19.85 22 2.82 4.98 22 8.0% 1.20 [0.55, 1.85]
Housman 2009 0.1 0.4 15 0.1 0.7 16 6.8% 0.00 [-0.70, 0.70]
Kahn 2006 0.2 0.4 10 0.3 0.5 9 4.1% -0.21 [-1.12, 0.69]
Lo 2011 -3.13 14.8 25 -7.54 15.4 27 11.2% 0.29 [-0.26, 0.83]
Lum 2002 3.3 2.52 13 1.6 1.12 14 5.3% 0.86 [0.06, 1.65]
Lum 2006 6.98 1.8 24 6.5 2.5 6 4.2% 0.24 [-0.66, 1.14]
Masiero 2007 15.8 8.1 17 10.3 12.1 18 7.4% 0.52 [-0.16, 1.19]
Masiero 2011 1.83 1.4 11 1 0.7 10 4.2% 0.71 [-0.18, 1.60]
Rabadi 2008 62.21 4.9 10 65.44 5.41 10 4.1% -0.60 [-1.50, 0.30]
Volpe 2000 6 3.5 30 4 2 26 11.5% 0.68 [0.14, 1.22]
Volpe 2008 19.46 13.27 11 17.7 8.22 10 4.6% 0.15 [-0.71, 1.01]
Subtotal (95% CI) 284 226 100.0% 0.34 [0.16, 0.52]
Heterogeneity: Chi² = 36.39, df = 16 (P = 0.003); I² = 56%
Test for overall effect: Z = 3.62 (P = 0.0003)
1.1.11 Splinting
Lannin 2007 (extended) 0.7 1.4 21 0.4 1.8 11 39.6% 0.19 [-0.54, 0.92]
Lannin 2007 (neutral) 0.9 2 20 0.4 1.8 10 36.5% 0.25 [-0.51, 1.01]
Poole 1990 15.44 9.99 9 21.44 12.74 9 23.9% -0.50 [-1.44, 0.44]
Subtotal (95% CI) 50 30 100.0% 0.05 [-0.41, 0.51]
Heterogeneity: Chi² = 1.71, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)
1.1.12 Virtual reality
Crosbie 2008 52.8 6.9 9 50.2 18.9 9 8.2% 0.17 [-0.75, 1.10]
Housman 2009 24.9 7.4 14 19.6 6.7 14 11.9% 0.73 [-0.04, 1.50]
Jang 2005 30 8.05 5 20 8.05 5 3.6% 1.12 [-0.27, 2.51]
Piron 2007 51.4 9.8 25 45.4 9.3 13 15.0% 0.61 [-0.08, 1.30]
Piron 2008 53.6 7.7 18 49.5 4.8 18 15.6% 0.62 [-0.05, 1.30]
Piron 2010 49.7 10.1 27 46.5 9.7 20 20.8% 0.32 [-0.27, 0.90]
Saposnik 2010 -19.8 3.4 9 -27.4 8.7 7 5.9% 1.15 [0.06, 2.24]
Sucar 2009 30 12.4 11 26.36 2.33 11 9.8% 0.39 [-0.45, 1.24]
Yavuzer 2008 3 1.5 10 2.8 0.9 10 9.1% 0.15 [-0.72, 1.03]
Subtotal (95% CI) 128 107 100.0% 0.52 [0.25, 0.78]
Heterogeneity: Chi² = 4.20, df = 8 (P = 0.84); I² = 0%
Test for overall effect: Z = 3.82 (P = 0.0001)
Test for subgroup differences: Chi² = 77.73, df = 11 (P < 0.00001), I² = 85.8%
-4
-2
0
2
4
Favours control
Favours intervention

3.4.5 Evidence for effects of interventions: Hand function

Eleven of the thirteen interventions (see Figure 3-3) were suitable for including in the hand function analyses. The most common measures of hand function were various peg tests. The intervention categories of constraint-induced movement therapy and repetitive task training showed statistically significant results for improvement of hand function (SMD 0.39 95% CI 0.11-0.68) and (SMD 0.27 95% CI 0.06-0.47) respectively. The analysis for hand function is limited due to the small number of trials reporting hand function outcomes.

Figure 3-3 - Forest plot of 8 interventions targeted at hand recovery compared to control group

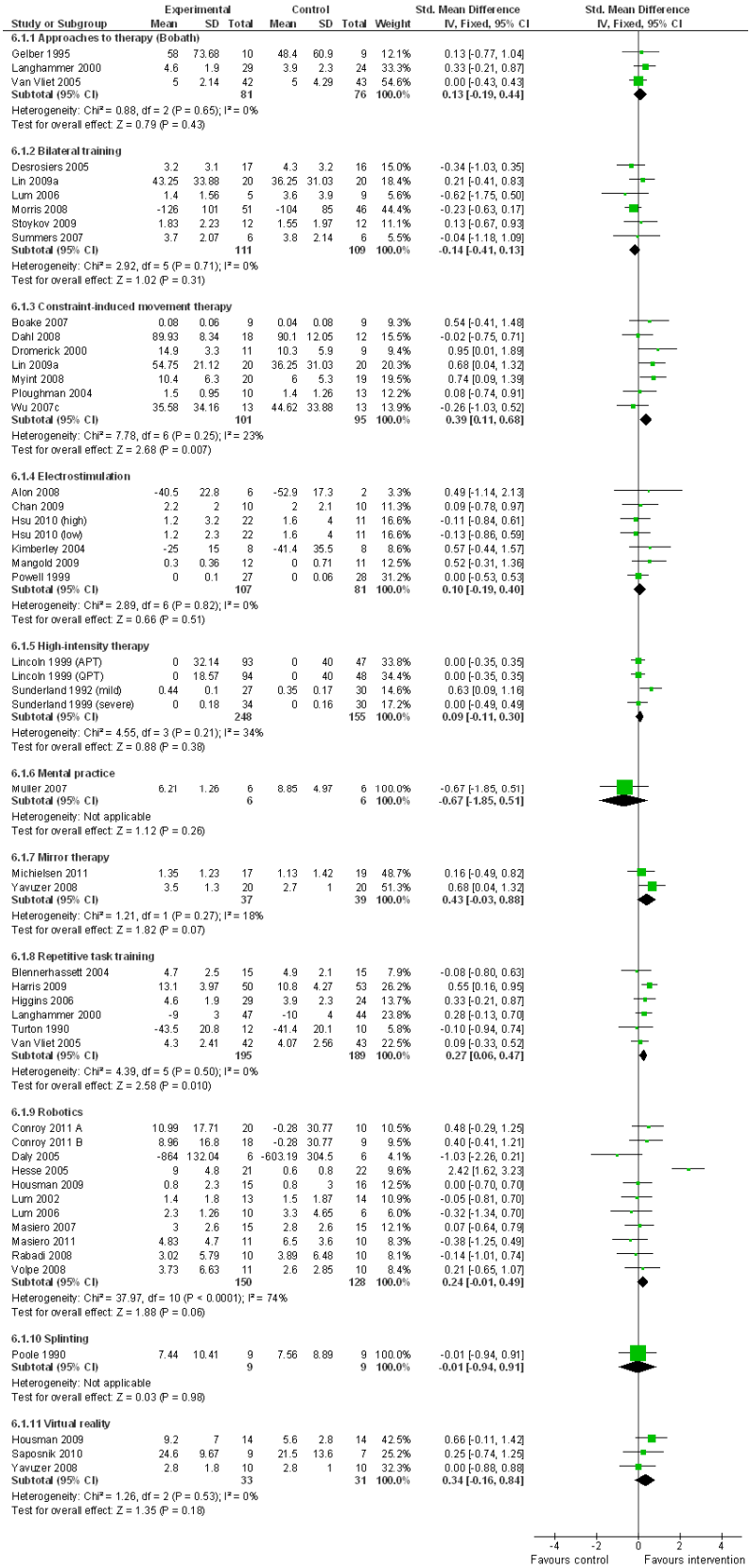


Table 3-3 - Summary of evidence for interventions aimed at promoting upper limb (arm and hand) recovery after stroke

Intervention	Evidence and considered judgement (n=recruited; n=analysed)	SMD (95% CI)	SIGN guideline recommendation	Comments
Approaches to therapy (Bobath)	**Arm function:** unknown effectiveness; 5 trials[169-173] (n=292; n=241) **Hand function**: unknown effectiveness; 3 trials[169;170;173] (n=208; n=157)	0.11 (-0.14-0.36) 0.13 (-0.19-0.44)	There is insufficient evidence to suggest that any one approach to therapy is more effective for improving upper limb function in stroke patients	Five RCTs identified. One trial[171] had two subgroups, which were analysed as different trials (thus the number of trials within forest plot for arm function is six)
Bilateral training	**Arm function:** unknown effectiveness; 10 trials[175-184] (n=327); 9 trials[176-184] in analysis (n=307; n=290) **Hand function:** unknown effectiveness; 6 trials[177;178;181-184] (n=237; n=220)	-0.12 (-0.35-0.12) -0.14 (-0.41-0.13)	There is insufficient evidence to recommend or refute bilateral training for improving arm function after stroke	Four RCTs[289-292] included in Cochrane review not included in this analysis as unsuitable outcomes. A further four studies[293-296] included in the Cochrane review not included in this review as unsuitable study design
Constraint-induced movement therapy	**Arm function:** likely to be beneficial; 23 trials[178;186-207] (n=719); 21 trials[178;187-193;195-207] in analysis (n=700; n=658) **Hand function:** likely to be beneficial; 7 trials[178;188;190;192;198;204;205] (n=217; n=196)	0.71 (0.54-0.87) (I^2=58.5%) 0.74 (0.44-1.03) (random effects model) 0.39 (0.11-0.68)	CIMT may be considered for carefully selected individuals with at least 10 degrees of finger extension, intact balance and cognition	Restrictive inclusion criteria for this intervention

EMG biofeedback	**Arm function:** likely to be beneficial; 4 trials[209-212] (n=126; n=126).	0.41 (0.05-0.77)	There is currently insufficient high quality evidence to support or refute the use of EMG biofeedback for improving upper limb function after stroke.	Data from review used – all identified as being measures of arm function and not split into arm and hand function
Electrostimulation	**Arm function:** likely to be beneficial; 19 trials[41;175;214-226;229-232] (n=532); 17 trials[175;214-225;229-232] in analysis (n=498; n=456) **Hand function:** unknown effectiveness 9 trials[41;218;221;224;225;227-230] (n=283); 6 trials[218;221;224;225;229;230] in analysis (n=223; n=188)	0.30 (0.11-0.50) (I^2=70%) 0.40 (0.02-0.77) (random effects model) 0.10 (-0.19-0.40)	There is currently insufficient high quality evidence to support or refute the use of electrostimulation for improving upper limb function after stroke.	17 RCTs identified. One trial[229] had two subgroups, which were analysed as different trials (thus the number of trials within forest plot is 18 for arm function and seven for hand function)
Hands-on therapy interventions	**Arm function:** unknown effectiveness; 3 trials[234-236] (n=86). No trials included in a meta-analysis	Not applicable	Not reviewed in guideline.	The authors of the Cochrane review concluded that the limited evidence of benefit of stretching, passive exercises and mobilisation, merits further research
High-intensity therapy	**Arm function:** unknown effectiveness; 4 trials[51;238-240] (n=612; n=571) **Hand function:** unknown effectiveness; 2 trials[239;240] (n=419; n=403)	-0.09 (-0.26-0.08) (I^2=59.5%) -0.09 (-0.36-0.18) (random effects model) 0.09 (-0.11-0.30)	Increased intensity of therapy for improving upper limb function in stroke patients is not recommended.	Four RCTs identified. Two trials[239;240] had two subgroups each, which were analysed as different trials (thus the number of trials within forest-plot is six for arm function and four for hand function)

Mental practice with motor imagery	**Arm function:** likely to be beneficial; 5 trials[243-247] (n=102; n=102) **Hand function:** unknown effectiveness; 1 trial[242] (n=12; n=12)	1.16 (0.71-1.60) (I^2=59.5%) 1.37 (0.60-2.15) (random effects model) -0.67 (-1.85-0.51)	Mental practice may be considered as an adjunct to normal practice to improve upper limb function after stroke.	
Mirror therapy	**Arm function:** likely to be beneficial; 5 trials[249-253] (n=153); 4 trials[249;250;252;253] in analysis (n=137; n=121) **Hand function:** unknown effectiveness 2 trials[252;253] (n=80; n=76)	0.41 (0.05-0.77) 0.43 (-0.03-0.88)	Not reviewed in guideline.	
Repetitive task training	**Arm function:** likely to be beneficial; 9 trials[62;170;173;238;255-259] (n=570; n=515) **Hand function:** likely to be beneficial; 6 trials[170;173;255-257;259] (n=427; n=384)	0.23 (0.06-0.41) 0.27 (0.06-0.47)	Repetitive task training is not routinely recommended for improving upper limb function.	
Electromechanical/Robotic devices	**Arm function:** likely to be beneficial; 16 trials[181;261-272;274;275] (n=553); 15 trials[181;262-275] in analysis (n=522; n=510) **Hand function:** unknown effectiveness 11 trials[181;262;264;266-269;271;272;274;275] (n=366); 10 trials in analysis[181;262;264;266;267;269;271;272;274;275]; n=310; n=278)	0.34 (0.16-0.52) (I^2=59%) 0.30 (0.02-0.58) (random effects model) 0.19 (-0.30-0.68) (I^2=74%) 0.24 (-0.01-0.49) (random effects model)	Electromechanical/robotic devices may be considered to improve arm motor function and motor strength in selected patients where the necessary equipment is already available and healthcare professionals are competent in the use of the equipment.	15 RCTs identified. Two trials[270;271] had 2 subgroups each, which were analysed as different trials (thus the number of trials within forest plot is 17 for arm function and 11 for hand function). One RCT[273] was a much larger study (n=127) than reported here. However only the comparison of robot-assisted therapy vs. usual care was used in this review One RCT[297] included in Cochrane review was excluded from this review as not suitable comparator. Two RCTs[265;266] not included in Cochrane review analysis

Splinting	**Arm function:** unknown effectiveness; 3 trials[277-279] (n=109); 2 trials[278;279] in analysis (n=81; n=80) **Hand function:** unknown effectiveness; 2 trials[277;278] (n=46); 1 trial[278] included in analysis (n=18; n=18)	0.05 (-0.41-0.51) -0.01 (-0.94-0.91)	Splinting is not recommended for improving upper limb function.	One trial[279] had two subgroups, which were analysed as different trials (thus the number of trials within forest plot is three for arm function)
Virtual reality	**Arm function:** likely to be beneficial; 9 trials[272;281-288] (n=250; n=235) **Hand function:** unknown effectiveness; 3 trials[272;286;288] (n=76; n=64)	0.52 (0.25-0.78) 0.34 (-0.16-0.84)	Due to the limited amount of high quality evidence and heterogeneity between the studies conclusions about the effects of virtual reality cannot be made.	Two trials[282;288] not included in Cochrane review analysis

3.4.6 Evidence in context

In addition to the meta-analyses outlined above in Figure 3-2 and Figure 3-3, a semi-quantitative classification of effectiveness (Table 3-3) was also carried out. This process involved classifying the effect of each intervention on the basis of published criteria[167]. These conclusions were also compared with the findings of the most recently published SIGN guidelines[33]. Generally, the considered judgement categories match those of the meta-analyses. With regard to consistency between the findings of this review and the clinical practice guidelines, discrepancies exist with regard to the interventions of EMG biofeedback, electrostimulation and repetitive task training; the guidelines suggest that these interventions should not be used on a routine basis. Additionally, no comment was made about the intervention of mirror therapy within the SIGN guidelines. These discrepancies could be related to differences in the way in which trial evidence was combined and analysed, the amount of evidence available at the time of publication of the guidelines or because of the process of considered judgement undertaken by clinical guideline review panels, which takes into account a number of factors including perceived applicability and availability of a particular intervention.

3.5 Discussion

3.5.1 Summary of findings

This systematic review and meta-analysis identified a broad range of interventions which have been developed to assist motor recovery (movement and related functions) of the upper limb (arm and hand function). In addition to the thirteen interventions reported in this review other interventions have been investigated in the literature, such as transcranial direct current stimulation[298], however those not included did not meet the original criteria for the review and/or were felt to be interventions still very

much in their infancy or not easily translated into routine physiotherapy or occupational therapy clinical practice.

Eight of thirteen interventions suggest potential benefit in improving arm function. However, when considering only outcomes relating to hand function only constraint-induced movement therapy and repetitive task training were found to suggest a beneficial effect. Very limited evidence was available relating specifically to hand function. The effect sizes were, in general, similar to that of arm function; however fewer trails were available for hand function outcomes, limiting statistical power.

Despite a number of interventions suggesting a potential beneficial effect on arm function, a number of issues limit the validity of these conclusions. In general, the results for constraint-induced movement therapy seem the most robust for the following reasons; the effect size (SMD) was large, the quality of the trials was high (Table 3-2) and a relatively large number of trials and participants were included, including one multi-centre study[201]. However applicability conclusions for this intervention are limited due to the variety of the CIMT approaches studied between the included trials and the fact that all trials focused on very selected populations (e.g. those with limited arm impairment and/or cognitively intact). Additionally constraint-induced movement therapy is a resource and time intensive intervention, which presents a challenge to compliance and applicability to routine clinical practice. Modifications to the original CIMT protocol are now being investigated with the aim of developing a more widely applicable intervention.

Trials of EMG biofeedback and mirror therapy are particularly limited by their small size. In addition, the EMG biofeedback trials reported low levels of use of a blinded outcome assessor and inadequate allocation concealment. Trials of mental practice and virtual reality have relatively high and moderate effect sizes respectively, but are again limited by small numbers of participants. Owing to these limitations, the results from the analyses of EMG biofeedback, mirror therapy, mental practice and virtual reality could be overturned by new, larger trials. The effect size for electromechanical

/robotic devices was relatively low, however a relatively large number of trials and participants were included in the analysis of this intervention category. However, general applicable conclusions are again limited due to the different devices and patient groups studied. Additionally, there is a lack of available evidence for most of the identified interventions, with regard to their effectiveness in a routine clinical setting. The intervention of repetitive task training, which also suggested a beneficial effect is limited due to the differing interventions studied within this intervention category; however, there is evidence to suggest such interventions could be more generally applied to routine clinical settings.

Of the interventions that have been identified which suggest a beneficial effect on upper limb (arm) motor recovery, most appear to include the characteristics of intensive, repetitive, task-specific practice (CIMT, mental practice, repetitive task training, robotics and virtual reality). Therefore, it is suggested that the elements of intensive, repetitive task-specific practice might be the most effective principles to include in interventions when trying to promote upper limb motor recovery following stroke.

It has also been found that despite a number of systematic reviews and randomised controlled trials relating to interventions targeting upper limb motor recovery following stroke being available, much further evaluation of these interventions is required. At present the only conclusions that can be drawn from the available evidence are that some interventions show a suggestion of beneficial outcome and that many of these interventions share similar characteristics. Further evaluation would allow for conclusions to be drawn regarding interventions for specific problems in specific patients and allow for translation of the evidence into broad, practical recommendations for the wider stroke population.

3.5.2 Limitations of the review

The main weaknesses of this review relate to the heterogeneity of the available data. For this reason the evidence from this review could not

provide guidance on which intervention should be given to a particular patient in a particular situation.

Within and between the thirteen identified interventions there were substantial differences in terms of the populations studied, the type, amount and duration of intervention delivered and control comparators and outcome measures used. Differences were also apparent in the methodological quality of the RCTs and several had methodological limitations. The quality of reporting in the trials was often identified to be poor. This limits confidence in the findings and makes interpretation of the findings problematic.

A range of outcome measures were used and combined in the analyses of this review to lead to a standardised effect measure in terms of the broad outcome of recovery of upper limb motor function, for each intervention category. Due to the heterogeneity of the available evidence some intervention categories were considered more in terms of motor impairment and others in terms of outcomes more relating to motor function. Therefore, direct comparisons between intervention categories may be problematic. However, due to the continuum which has been shown to exist between outcomes of motor impairment and motor function[299] the suggestion of effect for each intervention in this review is valid.

Lastly, even the trials which were found to have better methodological rigour (i.e. have good internal validity) were generally small in size, recruited selected populations and used outcome measures at the level of impairment or limb function. There are still only a few multicentre randomised trials that have tested interventions in routine clinical settings on relatively large numbers of patients and that have used outcome measures targeted at functional ability.

3.5.3 Strengths of the review

The main strengths of this review, which took a broad overview approach, relate to the comprehensive methods which were used to attempt to identify and synthesise all relevant, high-quality evidence relating to interventions targeting upper limb motor recovery.

Only systematic reviews of randomised controlled trials or individual RCTs were included in this review; such types of methodologies are the least likely to provide biased estimates of effect, increasing confidence in the conclusions gained. Thorough searching was used to identify all relevant systematic reviews and trials to ensure a comprehensive overview, which is an additional strength of this review.

As far as possible, an explicit and unbiased approach to data analysis was undertaken, and any conclusions were considered with reference to the key methodological features of the identified evidence. In an attempt to provide a contextual overview of the evidence, the conclusions of the meta-analyses were considered alongside a semi-quantitative assessment (considered judgement) and further cross-referencing to the most recent clinical guidelines. This also limited the amount of emphasis placed on the meta-analyses alone, as data from such could be limited due to the heterogeneity of the available evidence.

3.5.4 Implications for practice

The evidence from this review can only provide broad, indicative guidance due to the gaps that still exist in the evidence base of interventions to improve upper limb motor recovery and function after stroke. To a large extent, individual clinical decisions will continue to rely on the clinical reasoning of individual therapists. The general conclusion of this review is that interventions to improve upper limb motor recovery should (as much as possible) include elements of high-intensity, repetitive task-specific practice.

3.5.5 Implications for research

Research within this area is required to further define the interventions that carry benefit, to quantify that benefit within a routine clinical setting and to define the target populations for these interventions. Additional research is also required about how the complex interventions, identified in this review can be implemented into routine clinical settings.

Future research should focus on randomised controlled trials with key methodological elements (i.e. randomisation, allocation concealment, blinding of outcome assessor, intention-to-treat analysis) present and reported to reduce the risk of bias and increase confidence in the findings.

A wide range of outcome measures, used in the included trials were identified in this review. In order to enable comparison between interventions there is a real need for RCTs in this area to focus on a smaller number of robust, standardised and relevant outcome measures.

3.6 Conclusions

This systematic review provides a relatively concise and informative overview of the current available evidence relating to interventions for improving upper limb motor recovery following stroke.

There is evidence that several interventions might be beneficial or at least show promise for improving upper limb motor recovery following stroke. The most promising intervention for upper limb (arm) function appears to be constraint-induced movement therapy. Seven other interventions also suggest a promising effect. Among these seven promising interventions are electromechanical/robotic devices which, in contrast to some of the other interventions, potentially offer a less resource intensive approach to providing more intensive, repetitive therapy. Electromechanical/robotic devices are of particular interest at present and it is an area with many opportunities, and one which is constantly developing.

The limitations of this review, which particularly relate to heterogeneity of the available data, limit the conclusions that can be drawn. However, this review does appear to suggest that interventions with elements of intensive, repetitive, task-specific practice are beneficial for improving upper limb recovery after stroke.

Chapter 4

Systematic review of simultaneous bilateral training for improving arm function after stroke

Chapter 4 Systematic review of simultaneous bilateral training for improving arm function after stroke

4.1 Introduction

In Chapter 3 a number of interventions, targeted at upper limb recovery were investigated. A number of these interventions had been or were in the process of being systematically reviewed by Cochrane systematic reviews. Prior to the update (September 2011) of the review reported in Chapter 3 , bilateral training was identified as one intervention which still required rigorous systematic evaluation. The results gained from Chapter 4 (this chapter) were subsequently used in the update of Chapter 3 .

The process of systematic reviews was introduced in Chapter 2 . Systematic reviews of interventions are considered to be the highest level of evidence[160]. Therefore, subjecting interventions to the rigours of systematic evaluation will give the most explicit information about the specific effects of that intervention.

4.1.1 Cochrane reviews

Cochrane reviews are systematic reviews of primary research, through which effects of intervention are reviewed using predefined, rigorous and explicit methodology. Cochrane reviews are generally accepted as the highest standard in evidence-based health care and therefore to add to the evidence base of upper limb interventions I decided to complete a Cochrane systematic review of a specific intervention. Therefore, a Cochrane systematic review of bilateral training was completed.

4.1.2 Bilateral training

Simultaneous bilateral training involves the execution of identical activities with both arms simultaneously but independently[300]. Beneficial effects of bilateral training are assumed to arise from an interlimb coupling effect, in which the non-paretic arm facilitates movements in the impaired limb[182;301;302]. It has been further suggested[176;303] that bilateral practice of synchronous movements with the paretic and non-paretic limbs allows activation of the intact hemisphere to facilitate activation of the damaged hemisphere through enhanced interhemispheric inhibition. Bilateral training is often combined with other interventions, such as electrostimulation or assistive technology, to assist the affected arm to undertake the simultaneous movements.

Two reviews[304;305] have reported favourable effects of bilateral training. These reviews however, included studies other than randomised controlled trials (RCTs) and both acknowledged that there are inconsistencies across bilateral training studies. A further, more recent narrative review of bilateral training[306] suggested that bilateral studies have not shown improvements in all patients and that bilateral training has not been found to be more beneficial than other training approaches. However, this review was not systematic and included a range of study designs, including single case studies.

This current review sought to undertake a complete, up to date, systematic review of randomised controlled trials to determine the effects of bilateral training.

4.2 Objectives

To determine the effects of simultaneous bilateral training for improving arm function after stroke compared with:

- Placebo or no intervention

- Usual care
- Other specific upper limb interventions or programmes.

4.3 Methods

Cochrane guidelines for systematic reviews of interventions were used to complete and report this review[307].

4.3.1 Eligibility criteria

Types of studies

Only RCTs (that is, each participant is allocated to one of the available treatment groups at random (like the toss of a coin), where one of the groups was a control (comparator) group, for example ‘usual care’) were included. Only the first phases of cross-over studies were included to exclude any carry-over or learning effects.

One of the intervention groups must have included simultaneous bilateral training (see definition in Types of interventions), compared to another group, consisting of either: no-treatment, placebo, usual ('conventional' or 'traditional') care, or another specific upper limb intervention or programme.

Types of participants

Trials of participants with a clinical diagnosis of stroke, regardless of time since onset, initial upper limb impairment, ability to follow instructions, co-morbidities, previous strokes or location of stroke were included. Randomised controlled trials with participants with other neurological conditions were included if more than 75% of participants were stroke patients.

Types of interventions

Only trials which included simultaneous bilateral training were considered. The definition of simultaneous bilateral training used, was; 'when a motor activity is completed at the same time by both upper limbs independently'[300].

Trials that investigated simultaneous bilateral training in conjunction with another intervention (e.g. assistive technology such as machine, a robot or electrical stimulation) and compared to a control group, for example, simultaneous bilateral training and electrical stimulation compared to a control group were excluded. This was to ensure that the treatment effect under investigation was bilateral training. However, studies where assistive technology was given to both an intervention (bilateral training) and control (unilateral training) group were included, as in these cases it is the bilateral component of the training which is the active treatment under investigation, and not the assistive technology. Similarly, trials which investigated bilateral training completed using assistive technology which was compared with a control intervention, also completed using assistive technology were also included. Any duration or intensity of programme was included.

For studies comparing simultaneous bilateral training with 'usual care', any control intervention considered by the original trial authors to be a normal or usual component of stroke rehabilitation was accepted. The description of 'usual care', where this was provided by the authors, was documented.

Types of comparisons to be made

Three comparisons were investigated:

1. Simultaneous bilateral training versus placebo or no intervention
2. Simultaneous bilateral training versus usual care
3. Simultaneous bilateral training versus other specific upper limb interventions or programmes

Where trials included another intervention as an adjunct to bilateral training, which was also delivered to the control group, these studies were included in the appropriate comparison groups as listed above, regardless of the adjunct intervention. For example, comparisons of (i) robot-assisted simultaneous bilateral training versus robot-assisted unilateral training or (ii) simultaneous bilateral training plus electrical stimulation versus unilateral training plus electrical stimulation would both be included in comparison 3 (simultaneous

bilateral training versus other specific upper limb interventions). A sensitivity analysis was completed to explore the effect of including studies where the simultaneous bilateral training was combined with another intervention.

Types of outcome measures

The primary or initial aim of upper limb interventions is usually to improve functional movement and reduce impairment. However, arguably the most important goal for patients is to improve their ability to participate in and achieve independence with activities of daily living. Additionally, this is the over-arching aim of all rehabilitation interventions. Therefore, two primary outcomes of interest were identified for this review: performance in activities of daily living and functional movement of the upper limb. The primary outcomes of interest were (1) Performance in activities of daily living (ADL) and (2) Functional movement of the upper limb.

It was anticipated that the studies would use and report a large variety of different outcome measures relevant to the primary and secondary outcomes of this review. Therefore, for each outcome of interest (primary and secondary) an attempt was made to identify and list all the common, specific measurement tools or scales that could be included. If a study was identified which reported more than one measurement tool or scale, addressing the same outcome, the scale listed earliest in the hierarchical lists was used. If a study did not use any of the measures in the list, but measured the outcome using a different measurement tool or scale this was included and documented. The hierarchical lists are given below under each outcome.

Primary outcomes

Performance in activities of daily living (including feeding, dressing, bathing, toileting, simple mobility and transfers). Common outcome measures of global measures of activities of daily living include: Barthel Index (BI)[82], Rivermead ADL assessment[308], Rankin Scale[83], Functional Independence Measure (FIM)[84].

Functional movement of the upper limb (such as measures of active movement, co-ordination, dexterity, manipulation, grasp/grip/pinch). Common outcome measures include: Action Research Arm Test (ARAT)[85], Motor Assessment Scale (MAS) - upper arm function or combined arm score[86], Frenchay Arm Test (FAT)[161], Wolf Motor Function Test (WMFT)[309], Functional Test of the Hemiparetic Upper Extremity[310], Box and Block Test (BBT)[87], Upper extremity performance test for the elderly (TEMPA)[311], Chedoke arm and hand activity inventory[312], Sodring Motor Evaluation of stroke patients - arm section[313], Motor Activity Log (MAL)[199], Motor Assessment hand movement or advanced hand movement scales[86], Jebsen Hand Function Test[314], Nine Hole Peg Test (NHPT)[162] and Purdue Peg Test[315].

Secondary outcomes

Performance in extended activities of daily living (including shopping, household tasks). Common outcome measures: Nottingham Extended Activities of Daily Living[316], Rivermead Extended Activities of Daily Living[317], Frenchay Activities Index[318].

Motor impairment of the upper limb (measures/scales of upper limb impairment, muscle strength, muscle tone). Common outcome measures include: Fugl-Meyer (F-M) Assessment of Sensorimotor Recovery after Stroke (upper limb section)[88], Motricity Index (MI)[163], Rivermead motor assessment (arm section)[319], Motor Club Assessment[320], Ashworth Scale[321]/Modified Ashworth Scale[322], MRC scale[323], Dynamometer scores (including Jamar)[324], kinematic measures (e.g. movement time, movement efficiency, movement speed, spatial accuracy, velocity).

Additional outcomes

Adverse events (e.g. death, shoulder pain/subluxation).

Outcomes from the end of the intervention period were used for analysis as the primary aim of this review was to determine whether bilateral training had any immediate beneficial treatment effect.

4.3.2 Search methods for identification of studies

To identify appropriate studies the following resources were searched:

- The Cochrane Stroke Group Trials Register was searched by the Managing Editor (August 2009)
- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 3, 2009)
- MEDLINE (1966 to August 2009)
- EMBASE (1980 to August 2009)
- CINAHL (1982 to August 2009)
- AMED (1985 to August 2009)

The following occupational therapy and physiotherapy databases were searched: OTseeker (http://www.otseeker.com/) (August 2009), Physiotherapy Evidence database (PEDro, http://www.pedro.fhs.usyd.edu.au/index.html), Chartered Society of Physiotherapy Research Database (August 2009) and REHABDATA (http://www.naric.com/research/rehab/default.cfm) (August 2009).

Search strategies were developed in consultation with the Cochrane Stroke Group's Trials Search coordinator.

Search strategy (MEDLINE)

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or cerebrovascular accident/ or exp brain infarction/ or exp cerebrovascular trauma/ or exp hypoxia-ischemia, brain/ or exp intracranial arterial diseases/ or intracranial arteriovenous malformations/ or exp "Intracranial Embolism and Thrombosis"/ or exp intracranial hemorrhages/ or vasospasm, intracranial/ or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.

3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. hemiplegia/ or exp paresis/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. *cerebrovascular disorders/rh or exp *basal ganglia cerebrovascular disease/rh or exp *brain ischemia/rh or exp *carotid artery diseases/rh or *cerebrovascular accident/rh or exp *brain infarction/rh or exp *cerebrovascular trauma/rh or exp *hypoxia-ischemia, brain/rh or exp *intracranial arterial diseases/rh or *intracranial arteriovenous malformations/rh or exp *"Intracranial Embolism and Thrombosis"/rh or exp *intracranial hemorrhages/rh or *vasospasm, intracranial/rh or *vertebral artery dissection/rh
9. *hemiplegia/rh or exp *paresis/rh
10. 8 or 9
11. exp Upper Extremity/
12. (upper adj3 (limb$ or extremity)).tw.
13. (arm or shoulder or elbow or forearm or hand or wrist or finger or fingers).tw.
14. 11 or 12 or 13
15. rehabilitation/ or "recovery of function"/
16. physical therapy modalities/ or "Physical Therapy (Specialty)"/
17. exercise movement techniques/ or exercise/ or exercise therapy/
18. range of motion, articular/ or movement/ or motor activity/ or kinesiology, applied/
19. "task performance and analysis"/
20. occupational therapy/ or activities of daily living/
21. "Physical Education and Training"/ or motor skills/
22. (rehabilitation or recovery of function or physiotherap$ or physical therap$ or exercise$ or movement$ or motor activit$ or occupational therap$ or activities of daily living or adl).tw.

23. ((bilateral or bimanual) adj5 (train$ or retrain$ or facilitat$ or function$ or activit$)).tw.
24. ((mirror$ or coupled) adj5 movement$).tw
25. or/15-24
26. 10 and 14
27. 7 and 14 and 25
28. 26 or 27
29. limit 28 to humans

This search strategy was adapted for other databases.

In an effort to identify further published, unpublished and ongoing trials the following were also searched:

- Reference lists of all included studies and review papers
- ClinicalTrials.gov (http://www.clinicaltrials.gov/) and the National Research Register Archive (http://portal.niht.ac.uk/Pages/NNRArchive.aspx) (last searched February 2009)
- Science Citation Index Reference Search to track relevant papers (last searched February 2009)
- ProQuest Dissertations and Theses (PQDT) dissertation abstracts (lat searched February 2009)
- Index to Theses – dissertation abstracts (last searched September 2009)

4.3.3 Identification of relevant trials

Initially I read all identified titles and excluded any obviously irrelevant studies. The abstracts for the remaining studies were then obtained and, based on the inclusion criteria, two reviewers independently ranked these as 'possibly relevant' or 'definitely irrelevant'. If both reviewers identified a trial as 'definitely irrelevant' the study was excluded but all other trials were included at this stage. Consensus discussions were then held, with

assistance of additional reviewers, where appropriate and further studies were excluded. The full text of the remaining trials were then retrieved and reviewed by two independent reviewers. Where disagreement occurred between review authors, or a decision could not be reached, consensus was reached through discussion and/or the opinion of a third reviewer was sought.

4.3.4 Data extraction

Two reviewers independently performed data extraction. Where the information was provided the following information was extracted:

1. Trial setting
2. Participant details (age, gender, type of stroke, time since stroke)
3. Inclusion and exclusion criteria
4. Duration or intensity of the intervention
5. Description of the bilateral training intervention (including movement activities completed, number of repetitions, feedback provided, goals), as reported;
6. Comparison intervention
7. Outcomes

4.3.5 Documentation of methodological quality

Two reviewers independently assessed the methodological quality of the trials. Assessment of the quality of studies focused on potential areas of bias within the studies, as this has been shown to affect the estimation of effectiveness of interventions[164]. The following areas were considered and documented, where the information was available:

1. Methods, including method of randomisation
2. Allocation concealment
3. Blinding of outcome assessor
4. Intention-to-treat

5. Baseline similarity
6. Number of patients lost to follow-up
7. Other possible sources of bias

Consideration of blinding of participants and therapists led to the conclusion that blinding would not be possible in these types of trials; consequently this information was not documented.

Any disagreements between reviewers were resolved through discussion, involving a third reviewer, if necessary.

4.3.6 Data analysis

For each comparison the study results for performance in activities of daily living (ADL), measures of functional movement, measures of motor impairment, and adverse effects were used, if documented. The Cochrane Collaboration's Review Manager software, RevMan 5, was used for all analyses[165].

All outcome measures were analysed as continuous data. The standardised mean differences (SMD) and 95% confidence intervals were calculated. Heterogeneity was determined using the I-squared (I^2) statistic ($I^2 > 50\%$ considered substantial heterogeneity)[307]. If $I^2 \leqq 50\%$ a fixed-effect meta-analysis approach was used[325]. If $I^2 > 50\%$ individual trial characteristics were explored to identify potential sources of heterogeneity. Meta-analysis was then performed using both fixed-effect and random-effects[326] modelling to assess sensitivity to the choice of modelling approach.

Subgroup analyses, following Deeks method[327](a simple approach for a significance test to investigate differences between two or more subgroups and is the standard method in Revman), on differences between acute (time at entry to trials less than three months post-stroke) and chronic (time at entry to trials equal to or more than three months) patients, duration (intervention for less than four weeks and intervention equal to or more than

five days per week) and number of repetitions of the programme were planned. These subgroup analyses were to be undertaken where data permitted (sufficient data considered to be more than five trials reporting the information) and undertaken on the primary outcome only. A sensitivity analysis based on methodological quality of studies was also planned, where data allowed.

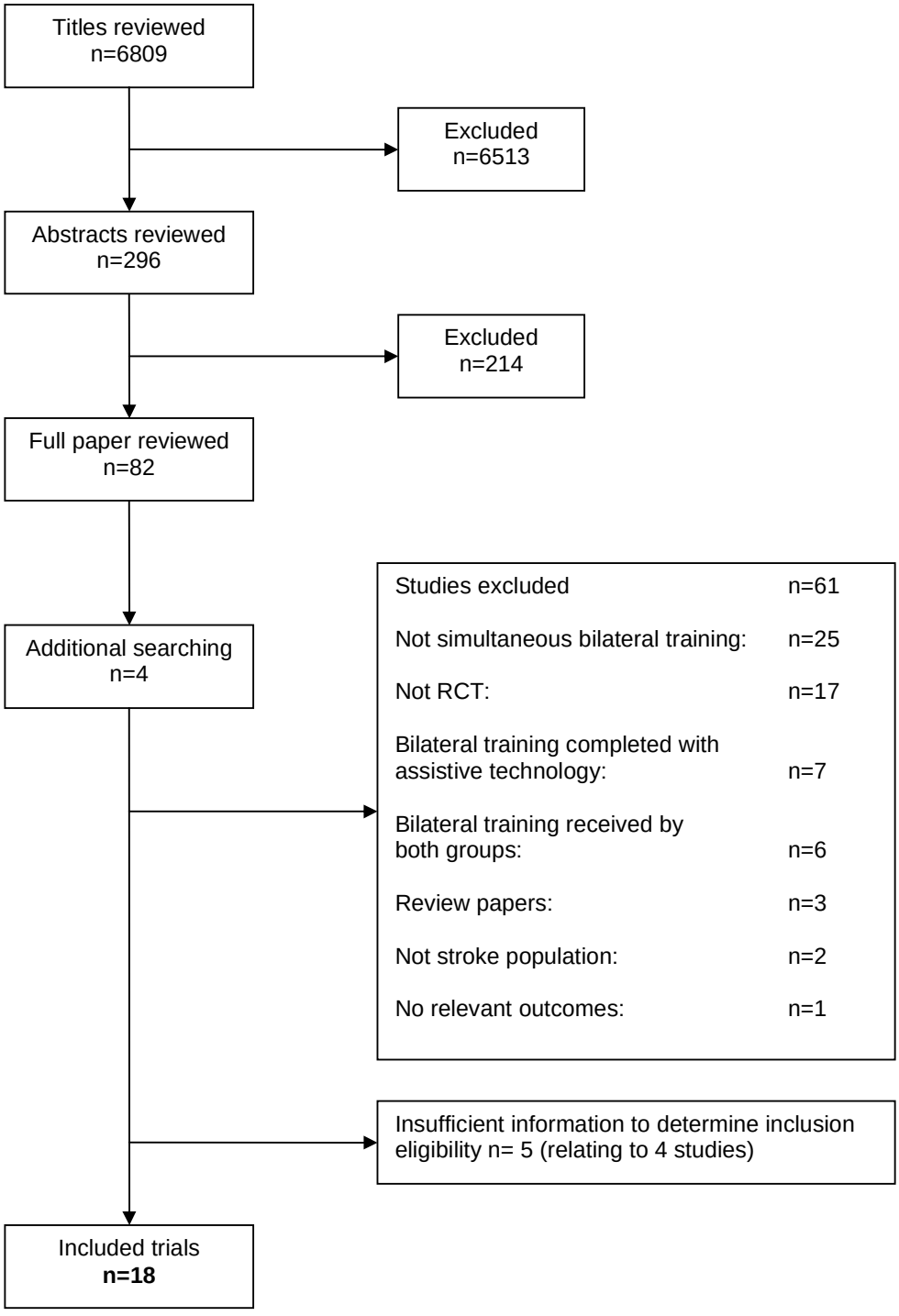
4.4 Results

4.4.1 Results of the search

A flow diagram of study selection is presented (Figure 4-1). Searching identified 6809 titles. After elimination of duplicates and obviously irrelevant studies 296 possibly relevant abstracts were identified. These 296 abstracts were independently assessed for inclusion by two reviewers. Eighty two abstracts were assessed as 'include' and the full papers of these studies were obtained. Of these 82 full papers, 61 were excluded; there was insufficient information to determine inclusion eligibility for five papers (referring to four studies); leaving 16 studies for inclusion. In addition, four ongoing trials were identified from searching additional databases. Contact with the principal investigator led to the identification of a relevant publication from one of these trials[183]. Published data relating to a further ongoing study[179] was identified from a journal online (ahead of print). These trials were assessed as relevant for inclusion. Thus, a total of 18 trials were included.

Contact with authors identified that two of the included trials[178;179] are still recruiting patients. However, as published data was available for both of these ongoing trials it was decided that it was appropriate to include these preliminary data within this review.

Figure 4-1 – Study selection flow diagram



4.4.2 Included studies

Eighteen trials (549 randomised stroke participants, of which 528 were relevant to this review (21 participants were randomised to additional groups not relevant to this review)) met the inclusion criteria for this review[175-184;289-296]. One study[291] reported data divided into two groups - acute and chronic. A brief description of the studies is presented below. Descriptions of the included studies can be found in Table 4-1 which provides a brief overview of characteristics of included studies and Appendix D which gives a full description of the studies.

Table 4-1 - Characteristics of included studies (abbreviated)

Study	Methods	Participants	Interventions	Relevant Outcomes
Cauraugh 2002[175]	RCT	N=25 (20 relevant to this review)	Group 1 (n=10) – unilateral training + EMG triggered stimulation Group 2 (n=10) - bilateral training + EMG triggered stimulation	BBT Premotor reaction time Muscle activity (EMG activity of wrist/fingers extensor muscles)
Cauraugh 2003a[289]	RCT	N=20	Group 1(n=10) - unilateral training + EMG triggered stimulation Group 2 (n=10) – bilateral training + EMG triggered stimulation	EMG activity level (wrist and finger extensor muscles)
Cauraugh 2005[290]	RCT	N=21	Group 1 (n=10) – unilateral training + EMG triggered stimulation Group 2 (n=11) - bilateral training + EMG triggered stimulation	Movement time for single aiming test recorded by EMG
Cauraugh 2008[176]	Randomly assigned to one of two treatment orders	N=16	Group 1(n=8) – unilateral training + EMG triggered neuromuscular stimulation Group 2(n=8) - bilateral training + EMG triggered neuromuscular stimulation	BBT Motor reaction time Maximal isometric contraction of wrist/finger extensors
Chang 2006[293]	Randomised cross-over design	N=20	Three movement tasks (i) reaching forward with affected limb (unilateral) (ii) reaching forward with both limbs simultaneously (bilateral) (iii) reaching forward with both limbs simultaneously + load applied to non -affected upper limb (bilateral + load).	Movement time of elbow flexion Elbow flexion-extension range
Desrosiers 2005[177]	RCT	N=41	Group 1 (n= 21) - usual care Group 2 (n= 20) – bilateral training	Measure de l'independence fonctionelle (FIM) BBT Purdue Pegboard Test F-M (upper limb section) Finger to nose (Number of movements) Grip strength

Dickstein 1993[294]	Randomised cross-over design	N=25	One familiarisation set of unilateral movements with unaffected arm, then 3 sets of movements presented in a random order (unilateral (unaffected), unilateral (affected) or bilateral) + auditory signal	Movement time of elbow flexion
Harris-Love 2005[295]	Randomised cross-over design	N=32	Four trials each of unilateral paretic, unilateral nonparetic and bilateral reaching, then 4 trials of 6 reaching tasks (unilateral paretic, unilateral nonparetic, bilateral reaching and 3 bilateral reaching tasks involving different loads added to the nonparetic hand)	Movement time of reaching task
Kilbreath 2006[296]	Randomised cross-over design	N=13	Two bimanual and one unimanual task	Movement time for specified reaching task
Lin 2009a[178]	RCT using stratified block allocation scheme	N=60	Group 1 (n= 20) - usual care. Group 2 (n= 20) – other upper limb intervention; Constraint–induced therapy (CIT) Group 3 (n=20) bilateral training	FIM MAL (amount of use) Stroke Impact Scale – hand function section Stroke Impact Scale (ADL/IADL section) F-M Meyer Scale (UL section)
Lin 2009b[179]	RCT	N=33	Group 1 (n= 17) - usual care. Group 2 (n= 16) – bilateral training	FIM MAL (amount of use) F-M Scale (UL section) Movement time for unilateral task Normalised total distance
Luft 2004[180]	RCT	N=21	Group 1 (n=12) - usual care Group 2 (n=9) - bilateral training with auditory cueing (BATRAC)	Wolf Motor Arm Test F-M (UL section) Wolf Motor Arm Test (strength)
Lum 2006[181]	Restricted RCT	N=30 (14 relevant to this review)	Group 1 (n=9) - robot-unilateral group Group 2 (n=5) - robot-bilateral group	FIM F-M (proximal UL section) Motor power examination
Morris 2008[182]	RCT	N=106	Group 1 (n=50) – unilateral training Group 2 (n=56) – bilateral training	BI ARAT NHPT Rivermead Motor Assessment (UL section)

Mudie 2001[291] (acute and chronic)	RCT with blocked randomisation according to side of stroke	N=36	Group 1 (n=18) – unilateral isometric contractions Group 2 (n=18) – bilateral isometric contractions	Muscle activity (EMG) for wrist extension
Platz 2001[292]	RCT	N=14	Group 1 (n=18) - unilateral training Group 2 (n=18) - bilateral training	Total movement time (ms) Spatial error (mm)
Stoykov 2009[183]	RCT stratified into 2 impairment levels	N=24	Group 1 (n=12): unilateral training Group 2 (n=12) – bilateral training	MAS (Upper arm scores) MAS (Hand movements) Motor Status Score (Total scale) Arm strength outcome
Summers 2007[184]	RCT	N=12	Group 1 (n=6) – unilateral training Group 2 (n=6) – bilateral training	Modified MAS (upper arm function) Modified MAS (hand movement scores) Movement time of dowel placement Elbow angle

Study Design

Fourteen[175;176;178-184;289-292;311] of the 18 included studies were randomised controlled trials. Four studies[293-296] were randomised cross-over design studies with random allocation to the order of treatment sequence. These studies are not traditional RCTs in the sense that participants are randomly allocated to one (or more) groups. Within these studies the participants were randomised to different treatment orders. No data were available for the first phases only, within the published studies; therefore these four studies are not incorporated in any of the analyses. Despite not being appropriate for incorporation in the data analysis these studies met the inclusion criteria for this review. Details of these four crossover studies are included within the characteristics of included studies tables, and Table 4-2 (Methodological quality summary). However, in order to avoid any confusion, these four cross-over studies are not discussed within the following text. All following text descriptions therefore only apply to the 14 included RCTs for which data was extracted and analysed.

Setting

Of the 14 included studies, seven[175;176;180;181;183;289;290] were carried out in the USA, three were carried out in Australia[177;184;291], two in Taiwan[178;179] and one in Germany[292] and the UK[182] respectively.

Sample sizes

On average, included studies randomised 30 stroke patients into their trial prior to attrition. This ranged from just 12 participants[184] to 106[182]. All except two studies[178;182] included less than 50 participants.

Participants

The 14 included trials randomised a total of 459 stroke participants; of which 438 were relevant to this review. Full demographic details of included participants are provided in Appendix D. Of the included participants 39% were female. Age ranged from 52.14 years[178] to 74.9 years[291]. Across the studies time since stroke varied from a mean of 22.9 days[182] to a mean of 9.85 years[183]. One study did not report time since stroke[292]. Seven of the

included studies did not provide any information on type of stroke. Side of stroke was reported in all studies except one [183]; 257 participants had a left hemisphere stroke and 267 participants had a right hemisphere stroke. Information relating to initial upper limb impairment could not be extracted due to the limited information provided by some of the studies.

Interventions

The interventions investigated in the included studies varied in terms of types of bilateral tasks completed, duration of interventions and use of combinations of interventions. Full details of the interventions, including types of tasks and durations are provided in the Characteristics of included studies table (Appendix D). Some of the key differences are summarised below.

The interventions of eight[175;176;180;181;184;289-291] of the 14 included studies each concentrated on one specific upper limb movement or task. In four studies[175;176;289;290] bilateral interventions were aimed at wrist/finger extension. In the other studies the intervention involved; isometric contractions of wrist extension[291], bilateral reaching[181], bilateral pushing and pulling[180] and a bilateral dowel placement task[184].

The interventions of six[177-179;182;183;292] of the 14 included studies involved more than one upper limb movement or task. Three studies[182;183;292] completed four, three and six separate bilateral tasks respectively, and one study[177] assessed a package of interventions, which included bilateral tasks in addition to unilateral and bimanually different tasks. The other two studies[178;179] investigated simultaneous movements during a number of functional tasks in symmetric or alternating patterns and simultaneous bilateral completion of functional tasks with symmetric patterns.

Thirteen[175-184;289;290;292] of the 14 included studies investigated the effect of training over a training period (rather than single training and evaluation sessions); the training period varied from four days[176] to eight weeks[183]. The

remaining RCT[291] did not have a training period, rather a single training and evaluation session was completed.

Five[175;176;181;289;290] of the 14 studies provided another intervention as an adjunct to treatment in both the bilateral training and control groups. Four studies[175;176;289;290] included EMG-triggered neuromuscular stimulation, delivered to both the bilateral training and control group. One study[181] used a robot to assist movement of the affected limb in both the bilateral training and control (unilateral) groups.

One study[180] evaluated bilateral training in conjunction with auditory cueing; auditory cueing was not provided to the control group. This study was included as auditory cueing was not assessed by the reviewers to be an 'assistive technology', but to be a mode of delivery of the bilateral training intervention.

Outcome measures

As anticipated, a variety of outcome measures were used by the included studies. All of the studies included a measure of motor impairment. Due to differences in the measures, it was considered inappropriate to combine some of the outcomes together within analyses. Therefore, following data extraction functional movement of the upper limb was further categorised into: (a) arm functional movement and (b) hand functional movement and motor impairment of the upper limb was categorised into the following subgroups: (a) motor impairment scales (b) temporal outcomes (c) spatial outcomes (d) strength outcomes. The outcomes selected from each individual study are listed in both characteristic of included studies tables (Table 4-1 and Appendix D).

4.4.3 Excluded studies

A total of 61 studies were excluded following consideration of full papers. Reasons for exclusion were: not a simultaneous bilateral training intervention (n=25), not stroke population (n=2), review papers (n=3), bilateral training

intervention but not a randomised controlled trial (n=17), bilateral training intervention completed with assistive technology (n=7), no relevant outcomes (n=1) and bilateral training intervention received by both groups (n=6).

4.4.4 Risk of bias in included studies

For full details of methodology see Table 4-2 and Appendix D. Generally, the included studied were judged to be of poor or uncertain methodological quality and therefore at high risk of bias. Assessment of risk of bias was difficult due to lack of adequate reporting of methods: for 11 of the 14 included studies at least one of the assessed components was judged to be unclear (or was not stated). Only three trials[177;178;182] reported adequate allocation concealment. Eight studies[177-184] reported blinding of outcome assessors. No trials reported use of an intention-to-treat analysis.

Table 4-2 - Risk of bias summary

+ Adequate - Not adequate ? Not clear	Allocation concealment?	Binding of outcome assessor?	Intention-to-treat analysis?	Baseline similarity
Cauraugh 2002	?	?	?	?
Cauraugh 2005	?	?	?	+
Cauraugh 2008	?	?	?	-
Cauraugh and Kim 2003	?	?	?	?
Chang 2006	?	?	?	?
Desrosiers 2005	+	+	-	+
Dickstein 1993	?	?	?	?
Harris-Love 2005	?	?	?	?
Kilbreath 2006	?	?	?	?
Lin 2009	+	+	?	+
Lin 2009b	?	+	?	+
Luft 2004	-	+	-	-
Lum 2006	-	+	?	+
Morris 2008	+	+	-	+
Mudie 2001	?	?	?	+
Platz 2001	?	?	?	+
Stoykov 2009	-	+	?	+
Summers 2007	?	+	?	-

4.4.5 Effects of interventions

Comparison interventions

Fourteen RCTs[175-184;289-292] were included in the meta-analyses. One RCT[178] is included in two of the comparisons and another study[291] had two subgroups (acute and chronic). Within these 14 trials 459 stroke participants were randomised and 421 participants' data was available for analysis. The missing data (n=38) relates to four studies[175;177;181;182]; one study[175] randomised participants to a control group (5 participants) which were not included in the analyses and another study[181] randomised participants to two other groups (n=16) which were not relevant to this review. Two studies[177;182] had eight and nine dropouts respectively.

Numbers of participants given below relate to the number of participants whose data were available for inclusion in each of the analyses and not the number of randomised participants.

Simultaneous bilateral training versus placebo or no intervention.

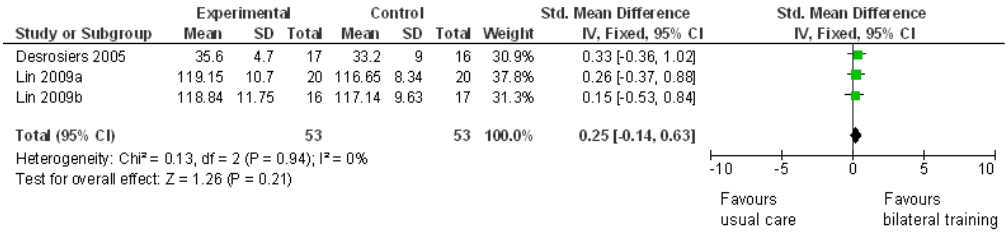
No RCTs compared simultaneous bilateral training with placebo or no intervention.

Simultaneous bilateral training versus usual care.

Four RCTs[177-180] (n=127) compared the effects of a bilateral training with usual care.

Performance in ADL: Three RCTs[177-179] (n=106) reported performance of ADL (Functional Independence Measure); SMD 0.25 (95% CI -0.14 to 0.63) (Figure 4-2).

Figure 4-2- Comparison: Bilateral training versus usual care. Outcome: Performance in ADL

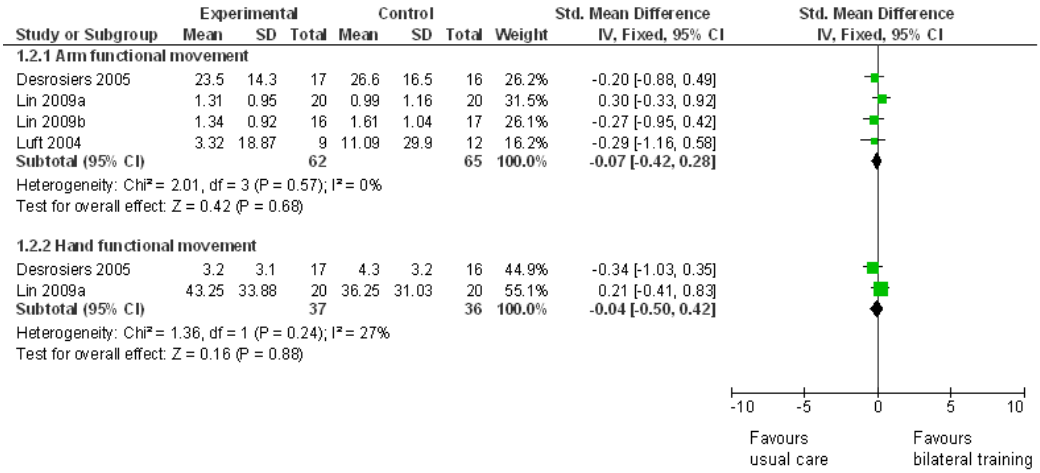


Functional movement of the upper limb: All four RCTs[177-180] (n=127) reported outcomes relevant to functional movement of the upper limb.

All four RCTs reported arm functional movement outcomes; Box and Block Test[177], Motor Activity Log (amount of use scale)[178;179] and Wolf Motor Function Test (time to complete)[180]. The pooled result was SMD -0.07 (95% CI -0.42 to 0.28) (Figure 4-3).

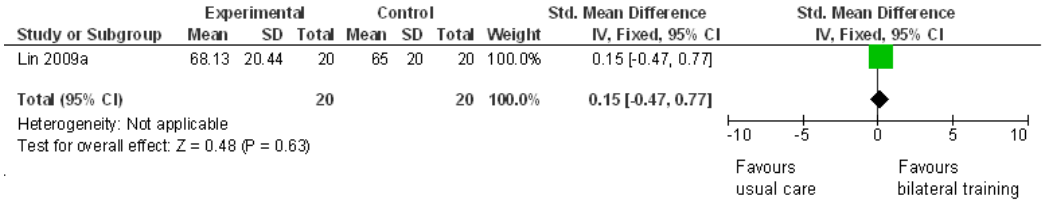
Two RCTs[177;178] (n=73) reported a hand functional movement outcome; Purdue Pegboard Test and Stroke Impact Scale (hand function subscale) respectively; SMD -0.04 (95% CI -0.50 to 0.42) (Figure 4-3).

Figure 4-3 - Comparison: Bilateral training versus usual care. Outcome: Functional movement of the upper limb



Performance in extended ADL: One RCT[178] (n=40) reported the effects of bilateral training on performance of extended ADL (Stroke Impact Scale; ADL/IADL section); SMD 0.15 (95% CI -0.47 to 0.77) (Figure 4-4).

Figure 4-4 - Comparison: Bilateral training versus usual care. Outcome: Performance in extended ADL



Motor impairment of the upper limb: Four RCTs[177-180] reported outcomes of motor impairment.

All four RCTs reported motor impairment scale outcome; Fugl-Meyer (upper limb section). The pooled result was SMD 0.67 (95% CI -0.43 to 1.77). A random-effects model was utilised due to I^2 = 88% (Figure 4-5) (Fixed effect result: SMD 0.43 (0.06 to 0.81) (Figure 4-6).

Two RCTs[177;179] (n=66) reported a temporal outcome; finger to nose coordination (number of movements completed) and movement time for unilateral reaching task respectively. The pooled result was SMD 0.04 (95% CI -0.45 to 0.52) (Figure 4-6).

One RCT[179] (n=33) reported a spatial outcome; normalised total distance for a unilateral reaching task; SMD 0.25 (95%CI -0.43 to 0.94) (Figure 4-6).

Two RCTs [177;180] (n=54) reported strength outcomes; grip strength and Wolf Motor Function Test (strength of hemiparetic limb) respectively. Pooled result was SMD -0.18 (95% CI -0.72 to 0.36) (Figure 4-6).

Figure 4-5 - Comparison: Bilateral training versus usual care. Outcome: Motor impairment of the upper limb (Motor impairment scales random effects model analysis)

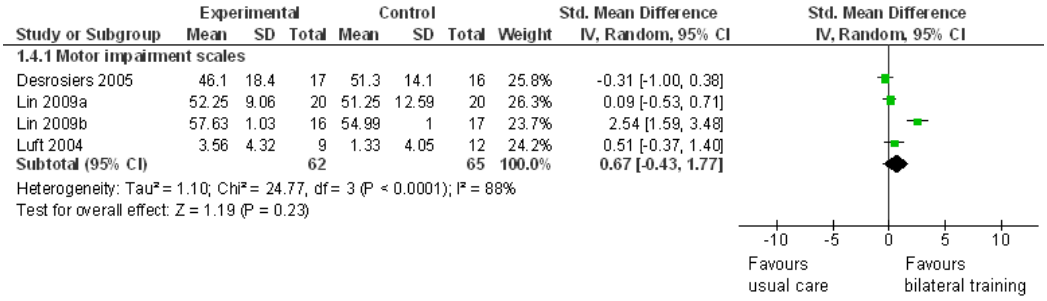
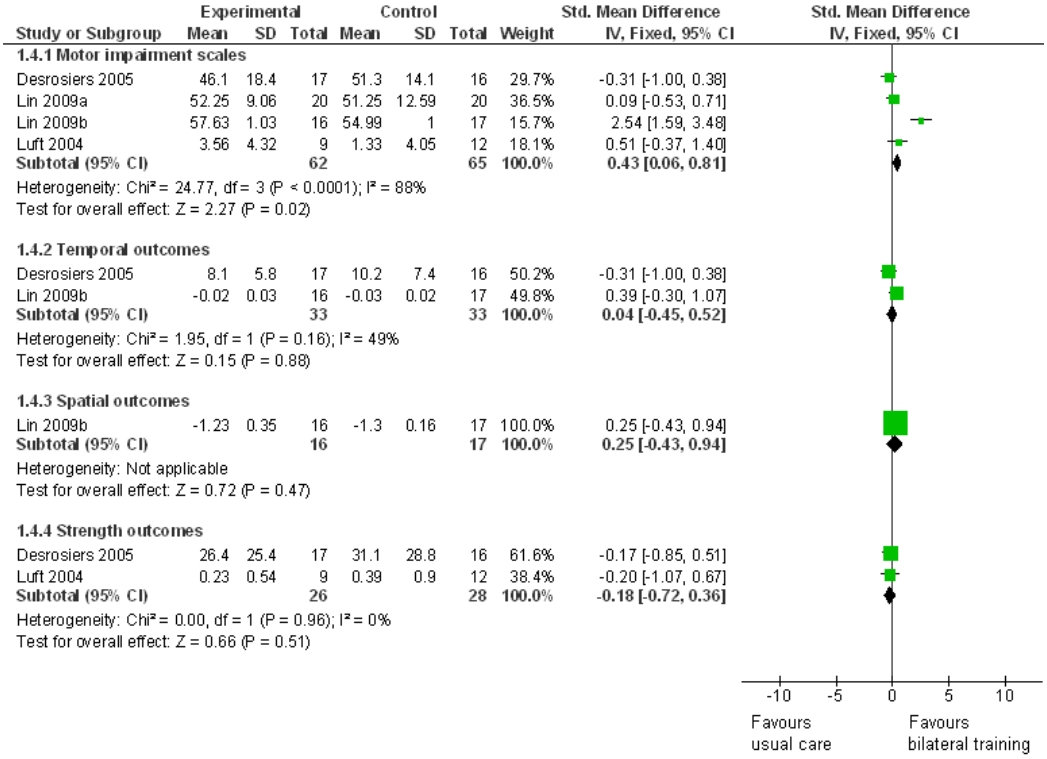


Figure 4-6 - Comparison: Bilateral training versus usual care. Outcome: Motor impairment of the upper limb

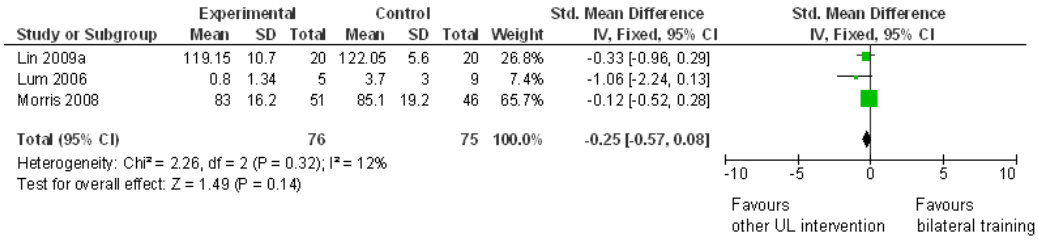


Simultaneous bilateral training versus other specific upper limb interventions or programmes.

Eleven RCTs [175;176;178;181-184;289-292] (n=314) compared the effects of a bilateral intervention with an unilateral intervention.

Performance in ADL: Three RCTs[178;181;182] (n=151) reported performance of ADL; Functional Independence Measure[178;181] and Barthel Index[182]; SMD -0.25 (95% CI -0.57 to 0.08) (Figure 4-7).

Figure 4-7 - Comparison: Bilateral training versus other specific upper limb intervention or programme. Outcome: Performance in ADL

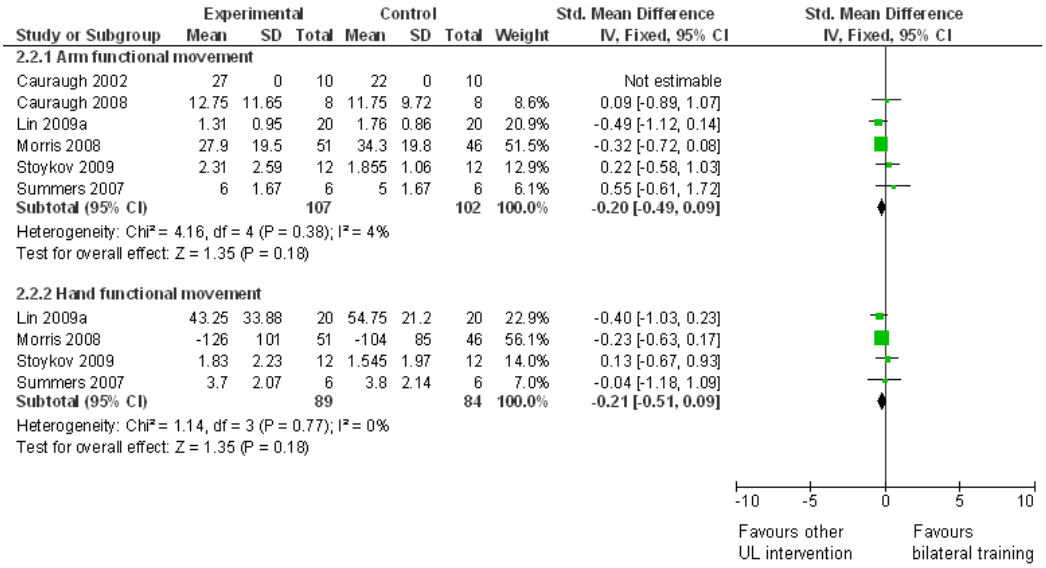


Functional movement of the upper limb: Six RCTs[175;176;178;182-184] (n=145) reported functional movement of the upper limb outcomes.

All six RCTs reported arm functional movement outcomes; Box and Block Test[175;176], Motor Activity Log (amount of use scale)[178], Action Research Arm Test[182], Motor Assessment Scale (upper arm section)[183] and Modified Motor Assessment Scale (upper arm section)[184]. Published data from one of the trials[175] (n=20) were unsuitable for pooling; a graphical display was presented of means with no standard deviations (results: bilateral training 27 blocks moved at post-test, unilateral training 22 blocks, as estimated from graph). The pooled result for the remaining five RCTs (n=189) was SMD -0.20 (95% CI -0.49 to 0.09) (Figure 4.8).

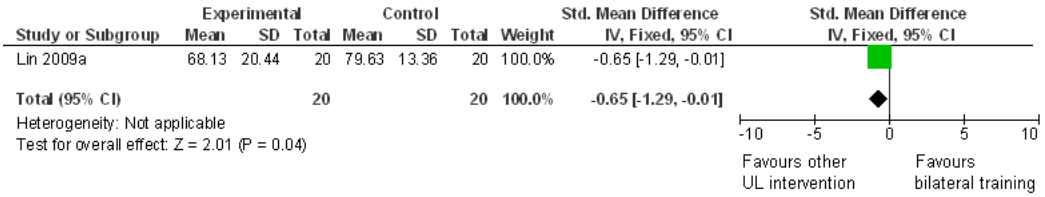
Four RCTs[178;182-184] (n=173) reported hand functional movement outcomes. The pooled result was SMD -0.21 (95% CI -0.51 to 0.09) (Figure 4-8).

Figure 4-8 - Comparison: Bilateral training versus other specific upper limb intervention or programme. Outcome: Functional movement of the upper limb



Performance in extended ADL: One RCT[178] (n=40) reported the effects of bilateral training on performance in extended ADL (Stroke Impact Scale ADL/IADL section); SMD -0.65 (95 % CI -1.29 to -0.01) (Figure 4-9).

Figure 4-9 - Comparison: Bilateral training versus other specific upper limb intervention or programme. Outcome: Performance in extended ADL



Motor impairment of the upper limb: Eleven RCTs[175;176;178;181-184;289-292] (n=310) reported motor impairment outcomes.

Four RCTs[178;181-183] (n=175) reported an upper limb motor impairment scale (Fugl-Meyer, Rivermead Motor Assessment and Motor Status Score); SMD -0.25 (95% CI -0.55 to 0.05) (Figure 4-10).

Five RCTs[175;176;184;290;292] (n=79) reported temporal outcomes. Data from one RCT[184] (n=10) were unsuitable for pooling: median movement time

values were reported without any standard deviations (bilateral training 1.89sec at post-test, unilateral training 2.74sec). The pooled result for the remaining four RCTs (n=69) was SMD 0.46 (95% CI -0.03 to 0.95) (Figure 4-10).

Two RCTs[184;292] (n= 24) reported spatial outcomes. Data from one RCT[184] (n=10) were unsuitable for pooling. This RCT reported an increase in mean elbow angle for both groups; however no standard deviations were reported. The result for the remaining RCT (n=14) SMD 0.00 (95 % CI -1.05 to 1.05) (Figure 4-10).

Six RCTs[175;176;181;183;289;291] (n=130) reported strength-related outcomes. Data from one RCT[175] (n=20) was unsuitable for pooling; data for sustained muscle contraction and force modulation were presented in a bar graph of median root mean square error with no standard deviations (bilateral training median root mean square error 0.42 at post-test, unilateral training 0.42; estimated from graph). Data from another RCT[176] (n=16) was also unsuitable for pooling; no means or standard deviations were presented (the authors of this study stated that analysis did not reveal any significant effects). Another RCT[183] (n=24) did not present means and standard deviations for the two groups and therefore data from this study could not be included in the data analysis either. The pooled result of the remaining three RCTs (n=70) was SMD 0.04 (-1.34 to 1.43). A random effect model was utilised due to I^2=85% (Figure 4-11) (Fixed effect result: SMD -0.07 (95% CI -0.59 to 0.46) (Figure 4-10).

Figure 4-10 - Comparison: Bilateral training versus other specific upper limb intervention or programme. Outcome: Motor impairment of the upper limb

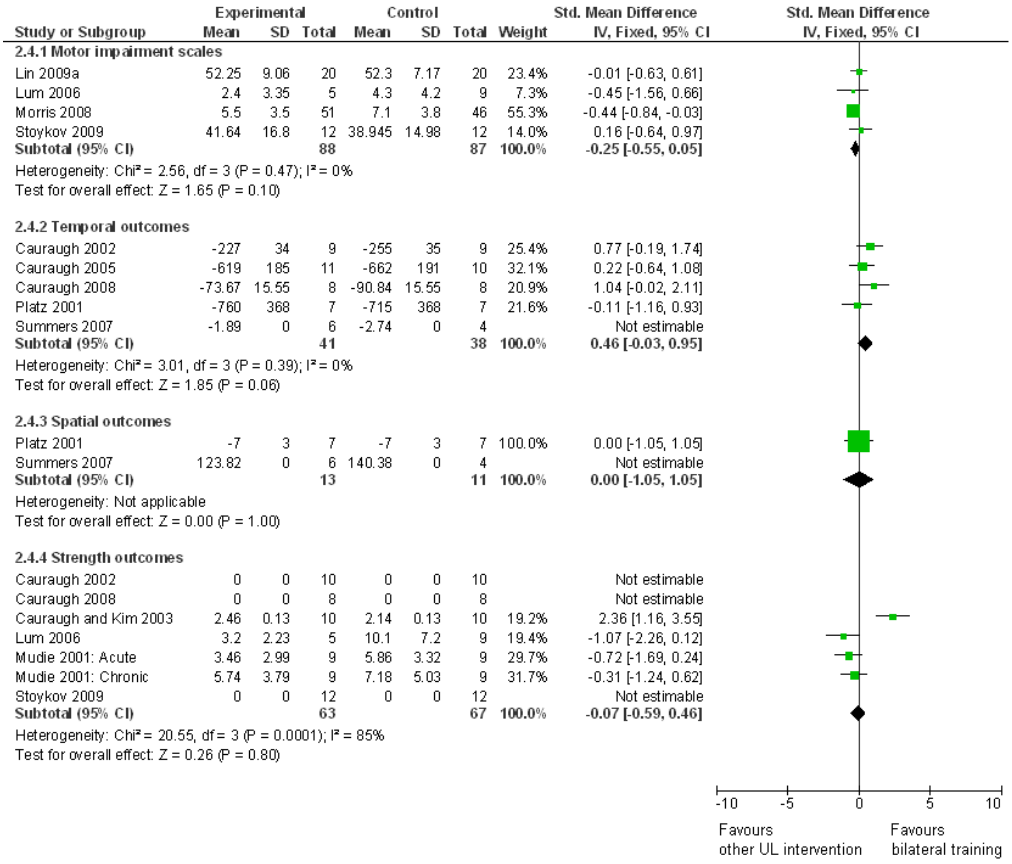
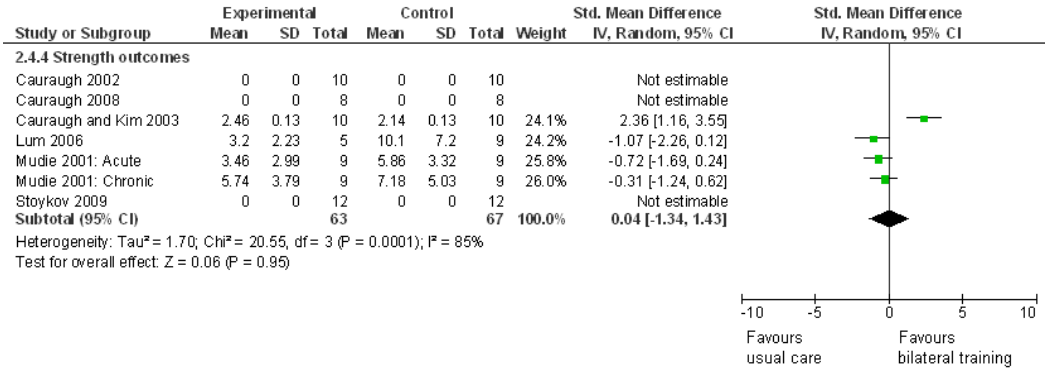


Figure 4-11- Comparison: Bilateral training versus other specific upper limb intervention or programme. Outcome: Motor impairment of the upper limb (Strength outcomes random effects model analysis)



Other outcomes: No studies reported adverse events.

4.4.6 Sensitivity and subgroup analyses

Sensitivity analyses that were carried out are discussed below.

A sensitivity analysis was completed to investigate the effect of trials that had a single treatment and evaluation session. One RCT[291] (with 2 subgroups) was removed, the result following removal for motor impairment; strength outcomes was SMD 0.64 (95% CI -2.72 to 4.00). A random effects model was used as I^2 = 94% (fixed effect: SMD 0.63 (95% CI -0.21 to 1.48)).

A further sensitivity analysis was undertaken, with regard to the effect of including trials that investigated the effect of an adjunct therapy / assistive technology in addition to the bilateral training and control interventions. Six RCTs were removed from analyses[175;176;180;181;289;290]. In the comparison bilateral training versus usual care, removing one RCT[180] did not affect the significance of the results (arm functional outcomes: SMD -0.03 (95% CI -0.42 to 0.35); motor impairment scales: SMD 0.73 (95% CI -0.76 to 2.23); motor impairment, strength outcomes: SMD -0.17 (95% CI -0.85 to 0.51)). For the comparison bilateral training versus other upper limb intervention, six RCTs were removed[175;176;181;183;289;290] from the analysis. With these studies removed the results were: performance in activities of daily living SMD -0.18 (95% CI -0.52 to 0.16); arm functional outcomes SMD -0.30 (95% CI -0.62 to 0.03 motor impairment scales SMD -0.31 (95% CI -0.65 to -0.03); motor impairment, temporal outcomes SMD -0.11 (-1.16 to 0.93) and motor impairment, strength outcomes SMD -0.51 (95% CI -1.18 to 0.16). Following sensitivity analysis a change of significance for motor impairment scales for the comparison bilateral training versus other upper limb intervention was found, however, this significant result in favour of other upper limb intervention was based on only two RCTs.

The lack of information provided by the majority of trials relating to methodological quality meant that sensitivity analyses to investigate the effect of including trials with low methodological quality could not be completed.

There was insufficient data to carry out planned subgroup analysis on differences between acute and chronic patients and duration of intervention programme.

4.5 Discussion

4.5.1 Summary of findings

This systematic review found no RCTs that compared simultaneous bilateral training with placebo or no intervention.

Four of 14 included RCTs compared simultaneous bilateral training with usual care and found no statistically significant effect of bilateral training on any analysed outcomes (performance activities of daily living (ADL), arm and hand functional movement, performance in extended ADL or motor impairment measures (motor impairment scales, temporal, spatial and strength outcomes)). As stated in the methods section a random-effects model was used where heterogeneity was greater than 50%, therefore these conclusions are based on random-effects analyses where appropriate. For motor impairment scales a significant result was found for the fixed effect analysis; however due to the heterogeneity (I^2=88%) a random-effects model was more appropriate and this result was non-significant.

Eleven of the 14 included RCTs compared the effects of a bilateral intervention with a unilateral intervention. No statistically significant effects were found in favour of bilateral training for any of the specified outcomes. Data from one trial found a statistically significant result in favour of another upper limb intervention (constraint-induced movement therapy) for a measure of performance in extended ADL. This result cannot be generalised to other outcomes and further research would be required to confirm this finding.

It must be noted that only six of the fourteen RCTs included in the analysis used a single bilateral training protocol. The other eight RCTs included other intervention protocols in combination with bilateral training.

In addition to the 14 RCTs included in the analyses, four relevant cross-over studies were indentified. These studies were not included in any of the analyses.

The evidence is currently insufficient to answer the review questions; the effects of bilateral training compared to placebo, usual care or other upper limb intervention in terms of performance in ADL, functional movement of the upper limb, performance in extended ADL, motor impairment of the upper limb and adverse events. The included studies, with the exception of one, had small numbers of participants and reported a diverse range of outcome measures, of which many were unique to single studies and/or specific to certain impairments. Both these factors limit the completeness of the evidence relevant to this review.

Due to limited data, subgroup analysis for different participant subgroups or duration of training was unable to be completed. The characteristics of the included studies indicate that participants varied in terms of time post stroke. Additionally the type, duration and intensity of training varied between the studies.

All of the included studies had inclusion criteria specifying either minimum or maximum levels of upper limb ability, and preservation of at least some cognitive abilities (including ability to comprehend simple instructions). Therefore the results of this review may not be generalisable to the wider population of stroke patients.

The lack of sufficient high quality evidence makes it inappropriate to draw conclusions from the results regarding the applicability of bilateral training within the context of current practice.

The quality of most of the evidence was poor, with incomplete reporting of methodological details. The number of participants within the included studies was generally small, only two studies had more than 50 participants and seven of the studies had 20 or fewer participants. Additionally few trials reported adequate allocation concealment and no studies reported using an intention-to-treat analysis. The overall quality of the trials limits confidence in the results.

The results of this review vary from the results presented in a previous review[305], which reported a significant overall effect in favour of bilateral movement training alone or in combination with auxiliary sensory feedback for improving motor recovery post-stroke (Fugl-Meyer, Box and Block or kinematic variables). While systematic methods were reported, this review[305] had a more limited search strategy and included trials that were not randomised controlled trials. The reviewers did assess trials for randomisation, which was defined as either randomly placed in a treatment or control group or if the treatment was randomly assigned to the participants. Eleven studies were included in this previous meta-analysis, seven of which were not included in this current review[215;300;328-332]. Five of these studies[215;300;328;330;331] did not meet the criteria for randomisation for this review. Many of these studies were considered not to have an appropriate control group, and these types of studies will give an inflated effect of the intervention. Two studies[291;294] were included in this current review which were identified by the previously highlighted review but not included in the meta-analysis. These studies were not included in the previous meta-analysis due to not having a functional outcome measure[294] and not involving bilateral movements as a treatment[291]. In contrast, these studies were included in this current review as other outcomes relevant to this review criterion were included[294] and for the other study it was assessed, for this review, to involve some element of bilateral intervention[291]. Ten studies included in this current review were published after the searching for the previous review was completed. Therefore, this review presents more up-to-date data. Additionally, a further two studies[289;292] were included in this

current review which were not acknowledged by the previous review, which may suggest a more comprehensive search strategy in this current review.

A narrative review[304] reported the findings from a number of studies, including non-randomised studies and concluded that favourable effects of bilateral training protocols have been found. However this review makes no attempt to discuss the quality of the reviewed studies and the potential impact this could have on the individual study results. Furthermore this review was not systematic and did not attempt to combine studies.

4.5.2 Limitations of the review

Through a thorough searching process it is assumed that all relevant published trials were identified, however, it must be acknowledged that there is a small possibility that there are additional trials (published and unpublished), that were not identified.

Four RCTs were categorised as comparing bilateral training with usual care. It should be noted that the intervention (categorised as usual care) in these studies was dose matched with the bilateral intervention. Therefore it is likely that these interventions were more intensive than the typical duration of usual care. Furthermore, the interventions which were classified as usual care differ between the four studies. However, it was felt that it was more appropriate to categorise these interventions within the usual care comparison than the other upper limb intervention comparison, as the interventions completed in these four studies were not specific other upper limb interventions or programmes. Within the other upper limb interventions comparison, all except one study investigated bilateral training compared to unilateral training (i.e. completing the same activities or activity with both arms compared to completing with affected arm only). One RCT compared the effects of bilateral training with constraint-induced movement therapy which, in addition to undertaking of functional tasks with the affected upper limb (which was dose matched to the bilateral training), involved restraint of the unaffected limb for six hours per day. Combining these studies within

these stated comparison groups further increases the heterogeneity between the included studies, limiting the conclusions that can be drawn.

The diversity of the bilateral training paradigms and the variations in reporting between trials led to some subjective decisions being made by the review team, and this may have introduced bias. The studies within this area are heterogeneous in terms of what is defined as bilateral training and there were a number of complex strands which required discussions among the reviewers and consensus decisions being made. This could be perceived as a limitation of this review.

Hierarchical lists were used to select which outcome measure should be included if a study reported a number of different relevant outcome measures. There could potentially be biases in the hierarchical order developed for each outcome. However, the order of the hierarchy was carefully considered and debated, and consensus reached. Despite the potential limitations and biases of this approach the pre-stating of a hierarchical list provides substantial advantages in comparison to the alternative option of having to make subjective decisions about the selection of outcome measures after data collection has been completed.

The included trials used a wide range of outcome measures, methodologies and time intervals for follow up making statistical pooling difficult. To overcome the variations in outcome measures and to maximise statistical pooling the outcomes of functional movement and motor impairment of the upper limb were categorised into subgroups. For four trials, mean values were not available (for at least some of the outcomes) and therefore median values (where these were provided instead of mean values) were imputed as mean values and standard deviations were calculated from reported standard error (SD= SE $\sqrt{n}$). Where data was presented in graphical form two reviewers independently estimated values from the graphs. This may have introduced some bias. However, it was felt that including imputed and estimated data from these studies was preferable to the exclusion of the data.

4.5.3 Strengths of the review

The main strengths of this review, relate to the following of rigorous Cochrane systematic review methodology to plan, undertake and write this review. This involved a comprehensive peer-review process to ensure quality and accuracy.

Thorough searching was undertaken to attempt to identify all appropriate trials relating to bilateral training and therefore this review is considered to be a comprehensive assessment of the effects of this intervention.

Only randomised controlled trials were included in this review, increasing confidence in the results.

4.5.4 Implications for practice

This review identified that there is currently insufficient evidence to make any recommendations about the relative effect of bilateral training compared to placebo, no intervention or usual care.

This review also identified evidence from trials of varied methodological quality, which suggests that bilateral training may be no more (or less) effective than unilateral training for performance in ADL, functional movement of the upper limb, performance in extended ADL or motor impairment outcomes.

4.5.5 Implications for research

Specific implications for research, based on the findings of this review, are outlined below.

Randomised controlled trials are required to determine the effect of simultaneous bilateral training compared to no treatment, placebo or usual care and simultaneous bilateral training compared to unilateral training.

Such randomised controlled trials must: have adequate power (i.e. with an appropriate power calculation undertaken based on existing trial evidence); have adequate allocation concealment, blinding of outcome assessor and intention-to-treat analysis; clearly define trial participants (e.g. time since stroke, initial upper limb deficits); clearly define types, frequency, durations and intensities of bilateral training; include global measures of functioning (i.e. performance of ADL measures) and upper limb function (e.g. MAS, ARAT) and report clear and usable data.

It is recommended that future RCTs concentrate on answering the specific question relating to the effectiveness of bilateral training and do not confound the answer to this question by introducing adjunct interventions such as robotics or electrical stimulation.

Future RCTs should also have a defined training period, and should not have a single treatment and intervention session. Further standard RCT methodology should be followed i.e. random allocation of participants to one of two (or more) groups and not random allocation to treatment order.

There is also a need for further research to identify optimal outcome measures for use within future RCTs in this area.

4.6 Conclusions

This systematic review included 18 trials. Methodological quality of these trials was generally poor, providing insufficient high quality evidence on which to reach generalisable conclusions.

Limited evidence suggests that bilateral training is no more or less effective than usual care or unilateral training for functional outcomes. Very limited evidence shows that bilateral training is no more or less effective than unilateral training for upper limb motor impairment outcomes. Therefore there is not enough evidence to recommend bilateral training as a clinical

intervention. High quality randomised controlled trials are needed to compare bilateral and unilateral training.

Chapter 5

Home-based therapy programmes for upper limb functional recovery following stroke

Chapter 5 Home-based therapy programmes for upper limb functional recovery following stroke

Through completion of the review of interventions (Chapter 3) it was evident that a number of interventions had been investigated using systematic review methodology. However, one intervention which was not identified through this process was home-based therapy programmes. Such interventions are important, as increasingly stroke services are being moved into the community and form an important part of the patient's journey. Therefore I felt it was appropriate to complete a systematic review of home-based therapy interventions targeted at the upper limb. For the same reasons outlined in the previous chapter this review was undertaken using Cochrane review methodology.

5.1 Introduction

Increasingly the trend within health service delivery (including stroke care) is toward decreasing length of inpatient stay and moving care into the community, which has led to the development of home-based stroke services[333]. A Cochrane review of therapy-based rehabilitation services for stroke patients at home[334] found such services reduce the odds of a poor outcome in ability to perform activities of daily living (ADL) and have a beneficial effect on a patient's ability to perform personal ADL and extended ADL compared to conventional or no care. This review specifically investigated therapy service interventions primarily aiming to improve task-orientated behaviour (not upper limb interventions or outcomes) and was based on a review of heterogeneous interventions. In contrast, this review will exclusively investigate the effects of home-based therapy programmes targeted at upper limb recovery.

As highlighted previously within this thesis the effectiveness of specific upper limb interventions have been reviewed within other Cochrane systematic reviews[174;185;208;213;233;241;254;260;280]. This review did not intend to replicate or overlap with these other reviews, as the focus was on programmes of interventions completed at home rather than on a specific intervention.

With an increased focus on home-based stroke services and the undertaking of programmes of interventions targeted at upper limb recovery within clinical practice, a systematic review of home-based therapy programmes for individuals with upper limb impairment following stroke was deemed appropriate.

5.2 Objectives

To determine the effects of home-based therapy programmes for upper limb recovery in patients with upper limb impairment following stroke, compared with:

1. Placebo or no intervention
2. Usual care

5.3 Methods

As with the previous chapter Cochrane guidelines for systematic reviews of interventions were used to complete and report this review[307]. The description of the methods for this chapter therefore only highlights the difference between this and the previous review, rather than repeating the same methods undertaken.

5.3.1 Eligibility criteria

Types of studies

Only randomised controlled trials (RCTs) were included. One of the intervention groups must have included an intervention group of a home-

based therapy programme and a comparison group of placebo or usual care ('conventional' or 'traditional'). Studies that included a home-based therapy programme in addition to usual care, compared with usual care alone were also included. Usual care was determined, as defined by the original trial authors when it is considered to be a normal or usual component of stroke rehabilitation. Where appropriate, the description of usual care was documented.

Only studies where the therapist had visited the patient in their own home (at least once) to prescribe treatment were included.

Types of participants

As with the previous chapter, trials of participants with a clinical diagnosis of stroke were included. Only participants living in their own homes (that is, at their permanent address) were included. This included care homes and other forms of supported or sheltered accommodation.

Types of interventions

The included studies had to include one group which received a home-based therapy programme, targeted at upper limb recovery following stroke. For the purposes of this review home-based therapy programmes were defined as those including all of the following elements:

1. Carried out in the patient's home (that is, at their permanent address; this may include care homes and other forms of supported or sheltered accommodation)
2. Prescribed by healthcare professionals or individuals under the supervision of healthcare professionals
3. Including more than one specific intervention targeted at upper limb recovery

The rationale for including only these trials with more than one specific intervention was to avoid studies of single upper limb interventions. The focus of this review was a 'programme' of therapy. A programme of therapy

will always include several different treatment interventions. The effectiveness of single interventions for the upper limb has been assessed in other reviews. Excluding trials that assess only one specific intervention effectively limited this review to trials of 'programmes' of interventions to reduce or avoid overlap with other reviews, and reflect clinical reality.

Studies of complex packages of rehabilitation were included if the administered package included interventions targeted at upper limb recovery and included the three elements outlined above.

Any duration or intensity of programme was included and subgroup analysis completed as appropriate. Where possible the professional background, training and experience of the person(s) delivering the intervention were documented.

Types of comparisons to be made

Two comparisons were investigated:

1. Home-based upper limb programme versus placebo or usual care
2. Home-based upper limb programme versus usual care

Types of outcome measures

The primary and secondary outcomes were the same as the previous review, and are outlined below. The same hierarchical lists used in the previous chapter were again used for this review.

Primary outcomes

Performance in activities of daily living (including feeding, toileting, dressing, bathing, simple mobility and transfers).

Functional movement of the upper limb (such as measures of active movement, co-ordination, dexterity, manipulation, grasp/grip/pinch).

Secondary outcomes

Performance in extended activities of daily living (including shopping, household tasks).

Motor impairment of the upper limb (measures/scales of upper limb impairment, muscle strength, muscle tone).

Additional outcomes

Adverse events (such as death, pain).

Analysis was planned using data from the end of the intervention period and the end of scheduled follow up.

5.3.2 Search methods for identification of studies

To identify appropriate studies the following resources were searched:

- The Cochrane Stroke Group Trials Register, last searched by the Managing Editor in May 2011
- Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011 Issue 2, searched May 2011)
- MEDLINE (1950 to May 2011)
- EMBASE (1980 to May 2011)
- AMED (1985 to May 2011)
- CINAHL (1982 to May 2010)

The following occupational therapy and physiotherapy databases were searched: OTseeker (http://www.otseeker.com/) (May 2010), Physiotherapy Evidence database (PEDro, http://www.pedro.org.au) (May 2010), Chartered Society of Physiotherapy Research Database (May 2010) and REHABDATA (http://www.naric.com/research/rehab/default.cfm) (May 2010). In an effort to identify further published, unpublished and ongoing trials the following were also searched: reference lists of all included studies; ClinicalTrials.gov (http://www.clinicaltrials.gov/) and the National Research Register

(http://www.nihr.ac.uk/Pages/NRRArchiveSearch.aspx); (May 2010) and dissertation abstracts (http://www.lib.umi.com/dissertations/search) (May 2010).

The search strategies were developed, using a combination of controlled vocabulary and free text terms, in consultation with the Cochrane Stroke Group's Trials Search Co-ordinator.

Search strategy (MEDLINE)

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or cerebrovascular accident/ or exp brain infarction/ or exp cerebrovascular trauma/ or exp hypoxia-ischemia, brain/ or exp intracranial arterial diseases/ or intracranial arteriovenous malformations/ or exp "Intracranial Embolism and Thrombosis"/ or exp intracranial hemorrhages/ or vasospasm, intracranial/ or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. hemiplegia/ or exp paresis/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Upper Extremity/
9. (upper adj3 (limb$ or extremity)).tw.
10. (arm or shoulder or elbow or forearm or hand or wrist or finger or fingers).tw.
11. 8 or 9 or 10
12. 7 and 11

13. community health services/ or community health nursing/ or community networks/ or home care services/ or home care services, hospital-based/ or home nursing/
14. homebound persons/ or home health aides/ or home care agencies/ or house calls/ or primary health care/ or aftercare/
15. residential facilities/ or assisted living facilities/ or group homes/ or halfway houses/ or homes for the aged/ or exp nursing homes/
16. housing for the elderly/ or long-term care/ or institutionalization/
17. (home$ or house$ or domicile or domiciliary or community or institution$ or outreach or sheltered accomm$).tw.
18. ((resident$ or long-term) adj5 (care or facilit$)).tw.
19. or/13-18
20. 12 and 19

Identification of relevant trials

To identify relevant trials a similar process to that outlined in the previous chapter was utilised. Initially, either I or one of the other reviewers read the titles of the identified references and eliminated any obviously irrelevant studies. The abstracts for the remaining studies were obtained, and then, based on the inclusion criteria, two reviewers independently ranked these as 'possibly relevant' or 'definitely irrelevant. Following this process the full text of those trials still categorised as 'possibly relevant' were retrieved. The full text of the remaining studies were then retrieved and reviewed by two independent reviewers.

5.3.3 Data extraction

Where possible, the following was documented by two independent reviewers:

1. Participant details (including age, gender, place of residence, type of stroke, time since stroke, initial upper limb impairment)
2. Inclusion and exclusion criteria
3. Duration/intensity/frequency of intervention

4. Brief description of the home-based therapy programme (including details of administered therapy programme (including if part of early supported discharge or standard discharge protocol), involvement of treating therapist and qualifications and experience of treating therapist(s))
5. Comparison intervention
6. Outcomes

5.3.4 Assessment of risk of bias in included studies

Two reviewers independently assessed the methodology of the included studies. Assessment of the quality of studies focused on potential areas of bias within the studies as this has been shown to affect the estimation of effectiveness of interventions[164]. For each included trial two reviewers independently extracted information about the method of randomisation and allocation concealment (selection bias), blinding of outcome assessment (detection bias), whether all the randomised patients were accounted for in the analysis (attrition bias) and the presence of selective outcome reporting (selective reporting bias).

Consideration of blinding of participants and therapists (performance bias) led to the conclusion that blinding would not be possible in these types of trials; consequently this information was not documented.

Any disagreements between the two reviewers were resolved through discussion, involving a third reviewer, if necessary.

5.3.5 Data analysis

For each comparison the study results for performance in activities of daily living (ADL), measures of upper limb functional movement, measures of motor impairment, and adverse effects were used, if available. All outcome measures analysed were presented as continuous data and thus means and standard deviations (SDs) were used, where available. If the studies used

the same outcome measures a pooled estimate of the mean differences (MD) was calculated with 95% confidence intervals (CI). If different outcome measures were used, within the same outcome category (for example one study used Action Research Arm Test and another study used Frenchay Arm Test to measure functional movement of the upper limb) analysis was completed using standardised mean difference (SMD) instead of MD. The Cochrane Collaboration's Review Manager software, RevMan 5[335] was used for all analyses.

Heterogeneity was assessed using the I-squared (I^2) statistic and dealt with in the same way as reported in the preceding chapter.

Subgroup analysis was planned using the Deeks method[327] on the following:

1. Initial upper limb severity
2. Place of residence (own home, residential or nursing care)
3. Self practice versus no self practice
4. Duration and frequency of intervention (intervention less than four weeks and intervention more than four weeks, intervention less than three times a week and intervention more than three times a week)

These planned subgroup analyses were to be undertaken where data permitted (sufficient data were considered to be >5 trials reporting the information) and undertaken on the primary outcome only. A sensitivity analyses based on the risk of bias criteria was planned (selection bias, detection bias, attrition bias and selective reporting).

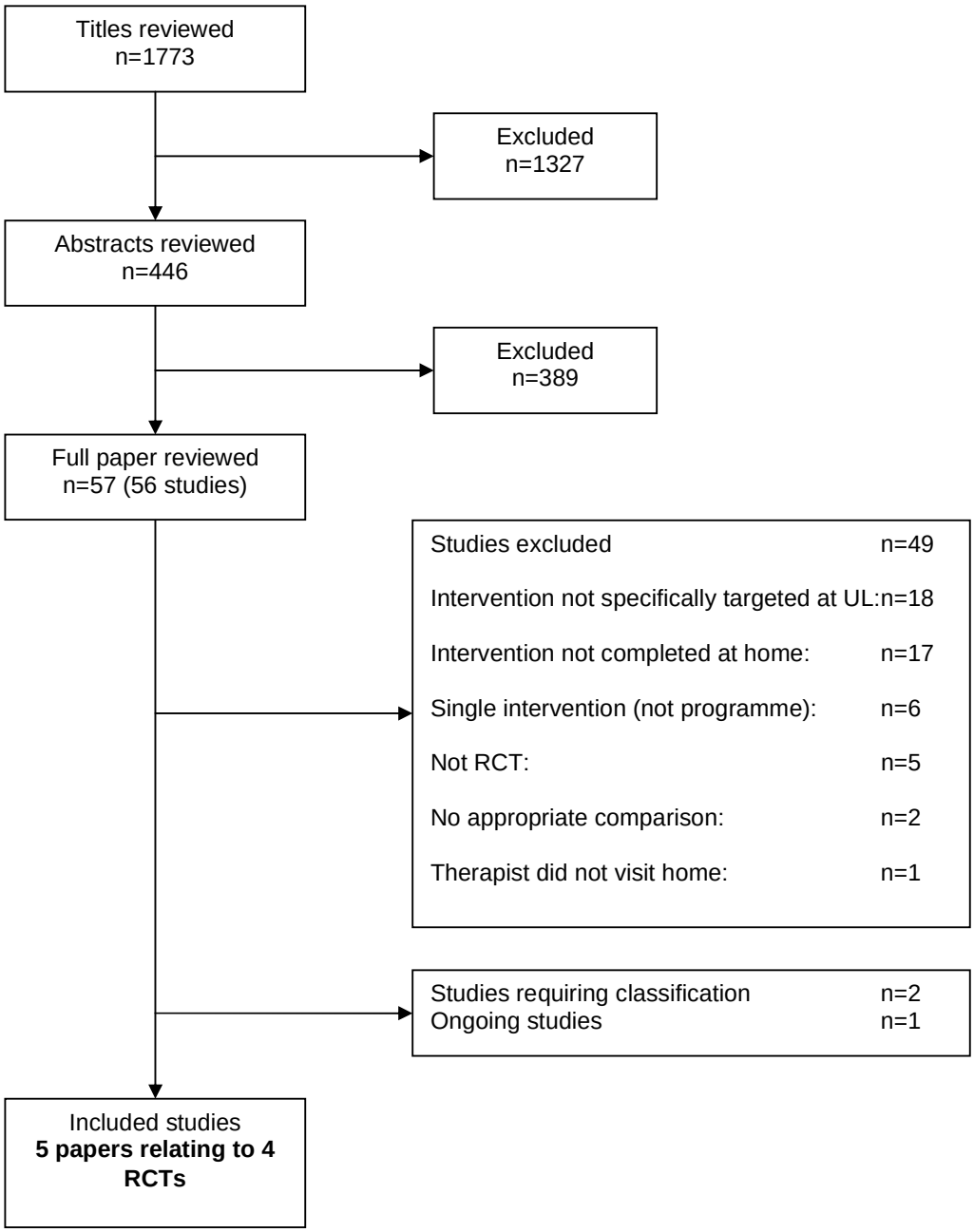
5.4 Results

5.4.1 Results of the search

Searches of the electronic bibliographic databases identified 1773 records after removal of duplicates (107 from Cochrane Trials Register, 1247 from MEDLINE, EMBASE, AMED and CINAHL, 52 from CENTRAL, 121 from OT

seeker, 78 from Physiotherapy Evidence Database and 168 from REHABDATA database). After elimination of obviously irrelevant studies and further duplicates, 446 potential papers were identified. The abstracts for these papers were obtained and assessed for inclusion by two independent reviewers. Papers with abstracts classified as 'possibly relevant' were then further reviewed as full papers. Where disagreement arose consensus was reached through discussion and/or opinion of a third reviewer was sought. From this process 56 studies were obtained. Of these 57 full papers (relating to 56 studies), 49 papers were excluded (see Figure 5-1). A further two studies were not included as a decision could not be made about their classification (based on published information) and one ongoing study was identified. This left four studies for inclusion (five papers included; one study with two associated papers).

Figure 5-1 - Study selection flow diagram



5.4.2 Included studies

Four trials[284;336-338] (166 randomised participants) were included in this review. A summary of the included trials is outlined below. An overview of the studies can be found in

Table 5-1 and a full description of the studies can be found in Appendix E.

Table 5-1 - Characteristics of included studies (abbreviated)

Study	Methods	Participants	Interventions	Relevant Outcomes
Duncan 1998[336]	RCT	N= 20	Group 1 (n=10) – usual care Group 2 (n=10) – home therapy programme (exercises to improve strength, balance and endurance and to improve use of affected UL)	Barthel Index Jebsen Test of Hand function Lawton Instrumental ADL scale Fugl-Meyer UL scale
Duncan 2003[337] Studenski 2005[339]	RCT	N=100	Group 1(n=50) – usual care Group 2 (n=10) – home therapy programme (exercises to improve strength, balance and endurance and to improve use of affected UL)	Barthel Index Wolf Motor Function Test Lawton Instrumental ADL scale Fugl-Meyer UL scale
Piron 2008[338]	RCT	N=10	Group 1 (n=5) – virtual training with therapist Group 2 (n=5) – virtual reality with telerehabilitation at home	Fugl-Meyer UL scale
Piron 2009[284]	RCT	N=36	Group 1(n=18) – usual care Group 2 (n=18) – telerehabilitation system at home	ABILHAND scale Fugl-Meyer UL scare

The four trials were completed by two different research groups. Two of the studies[336;337] were completed by one research group. Both of these studies were RCTs, which compared a home therapy programme to usual care and recruited individuals from the Kansas City Stroke Study registry. It is assumed that the first study[336] (20 participants) was a pilot study, undertaken prior to the larger study (100 participants)[337]. Both studies included an exercise program that was designed to improve strength, balance and endurance and to encourage more use of the affected extremity. This intervention met the inclusion criteria as it was explicitly stated that the program was targeted at upper limb recovery after stroke, the intervention was carried out in the patient's home, was prescribed and supervised by a physiotherapist or occupational therapist and clearly involved more than one specific intervention targeted at upper limb recovery.

The other two studies[284;338] were completed by another research group. Both were RCTs, which compared virtual reality plus telerehabilitation at home to either virtual reality training in hospital with a therapist present[338] or conventional therapy in the local health district[284]. Both studies aimed to improve motor impairment in the upper limb.

Disagreement occurred between reviewers as to whether virtual reality telerehabilitation training should be considered as a single intervention or a therapy program. The intervention described in the studies of virtual reality and telerehabilitation training consisted of different virtual tasks, comprising a number of arm movements, plus knowledge of results feedback and therapist instructions via teleconferencing[284]. The intervention combined virtual reality training and tele-medicine. In one of the studies[338] the intervention designed to be tested within the RCT was the teleconferencing itself; however the consequence of this design was a study which compared virtual reality arm training at home versus virtual reality arm training in hospital. In the other study[284] virtual reality arm training delivered at home using teleconferencing was compared with conventional or 'standard' care. As the reviewers could not reach consensus on whether the virtual reality intervention was single intervention or therapy program, a majority decision was taken and virtual reality training was included as a therapy program.

Study Design

All four of the included studies were RCTs[284;336-338].

Comparison groups

Three of the studies compared the effects of home therapy programmes for the upper limb with usual care[284;336;337]. One study[338]compared a home therapy programme with the same therapy programme in hospital (which was not considered usual care). This was considered to be a relevant study to include, despite not fitting into one of the pre-determined comparison groups. Therefore a further comparison group was added: upper limb home therapy versus same upper limb therapy in hospital.

Follow up

All four included studies completed outcomes at the end of the intervention period. One study[284] also completed outcomes after 1 month (follow-up) and another study[337] reported follow-up data at 6 months post-treatment.

Sample sizes

Sample sizes were 10[338], 20[336], 36[284] and 100[337].

Setting

All four studies were carried out in two settings - one group at home; and the other either at hospital or in the local health district. Two of the studies[336;337] were completed in the USA and the other two[284;338] in Italy.

Participants

Demographics of included participants are outlined in Appendix E. Of the randomised participants 64 were female and 82 were male. One study did not report gender[336]. The lowest reported mean age was 53 years (SD=15) and the highest mean age was 70.2 years (SD=11.4). Across the studies time since stroke varied from a mean of 56 to a mean of 412 days.

Interventions

Two of the included studies[336;337] delivered an exercise programme designed to increase strength, endurance and encourage use of the affected arm, which included functional exercises, assistive/resistive exercise with proprioceptive neuromuscular facilitation, and resistive exercise with theraband. This exercise programme was compared to usual care, as prescribed by their physicians. The remaining two studies[284;338] delivered a virtual reality intervention with telerehabilitation. This was compared with usual care[284] or the same therapy delivered with a therapist present[338]. Therapists delivered or supervised interventions in all four studies.

Outcome measures

Performance in ADL was measured using the Barthel Index[336;337]. Functional movements of the upper limb were measured using the Jebsen Test of Hand

Function[336] and the Wolf Motor Function test[337]. Extended activities of daily living were measured using the Lawton Instrumental Activities of Daily Living[336;337]. Upper limb motor impairment was measured using the Fugl-Meyer upper extremity scale in all four studies.

5.4.3 Excluded studies

A total of 49 papers were excluded following consideration of full papers.

The principal reasons for exclusion were: intervention not specifically targeted at the upper limb (18 papers), intervention not completed at home (17 papers), single intervention (not a programme of interventions) (6 papers), non randomised controlled trial (5 papers), no appropriate comparison (2 papers) and participants not visited by health professional at home (1 paper).

Several studies aimed to compare modes of service delivery, such as domiciliary versus hospital-based care. These studies delivered general rehabilitation rather than being specifically targeted to the upper limb. If a specific aim to target upper limb could not be found, these studies were excluded.

One paper[340] in particular was considered in detail. There was initially disagreement between reviewers regarding whether or not the intervention in this study met the inclusion criteria. This study investigated a home-based programme of individually prescribed exercises and activities. No response was gained from attempts to contact the authors of this study. Discussion between three reviewers led to consensus that there was insufficient information available within the published paper to definitively conclude that the programme did meet the criteria of including "more than one specific intervention targeted at upper limb recovery". However, all reviewers did acknowledge that this assessment was based on a lack of information, rather than on definitive information. This study was therefore excluded.

Where the comparison intervention was also conducted at home, these studies did not meet the criteria of the home intervention being compared to placebo, no treatment or usual care. These studies help to determine whether home-based intervention of one type improved upper limb function and impairment compared to home intervention of another type. This was not the purpose of this particular review and therefore this type of study was excluded.

5.4.4 Risk of bias in included studies

Full details of the included studies' methodology are presented in Table 5-2 and Appendix E. The inclusion criteria for this review required a study to be randomised. Three of the studies[284;336;337] reported an adequately generated allocation sequence and adequately concealed allocation. Blinding of outcome assessor was reported in three of the studies[284;337;338]. Three of the studies[284;336;338] did not report any drop-outs and therefore were considered to be at low risk of attrition bias. The other study[337] was also considered to be of low risk as the reasons for the drop-outs were provided and were similar across both groups. Additionally an intention-to–treat analysis was used to account for missing data. For performance in ADL and extended ADL outcomes, for this study[337], an associated paper[339] was used as this paper reported additional on-treatment data analysis; n=93 post-treatment and n=80 at 6 month follow-up that were available for inclusion in analysis (7% and 20% loss to follow-up respectively).

Table 5-2 - Risk of bias summary

+ Adequate - Not adequate ? Not clear	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Binding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Duncan 1998	+	+	?	?	+
Duncan 2003	+	+	+	+	+
Piron 2008	?	?	+	?	+
Piron 2009	+	+	+	?	+

5.4.5 Effects of interventions

Within the four included trials 166 stroke participants were randomised.

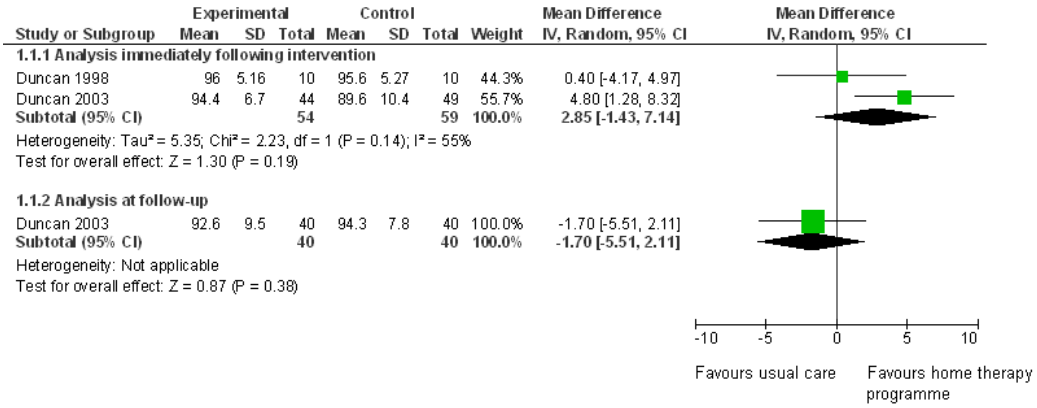
One study[338] did not include SDs in the paper. In order to include this study in the meta-analysis, the SDs reported by another study[284] were used. This study included participants with similar levels of initial upper limb motor impairment. The largest SD reported by this study was used in order to be conservative.

Home-based therapy programmes versus placebo or no intervention
No studies compared the effects of a programme of home therapy (targeted at the upper limb) with placebo or no intervention.

Home-based therapy programmes versus usual care
Three studies (n=156) compared the effects of a home therapy programme for upper limb with usual care [284;336;337].

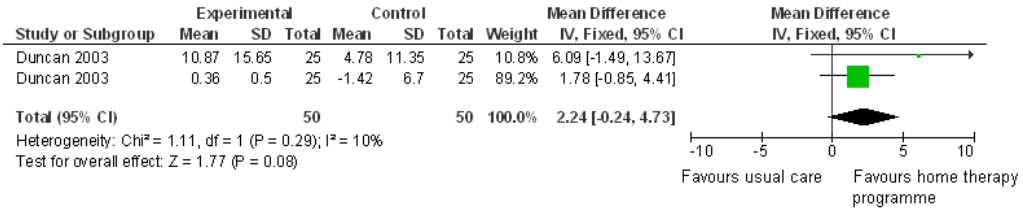
Performance in ADL: Two studies[336;337] (n=113) reported performance of ADL (Barthel Index): MD 2.85 (95% CI -1.43 to 7.14) (Figure 5-2). A random effects model was used for analysis as I^2>50% (55%). Fixed effects analysis produced a statistically significant result: MD 3.16 Barthel points (95% CI 0.37 to 5.95), in favour of home therapy programme. Follow-up data at 6 months post-treatment was reported by one study[337] (n=80): MD -1.70 (95% CI -5.51 to 2.11).

Figure 5-2 - Comparison: Home therapy programme versus usual care. Outcome: Performance in ADL



Functional movement of the upper limb: Two studies[336;337] reported outcomes relevant to functional movement of the upper limb (Jebsen Test of Hand Function and Wolf Motor Function Test respectively). The data from one study[336] were not available for inclusion in the analysis as total scores and SDs were not reported. The authors of this study reported no trends in changes in speed of upper extremity movements, as measured by the Jebsen Test of Hand Function, between the groups. One study[337] (n=100) reported data according to initial scores (above and below medians). Therefore this study has been entered as two subgroups (above median group presented first in forest plot). There was no significant difference between intervention and control groups: MD 2.24 (95% CI -0.24 to 4.73) (Figure 5-3).

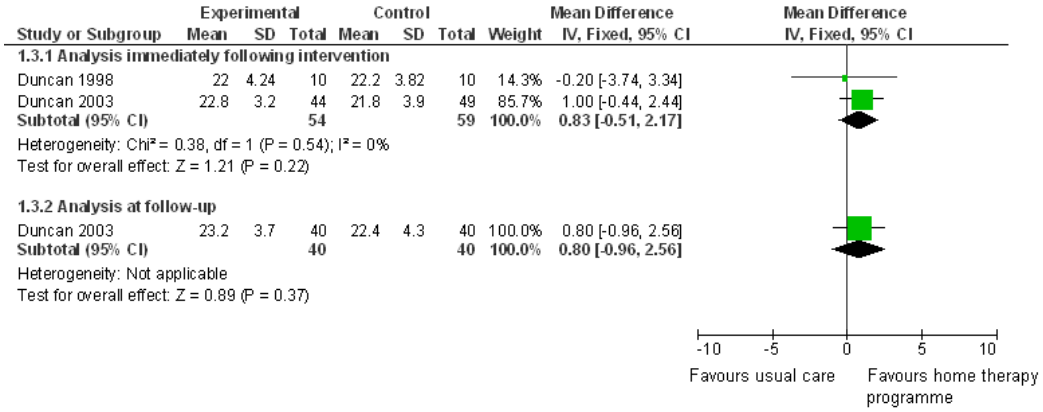
Figure 5-3 - Comparison: Home therapy programme versus usual care. Outcome: Functional movement of the upper limb



Performance in extended ADL: Two studies[336;337] (n=113) reported the effects of home-based therapy programmes (targeted at the upper limb) on performance of extended ADL (Lawton Instrumental ADL scale). No significant difference was found between groups: MD 0.83 Lawton

Instrumental ADL scale points (95% CI -0.51 to 2.17) (Figure 5-4). One study[337] reported follow-up data (n=80) at 6 months post-treatment; MD 0.80 (95% CI -0.96 to 2.56). A fixed effects model was used as no substantial heterogeneity was found.

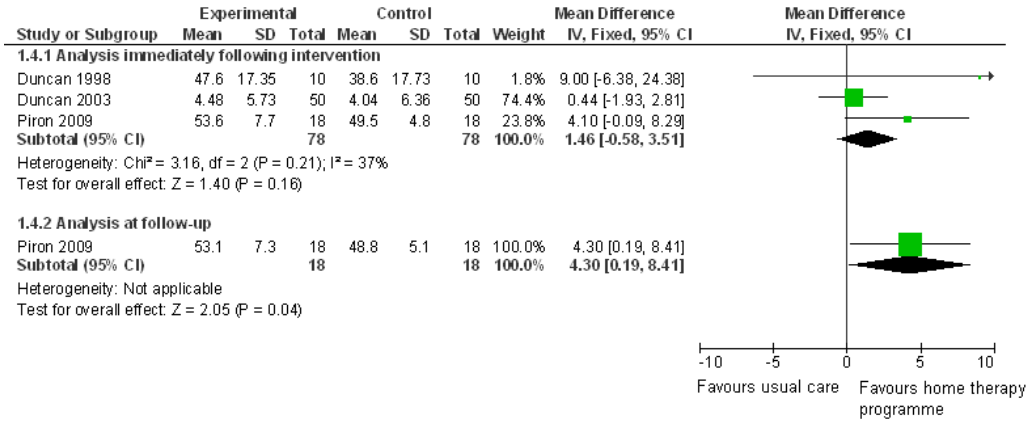
Figure 5-4 - Comparison: Home therapy programme versus usual care. Outcome: Performance in extended ADL



Motor impairment of the upper limb: Three studies[284;336;337] (n=156) reported outcomes of motor impairment.

All three studies reported a motor impairment score (Fugl-Meyer upper extremity scale). Two studies[284;336] presented mean final outcome scores. One study[337] presented mean change scores. There was no significant difference between groups: MD 1.46 Fugl-Meyer upper extremity scale points (95% CI -0.58 to 3.51) (Figure 5-5). A fixed effects model was used as no substantial heterogeneity found. One study[284] reported follow-up data (1 month after treatment ceased). A statistically significant difference was found: MD 4.30 (95%CI 0.19 to 8.41) (Figure 5-5).

Figure 5-5 - Comparison: Home therapy programme versus usual care. Outcome: Motor impairment of the upper limb

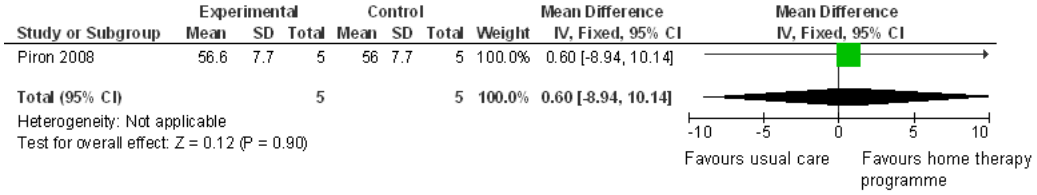


Home-based therapy programmes versus same therapy programme in hospital.

One study[338] (n=10) compared the effects of a home therapy programme for upper limb with the same therapy programme in hospital.

Motor impairment of the upper limb: The one study included in this comparison (n=10) reported a motor impairment score (Fugl-Meyer upper extremity scale). There was no significant difference between groups: MD 0.60 (95% CI -8.94 to10.14) (Figure 5-6).

Figure 5-6 - Comparison: Home therapy programme versus same therapy programme in hospital. Outcome: Motor impairment of the upper limb



Other outcomes: None of the studies reported any adverse events.

5.4.6 Subgroup and sensitivity analyses

As only four studies were included in this review none of the planned subgroup or sensitivity analysis could be undertaken.

5.5 Discussion

5.5.1 Summary of findings

This systematic review found no studies that compared home therapy programmes to placebo or no intervention.

Three studies were included which compared home therapy programmes to usual care and a further study was included which compared home-based therapy to same therapy completed in hospital. Two of the included studies had a small number of participants.

Therefore, this systematic review has identified that there is insufficient evidence to determine if home therapy programmes are more or less effective than usual care (visits to hospital or local health centre or hospital inpatient care), no intervention or a placebo intervention for any of the pre-determined outcomes. Within the notable limits of this review, the wide confidence intervals for the primary outcomes include the possibility that the intervention of home-based therapy programmes could plausibly be effective (as indicated by several points of improvement on the Barthel and Wolf Motor Function Test respectively).

Within all four of the included studies the initial level of impairment of participants was mild to moderate as measured by the Fugl-Meyer upper extremity scale. Other inclusion criteria relating to exclusion of other serious medical conditions or cognitive impairment which interfered with comprehension were also specified. These aspects further limit generalisability of the findings of this review to the wider population of stroke patients.

Additionally, only four studies were included and within these four studies essentially only two different programmes of therapy were investigated, which are not representative of all the therapies available.

All four studies used the Fugl-Meyer as a measure of upper limb motor impairment, however, only two studies reported outcomes relating to measures of activities of daily living, functional movement of the upper limb and extended activities of daily living. Therefore, overall, there was a lack of evidence concerning primary outcomes.

The lack of sufficient high quality evidence makes it inappropriate to draw conclusions from the results regarding the applicability of home therapy programmes within the context of current practice.

All of the included studies were randomised controlled trials and three of the studies reported adequate allocation concealment. Additionally, three studies reported using a blinded outcome assessor and one study reported an intention-to-treat analysis.

Within this review the reviewers encountered a number of difficulties in reaching consensus over the inclusion or exclusion of specific studies, despite attempts to create a clear and unambiguous definition of the intervention. Within the literature there were a limited number of studies reporting on specific home-based therapy programmes targeted at the upper limb. Many of the studies were service evaluations, which may have included elements of upper limb interventions; however it was unclear what, if any interventions were targeted at the upper limb. General lack of information about interventions made it difficult to decide on whether to include some studies. Considerations of home-based therapy versus other forms of service delivery have been covered in other reviews[334] and therefore were not included in this review. In addition, the aim of this review was to review studies that clearly had a programme of interventions targeted at the upper limb.

Particular difficulties were experienced in reaching a decision about the inclusion of two studies[284;338]. Consensus could not be reached between reviewers, and the majority decision was taken. This difficulty related to disagreement over whether virtual reality training comprised of more than one treatment component or not. Difficulties were also experienced in reaching consensus on the exclusion of studies in which part of the intervention had been delivered at home. These difficulties suggest that the definition was not sufficiently clear.

Whilst the research question posed had clear clinical relevance and focus, it is possible that in an attempt to apply rigorous and clearly defined criteria to the interventions may have inadvertently restricted the selection of relevant studies. Consequently it may be that the focus of this review was too narrow.

5.5.2 Limitations of the review

Despite rigorous searching it is possible that some relevant studies may not have been identified. By missing relevant studies, this potentially could have introduced bias into the review.

The diversity of the training carried out at home and the variations in reporting between studies led to the review team making some subjective decisions, particularly about the trials to include (see sections above) which may have introduced bias. The studies within this area are heterogeneous in terms of what can be classified as home therapy programmes targeted at the upper limb and there were a number of complex strands which required discussion among the review authors and consensus decisions being made. It is acknowledged that this is a clear limitation of this review.

For one study SDs were not reported and the SD from another paper (by the same research group which included similar patients) was imputed. Furthermore, standard deviations were calculated from reported standard error (SD = SE $\sqrt{n}$), with regard to another study. This may have introduced

some bias into the review process. However, it was considered that including imputed and estimated data from these studies was preferable to excluding the data.

5.5.3 Strengths of the review

As with the previous review the main strength of this review, relate to the rigors of the Cochrane review process.

Another strength relates to the perceived clinical relevance of this review as more and more stroke services are moved out into the community.

5.5.4 Implications for practice

There was insufficient evidence in this review to provide implications for practice. As no negative effect was demonstrated, it is reasonable to suggest that, given the lack of evidence, there is no reason to currently change clinical practice if home-based therapy programmes for the upper limb are being provided.

5.5.5 Implications for research

In order to be able to achieve the objective of this review: to determine the effects of home-based therapy programmes for upper limb recovery in patients with upper limb impairment following stroke, compared with: placebo or no intervention, usual care, same treatment in hospital, further research is required. Further research would provide evidence to ascertain if these interventions are effective, as proposed is possible, given the confidence intervals for the primary outcomes. High quality randomised controlled trials are needed which aim to test a therapy programme specifically targeted at the upper limb, in the home, and where participants are visited by health professionals at home. It is also desirable that future studies are explicit about the types of home therapy programmes provided and that an increased number of types of home therapy programmes are

investigated. Trials of adequate size and quality are required, not only to assess the clinical effectiveness of home-based therapy programmes for upper limb recovery but also to assess the cost effectiveness of undertaking such interventions.

5.6 Conclusions

Four studies were included in this systematic review. Due to the small number of included trials and small numbers of participants within these trials no conclusions can be drawn regarding the effects of home-based therapy programmes, targeted at the upper limb compared with placebo or no intervention, usual care or the same therapy completed in hospital.

Chapter 6

The feasibility and acceptability of a gravity-supported, computer-enhanced arm exerciser for acute stroke patients: a pilot randomised controlled trial

Chapter 6 The feasibility and acceptability of a gravity-supported, computer-enhanced arm exerciser for acute stroke patients: a pilot randomised controlled trial

6.1 Introduction

As identified in previous chapters' stroke is a major public health concern and upper limb rehabilitation continues to pose a particular challenge to rehabilitation professionals.

In Chapter 2 it was identified that the most predictive factor of upper limb outcome is initial level of motor impairment and function. A systematic review of interventions targeted at arm recovery (Chapter 3) identified a number of interventions which may be beneficial (or at least show promise) for improving upper limb recovery. These identified interventions were found to mainly incorporate elements of intensive, repetitive, task-specific practice. Therefore, these principles may be the most effective to incorporate into interventions, which are targeted at improving upper limb outcomes.

6.1.1 Upper limb intervention

Following the principles outlined above I wanted to pilot an intervention which could be easily integrated into clinical practice and incorporated the elements of intensive, repetitive, task-specific practice. Electromechanical/Robotic devices were one of the interventions which were shown to potentially have a positive effect on arm function outcomes. In contrast to some of the other interventions identified these devices offer an opportunity to provide high intensity, repetitive and task-specific practice without being labour-intensive.

Therefore, a randomised controlled trial of a device that could provide high-intensity, repetitive, task-specific practice was proposed. The chosen device;

the Armeo®Spring is an arm orthosis which combines an adjustable, arm gravity support with augmented feedback and a large 3-D workspace. This allows functional therapy exercises to be completed in a virtual reality environment[341]. Although this device has been licensed for the rehabilitation of a number of conditions, including stroke, limited research evidence exists regarding the efficacy of this device.

Furthermore the recent Cochrane review[260] (used in the analysis in Chapter 3) concluded that further research should focus on well-designed large-scale multicentre studies. It also suggested that further research should address questions relating to type, timing, frequency and duration of electromechanical and robot-assisted training as it is still unclear if such devices should be applied in routine rehabilitation, or when and how often they should be used. These uncertainties still exist as the current trials are small in size, include a number of different devices, focus on patients in the chronic phase and tend to use impairment rather than functional measures[342]. Additionally none of the current trials have been completed in the UK.

In addition, while the Armeo®Spring is licensed for use with stroke patients, only one randomised controlled trial has been published[272]. This trial was completed with chronic stroke patients in an outpatient setting in the United States. This trial of 28 participants found no significant difference between those who undertook the experimental intervention and those who received the control intervention (dose-matched table top exercises) on any outcome measures at end of intervention period. A significant difference in favour of the experimental intervention was found, in terms of the Fugl-Meyer at 6 month follow-up. Following consideration of this trial, in conjunction with a review of the other relevant literature it was felt a feasibility study for acute stroke inpatients, in the UK was required prior to a proposal for a large-scale trial.

The Medical Research Council (MRC)[59] framework for the design and evaluation of RCTs for complex interventions states that data concerning the

feasibility, acceptability and safety of any intervention should be acquired prior to undertaking a phase III randomised controlled trial.

For all of the outlined reasons a pilot, randomised phase II trial to assess the feasibility and acceptability of the Armeo®Spring was deemed appropriate to provide information relating to the suitability of a phase III trial and inform the design of such a trial. Following the update of the intervention review (September 2011) evidence relating to virtual reality was also available, which is relevant as the Armeo®Spring incorporates elements of virtual reality training. The intervention category of virtual reality was deemed as likely to be beneficial, reflecting evidence gained from a Cochrane systematic review[280]. This Cochrane review concluded that caution must be exercised when drawing conclusions from the evidence, as the studies of virtual reality are still too few and too small, and it is unclear what characteristics of the intervention are the most important. As with the evidence relating to electromechanical/robotic devices the applicability of the intervention to stroke survivors still requires to be clarified in terms of which type of patient is most likely to benefit, at which point such interventions should be delivered and how acceptable such interventions are to stroke patients.

The hypothesis of this pilot trial was that arm rehabilitation provided by the Armeo®Spring would be a feasible and acceptable intervention to implement with acute stroke patients with arm deficits.

6.2 Objectives

This phase II study had 3 main objectives:

- To determine the feasibility and acceptability of the Armeo®Spring arm orthosis for arm rehabilitation in acute stroke patients compared with standard therapy
- To assess the safety of the Armeo®Spring arm orthosis for acute stroke patients compared with standard therapy

- To assess the efficacy of the Armeo®Spring arm orthosis at two different intensities for acute stroke patients compared with standard therapy

6.3 Methods

This study was a phase II pilot prospective, randomised controlled trial with blinded outcome assessment, conducted within a single-centre (Glasgow Royal Infirmary stroke unit). Ethical approval was given by the health authority involved (NHS Greater Glasgow and Clyde).

6.3.1 Study population

Patients with a clinical diagnosis of stroke admitted to Glasgow Royal Infirmary stroke unit between August 2009 - November 2009 and January 2011 - June 2011 were considered for inclusion. An attempt was made to screen all consecutive admissions. Inclusion criteria for the study were: ≥18 years; clinical diagnosis of stroke; grade 1-4 on MRC scale of arm impairment; medically stable; ≤10 days post-stroke; able to give informed consent; able to understand and follow simple instructions and sitting balance sufficient to use the device safely. The exclusion criteria were: orthosis could not be fitted to the affected limb; bone instability of affected upper limb; no prior functional use of affected upper limb due to previous stroke or other condition; pronounced, fixed contractures of affected upper limb; open skin lesions on affected upper limb; major sensory deficit of affected upper limb; shoulder instability or excessive pain; severe spasticity; severe spontaneous movements; confused or non-cooperative; isolation due to infection; visual, perceptual or cognitive problems precluding participation in study protocol or involvement in any other intervention study. Initially it was estimated that 18 patients would be suitable for inclusion into the study, however due to feasibility nature of this trial no specific recruitment target was set.

Participants who met the inclusion criteria and who consented (Appendix F) were randomly assigned to one of three groups. A computer generated random number sequence in blocks of 6 was used to generate sequentially numbered opaque sealed envelopes, containing the participant allocation (1:1:1 for control: low intensity intervention: high intensity intervention). Group allocation for each participant was concealed in a sealed envelope and opened sequentially by a third party who was not otherwise involved in the study.

From information gained from the systematic review of predictor variables (Chapter 2) stratification of participants according to severity of arm impairment (MRC motor power scale[323]); 'severe' impairment (MRC 1 or 2) or 'mild/moderate' (MRC 3 or 4) was planned. The aim was to recruit equal numbers of participants with mild/moderate and severe upper limb deficits. However, due to limited numbers of appropriate patients with an initial 'severe' MRC score this planned stratification was not possible.

6.3.2 Study interventions

Participants were randomised to one of three groups (i) standard care (SC) (control group) or standard care plus one of two intensities of the experimental intervention (ii) Armeo®Spring arm orthosis 40 minutes per day, 3 days per week (low intensity intervention group) (iii) Armeo®Spring arm orthosis 60 minutes per day, 5 days per week (high intensity intervention group). The intervention period lasted for 2 weeks or until discharge from the acute stroke unit (whichever was sooner).

The interventions in the two experimental groups (groups 2 and 3) were, on occasions completed in more than one session e.g. 40 minutes per day in group 2 was completed over 2 sessions of 20 minute duration. This decision was based on the participants' tolerance and other commitments.

The experimental intervention was the Armeo®Spring arm orthosis. This device is a commercially available product which facilitates intensive task-

oriented arm rehabilitation. This arm orthosis provides support for the arm against gravity, which enables individuals with moderate to severe arm impairment to achieve an increased range of movement. The Armeo®Spring offers variable levels of support against gravity, provides a large 3D workspace and incorporates sensors of arm movement and hand grip which allows users to interact with therapeutic computer games and receive feedback about performance[272;341]. Visual representation of the device is provided in 7.3Appendix F.

Participants within the intervention groups were taken off the ward to a research office where the Armeo®Spring arm orthosis was located. Patients sat in a wheelchair (with armrest on affected side removed) or were transferred onto a standard chair with no armrests. At the beginning of each session the principal investigator adjusted the device to the individual, in terms of size adjustment and gravity support. Gravity balance compensation was gradually decreased, as deemed appropriate by the principal investigator. The principal investigator provided direct training/supervision throughout all the sessions.

The games played during the session were decided by the principal investigator and were dependent on each participant's abilities. Each game had different levels of difficulty. Games such as catching rain drops, picking apples and placing into a basket, cleaning a cooker top and revealing a picture were frequently used. The games principally focused on shoulder and elbow movements (flexion/extension, adduction/abduction, internal/external rotation). For participants with some wrist/hand movement games incorporating wrist flexion/extension, pronation/supination and grasp/release were also used. Throughout all the games auditory and visual feedback is provided to maintain attention and motivation. Additionally the end of each game feedback on performance was provided.

Standard therapy was provided by the usual therapists on the ward and the experimental intervention was provided by the principal investigator. Time spent in standard care and the activities completed were recorded.

Standard therapy interventions were chosen as the control intervention as it would be unethical to deny stroke patients usual care and this is the standard against which any new interventions would be compared. An attention control was not chosen as this is not representative of routine clinical practice and the purpose of the study was to assess the feasibility of the experimental intervention, in relation to usual clinical practice. Two different intensities of the experimental intervention were chosen as there is good evidence to suggest that increased intensity of practice leads to better outcomes, however, it is unclear what the optimum level of intensity actually is and it is also apparent that high intensity intervention can be difficult to achieve[51].

6.3.3 Outcome measures

Several characteristics of the participants (e.g. age, initial MRC classification) were recorded for descriptive and comparative purposes. Measures were completed at baseline, completion of intervention (2 weeks or discharge from stroke unit) and at 3 month follow-up. At baseline the measures were completed by the principal investigator and at the end of intervention and at 3 month follow-up the measures were completed by an external individual who was blinded to group allocation and had no contact with the study participants during the intervention period.

Primary outcomes

The primary outcomes of this trial were the feasibility and acceptability of the Armeo®Spring arm orthosis for arm rehabilitation in acute stroke patients. To assess feasibility, the number of sessions completed per-protocol and reasons for non-compliance with protocol at end of intervention period were documented.

To gauge opinions, particularly relating to acceptability of the arm interventions that were received, informal, semi-structured interviews, guided by a topic guide (Appendix H) were completed at the end of the intervention period. At the beginning of each interview the interviewer (PI) provided an

explanation of the purpose of the interview and highlighted that all information gained was confidential. The purpose of audio-recording was outlined, in addition to information regarding how the gained data would be used. To encourage open and honest feedback an explicit statement was made that all thoughts and opinions were valued and appreciated. A number of background questions were initially asked and then questions relating to arm interventions were focused on.

Interviews were chosen as the method of data collection to allow closed and open questions to be posed to participants. Closed questions were used to enable particular opinions to be gained e.g. did you find the intervention acceptable? Through the process of the interview probing questions were asked to explore opinions, feelings and experiences relating to the arm interventions. Due to the knowledge, skills and abilities of the participants involved, a flexible approach to undertaking the interviews was required and on occasions limited probing was relevant and/or possible. A topic guide was used as a prompt to ensure that all topics of interest were covered and to ensure a degree of standardisation between the interviews. Interviews were conducted by the principal investigator, who was not blinded to group assignment.

Secondary outcomes

Safety outcomes were assessed using a checklist (Appendix I). Arm pain was recorded by patient report and rated on a likert scale. The Borg Perceived Exertion Scale[343] (scale 6-13) was used to assess perceived level of exertion at the end of the intervention assessment. Other factors, assessed by patient report were: subluxation, spasticity, skin breakdown (at end of intervention period), falls, chest infection, urinary tract infection and recurrent stroke (at end of intervention period and at 3 month follow-up).

Upper limb function was assessed using the Action Research Arm Test (ARAT)[85] (Appendix J). This is a 19 item scale divided into 4 subscales (grasp, grip, pinch and gross movement) with a maximum score of 57. The Fugl-Meyer upper limb section (F-M)[88] (scale 0-66) was used to assess the

level of upper limb impairment (Appendix K) and the Barthel index (BI)[82] (scale 0-20) (Appendix L) was used to assess the level of disability in activities of daily living. The reliability and validity of these measures have been established[344-347].

Exploratory Outcome

To provide data to allow for a sample size calculation to determine the number of subjects required for a phase III randomised controlled trial. This was determined from data at end of 3 month follow up.

6.3.4 Data analysis

The feasibility of the intervention of interest was assessed by analysing the number and percentage of participants completing all of the assigned intervention sessions. Additionally, descriptive statistics (mean±standard deviation (SD) and median (range)) were used to summarise the number of days, sessions and minutes of intervention received by the participants in both of the intervention groups. Reasons for non-compliance with the protocol were explored. Time spent in standard care was analysed using descriptive statistics (as above) according to individual therapies (occupational therapy and physiotherapy) and by allocated group. Analysis was also completed related to time spent in therapies, according to number of days participating in the trial.

To assess acceptability of the arm interventions that were received, interviews were audio-taped and transcribed. Initially the transcripts were read and re-read to allow for increased understanding of the raw data. In the first instance frequency counts were used to provide a summary of the data, in relation to the closed questions that were posed using the topic guide (Appendix G). Constant comparative analysis[348] was then used to further explore the data. The themes were principally generated from the questions asked and the data within the codes from each of the interviews were then compared with those in the other interviews, to create broader categories; linking the codes from different interviews together. This process was initially

completed by myself, following the reading and re-reading of all the transcripts and then grouping similar aspects together using colour coding in the first instance and then within an excel spreadsheet. Another individual assisted in the coding process to attempt to increase validity of the findings. Participant validation of the findings was not completed. Quotes from participants were used to highlight the main themes.

The number of adverse events was analysed using descriptive statistics, by the overall group and each individual group. The scales used to assess particular safety outcomes i.e. arm pain scale and fatigue scale were analysed using mean±SD and median (range), with regard to allocated group.

An intention-to-treat analysis was planned as the means of data analysis for efficacy outcomes. However, two participants' data were missing at 3 month follow-up and analysis was completed only on those participants with available data. It was originally planned that any differences between groups would be investigated using analysis of covariance (ANCOVA), adjusting for baseline MRC score. However, due to the small number of included participants this form of analysis was considered inappropriate and the data was analysed using descriptive statistics only.

Change scores were used for the analysis of all three efficacy outcomes. The mean±SD and median (range) were calculated for the three efficacy outcomes. SPSS software (version19.0)[349] was used to conduct all statistical analysis.

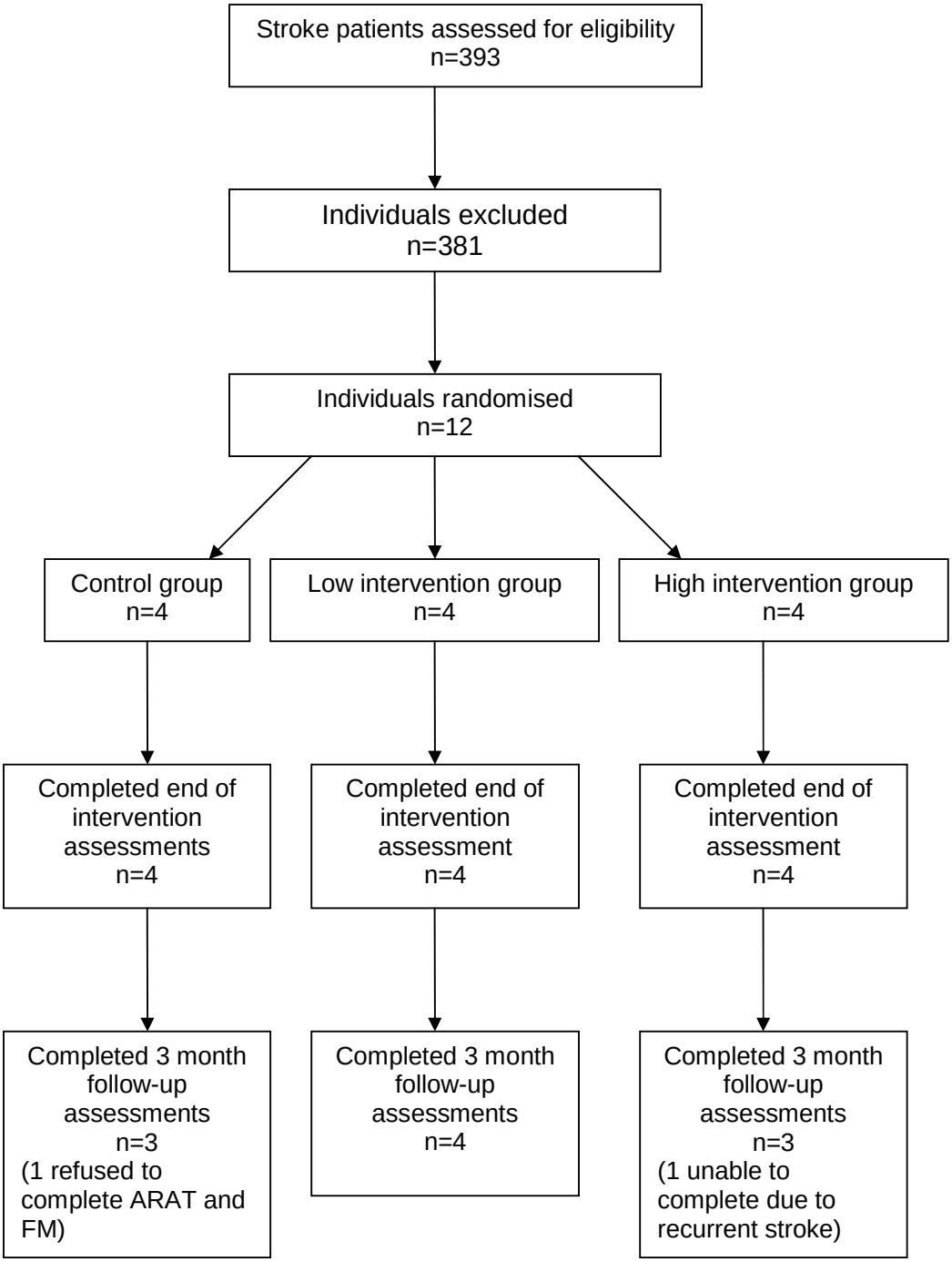
To estimate the required sample size for a phase III trial SPSS was initially used to apply a one-way analysis of variance (ANOVA) to the data of change in ARAT at 3 months (10 participant's data available) to gain the residual standard deviation (variability in the data after taking account of any mean differences in 3-month ARAT change between groups). This standard deviation was then used as a basis for the sample size calculation. The statistical package nQuery[350] was used to make the calculation, and the

following assumptions were made; that a two-group t-test would be used, at a significance level of 0.05, the test would be 2 sided, the difference in means to be detected was set at 6 points, power set at 90% and the standard deviation in both groups (estimated from the ANOVA analysis of residuals) was 15.76. The difference of means was set at 6 points based on previous literature[351] and knowledge of the ARAT measure.

6.4 Results

A total of 393 stroke patients were admitted and screened within the eight month recruitment period. Three hundred and eighty one individuals were excluded. The reasons for exclusion were: no upper limb deficit (n=231), not medically stable (n=44), >10 days post-stroke (n=29), discharge scheduled (n=12), no UL return (n=12), non compliant/cooperative (n=9), unable to follow commands (n=6), pre-existing upper limb issues (n=6), cognitive issues (n=5), poor vision (n=5), declined to participate (n=5), other upper limb issues (n=4), ataxia (n=4), poor sitting balance (n=3), neglect (n=3), participation in another intervention trial (n=1), unable to give consent (n=1) and infection (n=1). Twelve participants met the inclusion criteria, agreed to participate and were randomly allocated to control group (n=4), low intensity intervention group (n=4) or high intensity intervention group (n=4). All participants completed end of intervention assessments. Two participants did not complete 3-month follow-up assessments. One participant from the control group refused to complete ARAT and F-M assessments and one participant (from high intervention group) suffered a recurrent stroke. The flow of participants through the study is illustrated in Figure 6-1.

Figure 6-1 - Flow of participants through the study



For descriptive characteristics of the included participants see Table 6-1. The median age of participants was 70.50 (range 36-80) years and 67% of the participants' were male.

The baseline characteristics of the groups were similar, except for a few variables. A difference in age was evident between the control group (median 64, range 36-72) and the low intervention group (median 74.5, range 58-80). All participants in the low intervention group had a left sided paresis compared to one and two participants in the control and high intervention groups respectively. The most notable difference was on baseline ARAT scores. Participants in the control group had a mean of 36.50±23.22, compared to means of 16±22.04 and 18.75±12.18 in the low and high intervention groups.

Table 6-1 - Baseline characteristics of participants per allocated group

	Control (n=4)	**Low intervention (n=4)**	**High intervention (n=4)**
Age, mean±SD; median (range), yrs	59±16.31; 64 (36-72)	71.75±9.53; 74.5 (58-80)	65±13.56; 66 (49-79)
Sex, n	2M/2F	3M/1F	3M/1F
Side of paresis, n	3R/1L	0R/4L	2R/2L
Type of stroke	3 Infarct/ 1 Haemorrhage	2 Infarct/ 2 Haemorrhage	2 Infarct/ 1 Haemorrhage/1 SVD
Stroke classification (OCSP)	2 PACs/ 2 LACs	2 PACs/ 2 LACs	1 PACs/ 3 LACs
Symptom onset to randomisation, mean±SD; median (range), days	7.75±3.20; 7.50 (5-11)	9.25±1.71; 9.50 (7-11)	7.50±0.58; 7.50 (7-8)
Randomisation to end of intervention assessment, mean±SD; median (range), days	8±3.92; 8.50 (3-12)	9.25±6.18; 9 (2-17)	11.50±7.05; 8.50 (7-22)
Randomisation to 3 month follow up assessment, mean±SD; median (range), days	92.25±3.59; 91.50 (89-97)	91.75±4.27; 91.50 (87-97)	91.33±3.12; 92 (90-92)
MRC classification (0-5), mean±SD; median (range)	3±1.08; 3.50 (1-4)	3±1.41; 3.50 (1-4)	3.25±0.5; 3 (3-4)
ARAT (0-57), mean ±SD; median (range)	36.50±23.22; 44.50 (3-54)	16±22.04; 20.50 (0-48)	18.75±12.18; 20.50 (3-31)
Fugl-Meyer (UL section, 0-66), mean±SD, median (range)	37.25±21.72; 45.50 (6-52)	30.75±16.09; 33 (10-47)	36.25±10.34; 40 (21-44)
Barthel Index (0-20), mean±SD; median (range)	9.50±5.32; 9.50 (4-15)	6.50±2.38; 5.50 (5-10)	9±3.92; 8.50 (5-14)

6.4.1 Primary outcome: Feasibility

Details of the intervention completed by the two experimental groups (low and high intervention groups) are detailed in Table 6-2 and summarised in Table 6-3.

The median amount of time spent completing intervention using the experimental device was 140 (range 30-237) minutes in the low experimental group and 165.50 (range 35-445) minutes in the high experimental group. This was compared to the target of 240 minutes and 600 minutes respectively. Only one individual (low intervention group) achieved the target number of days of intervention (6/6) and came very close to achieving the target number of minutes (237/240).

The reasons for not achieving the target amounts of intervention were fairly consistent between participants and between the two groups. The most common reason for not achieving the target amount of intervention was transfer to a rehabilitation facility. Other common reasons mainly related to ward routines e.g. other therapies being delivered, patients not dressed and meal times.

Table 6-2 - Amount of actual intervention using experimental device received by participants in both intervention groups

Number of: days, sessions, minutes per participant	Percentage achieved	Reasons protocol target not achieved
Low intervention (n=4; Target 6 days, 240 minutes)		
6 days 11 sessions 237 minutes	100% - 98.75%	Set-up of machine; pt tired; ward routines (meals, visiting, therapy), availability of patient (dialysis))
4 days 6 sessions 163 minutes	66.67% - 67.91%	Transfer to rehab facility
2 days 2 sessions 30 minutes	33.33% - 12.50%	Transfer to rehab facility; pt issues (needing toilet; tired); limitation in what could be achieved due to poor movement
3 days 3 sessions 117 minutes	50% - 48.75%	Transfer to rehab facility; pt tired
High Intervention (n=4; Target 10 days, 600 minutes)		
5 days 7 sessions 202 minutes	50% - 33.67%	Transfer to rehab facility; pt tired; ward routines (not up till late, meals, therapy, visiting); IV antibiotics in affected arm;

		Machine set-up
1 day 1 session 35 minutes	10% - 5.83%	Transfer to rehab facility
8 days 10 sessions 445 minutes	80% - 74.17%	Machine not working; machine adjustments required; ward routines (visitors, meals); pt attending investigations; pt cramp in hand
4 days 5 sessions 129 minutes	40% - 21.5%	Transfer to rehab facility; pt waiting to see Dr; other pt in trial therefore time limited; ward routines (lunch, therapies, not dressed on arrival)

Table 6-3 - Amount of intervention completed; days, sessions and minutes, by intervention group

	Low intervention group	**High intervention group**
Mean±SD; median (range), days	3.75 ±1.71; 3.50 (2-6)	4.50±2.89; 4.50 (1-8)
Mean± SD; median (range), sessions	5.50±4.04; 4.50 (2-11)	5.75±3.77; 6 (1-10)
Mean±SD; median (range), minutes	136.75±86.65; 140 (30-237)	202.75±175.37; 165.50 (35-445)

The amount of standard care received by the three groups was also recorded and is presented in Table 6-4 and Table 6-5. The low and high intervention groups received more minutes of standard care than the control group. The low intervention group received the most amount of standard care but also had the largest range of observable days (i.e. the length of time spent in the trial).

Activities completed within standard care varied between patients. The recorded direct interventions (number of sessions) were: upper limb activities (n=40), dressing (n=26), gait (n=13), transfers (n=16), standing balance (n=14), lower limb activities (n=13), assessment (n=7), sitting balance (n=2), kitchen tasks (n=2), cognitive tasks (n=1) and chest physiotherapy (n=1).

Table 6-4 - Total amount of standard care (SC) received (time in minutes) during intervention period by intervention group

	Control group (n=4)	Low intervention group (n=4)	High intervention group (n=4)
Occupational Therapy	71.25±51.21; 55 (30-145)	96.25±61.42; 77.50 (45-185)	85±44.91; 92.50 (25-130)
Physiotherapy	68.75±57.50; 60 (15-140)	156.25±105.62; 135 (60-295)	100±86.51; 100 (0-200)
Total amount of SC	140±107.24; 115 (45-185)	252.50±155.59; 192.50 (145-480)	185±126.16; 192.50 (25-330)

Data presented as Mean±SD; Median (range)

Table 6-5 - Amount of standard care received (time in minutes per observable day during intervention period) by intervention group

	Control group (n=4)	Low intervention group (n=4)	High intervention group (n=4)
No. of observable days	4.25 (1.26); 4 (3-6)	5.25 (3.95); 4 (2-11)	4.75 (3.30); 4.50 (1-9)
Occupational therapy	15.73 (6.82); 15.62 (7.50-24.17)	22.01 (13.94); 17.15 (11.25-42.50)	21.29 (9.31); 20.50 (11.67-32.50)
Physiotherapy	14.89 (9.61); 16.25 (3.75-23.33)	31.08 (9.77); 28.41 (22.50-45)	20.80 (22.34); 16.61 (0-50)
Total amount of SC	30.62 (15.89); 31.87 (11.25-47.50)	53.09 (14.69); 49.94 (40-72.50)	42.10 (28.65); 33.50 (18.89-82.50)

Data presented as Mean±SD; Median (range)

6.4.2 Primary outcome: Opinions of therapy – Acceptability

Data gained from the qualitative interviews is reported below, in terms of the main themes generated from the questions that were posed.

Hopes

All participants had hopes for arm recovery. From the data gained it was clear that three participants had particular hopes for recovery, had a target and were able to assess own progress;

> *"….well I hoped to get back to, initially to get back to normal, the way it was originally but it still isn't back to what it was prior to the stroke…but it's a lot better, I must say it's a lot better."* (Participant number 12 – Low intervention group)

Another theme to emerge was an acknowledgement that full recovery may not be possible, but targets were still set;

> "the hopes is… I'd be happy with 90% better, not the 100% because I'm not expecting that, if I get 90% of my fitness back, yes I'd be happy, body, arm, leg…" (Participant number 9 – High intervention group)

Alongside hopes for recovery, one participant raised concerns;

> *"I was hoping that my arm to progress as much as my leg… because I'm no getting any feeling yet and that's what I'm worried about…"* (Participant number 11 – Control group)

Importance

All twelve participants reported that it was important to have therapy which was targeted at their arm. One participant perceived targeted intervention to be important as it provided them with a gauge of their recovery. They also used this as a source of influence and motivation for engaging in therapy.

> *"…everyday I look forward to getting that (physiotherapy usual care) because I know that way I would know if I was getting better*

> *or worse... I was grateful for that because I did try really, really hard. I had to try hard."* (Participant number 3 – Control group)

Frequently participants recognised the perceived value of therapy targeted towards the arm, and this particularly related to the recovery of movement and ability to complete activities;

> *"I think it was very important…I don't know if it would ever recover without therapy. I can't see it (arm) recovering on it's own…"* (Participant number 7 – High intervention group)

> *"It was very important; because obviously I need my hands… obviously you need your hands for a lot of things…"* (Participant number 3)

Acceptability

All twelve participants reported that the arm interventions received had been acceptable. One participant outlined particular components of acceptability, which included; level of difficulty, level of pain involved and necessary output required (tiredness);

> *"Well there was nothing hard about it, you weren't told to do anything hard…likes of your one you said if you're getting tired tell me and I'd say no we'll just keep going , I'm alright…One time, I had to say I'm getting a wee bit tired but that was because it wasn't working right that day."* (Participant number 5 – Low robot group)

Another participant outlined that the intervention was acceptable as it was perceived to be beneficial;

> *"Yes, I certainly did find it acceptable, aye, more than acceptable, once I realised what it was doing…"* (Participant number 6 – High intervention group)

Satisfaction

All participants reported being satisfied with the therapy they had received. The most frequently given reason for satisfaction was that outcomes were being achieved that were personally important;

> *"Yes, very much so…because I can see improvements going on in my arm, my arm is moving. I can pick up things with my fingers now which I wasn't doing before, so obviously I'm satisfied."* (Participant number 9 – High intervention group)

Expectations

Some participants did not have any preconceived ideas about therapy;

> *"I didn't know what to expect to be honest… it was all new to me but I enjoyed it actually…I'm getting there."* (Participant number 3 – Control group)

Other participants had preconceived ideas; however these were either challenged or surpassed by the therapy that was received;

> *"…well I did have expectations but did it, yes it did, it outweighed my expectations… well I expected that it would help me…but it did more than help me, it would give me confidence as well because it was getting better and that do you know what I mean?"* (Participant number 12 – Low intervention group)

Likes and Dislikes

The main theme to emerge throughout the interviews was that the participants perceived that there were benefits from the received therapy. All participants reported that they felt that the intervention they received made a difference to their arm.

> *"Just being able to do it myself again… being able to do it myself again and it was good cause you knew like, oh I'm getting better at that, you're getting better and that gives you a wee sort of praise sort of thing. You know at least I'm going to have the use of them back soon, do you know what I mean rather than not having the use of them at all, so aye I enjoyed it because it was helping me to get better and you've got to do what they tell you and it does help, it really, really does help."* (Participant number 3 – Control group)

> *"You know I think it helped…"* (Participant number 2 – High intervention group)

> *"…well I've got wee tiny bits of movement now with probably the therapy I've been having…"* (Participant number 7 – Low intervention group)

> *"…Well I think that it has helped…if it hadn't have been done, it may not have came to being used so much and as well…as well as what I'm doing now"* (Participant number 2 – high intervention group)

Specific reasons for liking the Armeo®Spring intervention related to the therapy characteristics (full range of movement possible, feedback, motivating, support against gravity, diversity of therapy, challenging, and regular intervention);

> *"That machine that you had that's good, because you're not going one way with your arm, you're going everyway, up, down and across, 45 degrees, 90 degrees and all this, chasing stuff. At the end of the day, after a wee while you start to catch it so once you get a plan and it starts to work and you say oh I can do this, and you try harder and harder get ahead and get more."* (Participant number 5 – Low intervention group)

Negative comments were made infrequently. Generally all twelve participants were positive about their experiences and there was a clear sense from the data that the participants were grateful for the assistance that had been received.

However some downsides of participating in the Armeo®Spring therapy were reported, which included; post therapy tiredness, pain (on one occasion), boring at times, frustrating when desired movements could not be achieved and device breakdowns;

> *"…sometimes after I was a bit tired."* (Participant number 1 – Low intervention group)

> *"…the fact there was a couple of break downs…"* (Participant number 8 – High intervention group)

One participant in the control group (participant number 10) reported having to deal with numerous activities *"…sometimes it was just one thing after another."*

A number of participants explicitly stated that they would have liked longer intervention time (four from intervention groups and one from control group) and one participant reported that they would have liked to have been pushed harder;

> *"I couldn't tell you if there's anything better…..push me harder"*
> (Participant number 5 – Low intervention group).

Another participant reported that they were unable to comment on possible improvements to the Armeo®Spring intervention due to short term nature of the intervention and several participants reported that they felt unable to comment on possible improvements to therapy due to a lack of knowledge or experience of alternatives.

One participant in the control group reported that he would have liked to have used the Armeo®Spring;

> *"... nah the only thing was maybe that machine you were talking about I want to try that, never got the chance at that…"*
> (Participant number 11 – Control group)

While every participant stated that they would recommend the intervention that they had received, only one participant stated that;

> *"the therapy that I got, I thought it helped and that I think that should be continued with anyone else with the same problems."*
> (Participant number 2 – Low intervention group).

6.4.3 Secondary outcomes: Safety

There were no treatment-related serious adverse events. During the intervention phase only one participant reported any adverse events (pain in hand). At end of intervention three participants were not asked the specific questions relating to safety outcomes due to an administrative oversight. However no specific complaints were volunteered. Therefore the following reporting of safety outcomes is based on nine participants.

At the end of the intervention period three adverse events were reported (Table 6-6). Two participants reported some form of arm pain (one each from the control and low intervention group). Pain analogue scale scores were reported as 3 (mild) and 5 (moderate). A further participant (control group) reported increased spasticity in upper limb.

In relation to the therapy received, reports of fatigue (Borg Scale) (recorded at the end of the intervention period) ranged from 9 (very light) to 13 (moderately hard) (Table 6-7).

At the three month follow up assessment (n=12) ten adverse events were reported (Table 6-6). Five adverse events were reported in the control group. One participant reported falls and another participant reported arm pain (reported as 8 on pain analogue scale). One participant reported three adverse events; arm pain (5 on pain analogue scale), chest infection and recurrent stroke. The three adverse events reported by three participants in the low intervention group all related to arm pain (scores of 5, 8 and 6 reported on pain analogue scale). Within the high intervention group one participant reported falls and another patient had suffered a recurrent stroke (reported by wife).

Table 6-6 - Number of reported adverse events; number of participants experiencing an adverse event (number of participants available for analysis)

	Control group	Low intervention group	High intervention group
End of intervention	2; 2 (n=4)	1; 1 (n=2)	None (n=3)
3 month follow-up	5; 3 (n=4)	3; 3 (n=4)	2 (n=4)

Table 6-7 -Borg Perceived Exertion Scale recorded at end of intervention

	Control group (n=4)	Low intervention group (n=2)	High intervention group (n=3)
Borg Perceived Exertion Scale (6-13)	11.50 ±1; 11 (11-13)	12±1.41; 12 (11-13)	11±2; 11 (9-13)

Data presented as Mean±SD; Median (range)

6.4.4 Secondary outcome: Efficacy outcomes

Mean time between randomisation and the end of intervention assessment was 9.58 (±SD 5.52) days (median 8.50, range 2-22) and the 3 month follow-up assessment was 91.82 (± SD 3.12) days (median 92, range 87-97).

Results for the three efficacy outcomes are presented in Table 6-8 and Table 6-9. Change scores between baseline and the end of intervention assessments (Table 6-8) were higher for both intervention groups than the control group for all three efficacy outcomes (ARAT, F-M and BI). This trend of higher change scores in the intervention groups was also evident between baseline and the 3 month follow-up assessments (Table 6-9).

Table 6-8 - Efficacy outcomes at baseline, end of intervention and change score between baseline and end of intervention

	Control group	Low intervention group	High intervention group
Action Research Arm Test			
Baseline	36.50±23.22; 44.50 (3-54)	16±22.04; 8 (0-48)	18.75±12.18; 20.50 (3-31)
End of intervention	42.50±28.34; 56.50 (0-57)	26.50±23.39; 24.50 (0-57)	32.75±24.13; 37 (0-57)
Change	6.00±8.83; 4.50 (-3-18)	10.50±8.66; 10.50 (0-21)	14.00±18.94; 9 (-3-41)
Fugl-Meyer			
Baseline	37.25±21.72; 45.50 (6-52)	30.75±16.09; 33 (10-47)	36.25±10.34; 40 (21-44)
End of intervention	44.25±24.96; 55 (7-60)	40.75±17.23; 45.50 (16-56)	44±15.98; 47 (22-60)
Change	7±6.05; 6 (1-15)	10±5.48; 8 (6-18)	7.75±6.40 7 (1-16)
Barthel Index			
Baseline	9.50±5.32; 9.50 (4-15)	6.50±2.38; 5.50 (5-10)	9±3.92; 8 (5-14)
End of intervention	12.50±5.26; 12 (8-18)	12.75±4.79); 14 (6-17)	13.25±5.85; 13.50 (6-20)
Change	3±1.83; 3 (1-5)	6.25±3.77; 7 (1-10)	4.25±2.22; 5 (1-6)

Data presented as Mean±SD; median (range)

Table 6-9 - Efficacy outcomes at baseline, 3 month follow-up and change score between baseline and 3 month follow-up (n=4 unless otherwise stated)

	Control group	Low intervention group	High intervention group

Action Research Arm Test			
Baseline	36.50±23.22; 44.50 (3-54)	16±22.04; 8 (0-48)	18.75±12.18; 20.50 (3-31)
3 month follow-up	38±32.91; 57 (0-57) (n=3)	41.25±14.52; 43 (22-57)	36.67±31.82; 53 (0-57)(n=3)
Change	6±10.82; 3 (-3-18) (n=3)	25.25±12.68; 27 (9-38)	22±22.60; 28 (-3-41) (n=3)
Fugl-Meyer			
Baseline	37.25±21.72; 45.50 (6-52)	30.75±16.09; 33 (10-47)	36.25±10.34; 40 (21-44)
3 month follow-up	43.67±22.59; 46 (20-65) (n=3)	54±9.63; 54.50 (42-65)	49 ±24.27; 62 (21-64) (n=3)
Change	7±11.27; 13 (-6-14) (n=3)	23.25±6.70; 21.50 (18-32)	14±12.49; 18 (0-24) (n=3)
Barthel Index			
Baseline	9.50±5.32; 9.50 (4-15)	6.50±2.38; 5.50 (5-10)	9±3.92; 8 (5-14)
3 month follow-up	17.50±1.00; 18 (16-18)	18.75±1.26; 19 (17-20)	19.33±1.15; 20 (18-20) (n=3)
Change	8±4.69; 8.50 (3-12)	12.25±1.71; 12.50 (10-14)	12±2.64; 11 (10-15) (n=3)

Data presented as Mean±SD; Median (range)

As fewer participants were recruited than had originally been anticipated, the intervention groups were combined to assess the effects of any dosage of intervention compared to the control group (Table 6-10 and Table 6-11). The trend for higher change scores between baseline and the end of intervention assessments and baseline and 3 month follow-up assessments was again evident.

Table 6-10 - Change scores between baseline and end of intervention for control and low and high intervention groups combined

	Control (n=4)	Intervention groups combined (n=8)
Action Research Arm Test	6 (8.83); 4.50 (-3-18)	12.25 (13.76); 10 (-3-41)
Fugl-Meyer	7 (6.05); 6 (1-15)	8.87 (5.64); 8 (1-18)
Barthel Index	3 (1.83); 3 (1-5)	5.25 (3.06); 5.50 (1-10)

Data presented as Mean±SD; Median (range)

Table 6-11 - Change scores between baseline and 3 month follow-up for control and low and high intervention groups combined

	Control (n=4)	Intervention groups combined (n=7)
Action Research Arm Test	6 (10.82); 3 (-3-18) (n=3)	23.86 (15.93); 28 (-3-41)
Fugl-Meyer	7 (11.27); 13 (-6-14) (n=3)	19.28 (9.94); 18 (0-32)
Barthel Index	8 (4.69); 8.50 (3-12)	12.14 (1.95); 12 (10-15)

Data presented as Mean±SD; Median (range)

Blinding of outcome assessor was not achieved in seven cases due to participants discussing the interventions that they had received, despite being advised not to reveal group assignment to the outcome assessor.

6.4.5 Secondary outcome: Exploratory outcome

Following the assumptions outlined in the data analysis section it was estimated that 146 participants per group would be required. As this calculation was based on a relatively small number of participants further calculations were completed varying the standard deviation by 30% to assess the impact on the sample size required. For a 30% increase in the standard deviation (20.49) the sample size requirement is increased to 247 participants per group and for a 30% reduction in standard deviation (11.03) a sample size of 72 per group would be required. For a larger variability in data (using 30% increase in residual standard deviation) 190 participants per group would be required for the study still to achieve 80% power.

6.5 Discussion

6.5.1 Summary of findings

This pilot study primarily examined the feasibility and acceptability of a novel device within an acute setting for individuals with arm deficits following stroke. In addition to the primary aims the safety and efficacy of this device, compared to standard care was also investigated.

Difficulty recruiting patients into this pilot trial was evident as only 3% (12/393) of those admitted to the acute stroke unit were recruited. Including only those with upper limb deficits (n=162) the recruitment rate rises to 7%. The limited amount of people eligible to participate in the study was the biggest draw back to the feasibility of this intervention within the acute stroke setting. Comparisons between the level of recruitment achieved in this study and other studies of upper limb interventions are difficult as few other studies have been completed with patients <10 days post-stroke. Eligibility of

individuals recruited to stroke rehabilitation units for constraint-induced movement therapy has been reported as 10%[352]. For a self-administered graded repetitive upper limb supplementary program (GRASP)[259] 40% of patients admitted to a rehabilitation facility with upper limb deficits were eligible. The problems encountered with recruitment to this study may have been compounded by the nature of the acute and comprehensive ward on which this trial was completed; the full spectrum of stroke patients were admitted to this ward, which is different to a rehabilitation setting.

Per-protocol levels of intensity, using the Armeo®Spring were not found to be feasible within the acute setting. However, increased intensity of direct therapeutic intervention, using the novel device was achieved (means of 2 hours 16 minutes and 3 hours 22 minutes for low and high intervention groups respectively). If transfer to the rehabilitation facility had not occurred (as was the case for 6 out of the 8 participants in the intervention groups) and if the device was used outwith the context of a trial (less time required to commence intervention) it is surmised that more therapy using the Armeo®Spring could be achieved.

The Armeo®Spring was found to be an acceptable intervention and positive feedback was received regarding the experience of using the device. However, participants also reported that standard care was acceptable. Therefore it would be inappropriate to surmise if the intervention under investigation was more acceptable to participants than standard care. These findings are only applicable to the participants included in this study. The only other reported trial of a similar device[272] also found users were satisfied with the device and reported that 90% of subjects preferred this type of therapy over conventional training.

The intervention was found to be safe with no participants suffering any serious adverse events during the intervention period.

Higher change scores for the intervention groups were found between the baseline and the end of intervention assessments and baseline and the 3

month follow-up assessments on the outcomes relating to (1) upper limb functional movement (ARAT) (2) upper limb impairment (F-M) and (3) level of disability (BI), when compared to the control group. On two of the three efficacy outcomes (F-M and BI) at the end of the intervention period and on all three measures at the 3 month follow-up assessment the mean change score was highest in the low intervention group. Statistical analysis was not appropriate due to the small number of participants, and therefore limited conclusions can be drawn. Nevertheless, this suggestion of a positive effect of the intervention concurs with other studies of interventions which have included aspects of intensive, task-specific repetitive practice. Also the previous study[272] of therapy delivered using a similar device found that intervention was associated with modest sustained gains at 6 month follow-up when compared to conventional training. However, comparisons between studies is difficult as this current study recruited patients much earlier than most studies (most robotic studies have recruited patients in the chronic phase)[181;268;269;272;273] and involved a less intensive protocol.

Group differences on the ARAT in favour of both intervention groups (4.5 points for the low intervention group and 8 points for the high intervention group) were found at the end of intervention. A group difference of 3 points on the ARAT has been reported as meaningful[353]. Minimal clinically important change on the ARAT has been reported in different ways. In acute population (as in this study) a minimal clinically important change was found to be 12 for affected dominant side and 17 for non-dominant affected side[354]. Within this current study change scores at end of intervention were 6, 10.5 and 14 (control, low intervention and high intervention groups respectively). A change of 6 points on the ARAT has also been suggested as clinically significant for individuals with chronic hemiparesis as it represents 10% of the total scale[351].

Due to a small sample size and other possible confounding factors the findings of this study must be interpreted with caution. Firstly, imbalance between the groups must be considered as weakening the validity of the between group comparisons. The participants in the control group scored

considerably higher on the ARAT at baseline than the two intervention groups, therefore it must be considered that these subjects had less potential for improvement than the subjects in the intervention groups. This issue was compounded by the ceiling effects of the chosen outcome measures. A ceiling effect occurs when a measure possesses a distinct upper limit for potential responses and a large concentration of participants score at or near this limit (as evident in this study). Thus further improvement may have occurred; however the outcome measures used did not reflect this improvement.

Additionally, the participants in both the intervention groups received more standard care, and this may have been a confounding factor.

The higher change scores at end of intervention assessment and retained at 3 month follow-up would suggest that there is some beneficial effect of the intervention of interest. However as stated above these findings are tentative.

Within this trial the intervention delivered using the Armeo®Spring was conducted on a one-to-one basis with the principal investigator. Therefore the way the intervention was delivered in this trial was no less labour intensive than standard therapy.

With regard to the sample size calculations, caution must be exercised due to the number of assumptions made and the fact that the estimation of variability of the data was based on only 10 participants. This note of caution is referred to within the MRC complex intervention framework as it is acknowledged that when evaluations are scaled up effects may be smaller or more variable and response rates lower when the intervention is carried out within a wider range of settings and participants[59].

6.5.2 Limitations of the study

Several potential limitations of this present study must be considered. Primarily the study enrolled only a small number of subjects and therefore generalising the results beyond this study population is problematic. Secondly it is impossible to determine which components of the therapy; the actual Armeo®Spring intervention, the increased therapy time or both contributed to the suggestion of positive effect. A further source of potential bias could have been the failure to blind patients and members of the clinical team e.g. nursing and therapy to the allocation of treatment group. However, it is generally considered difficult to achieve blinding on this level within rehabilitation studies. Blinding of outcome assessor was also compromised as seven participants indicated to the outcome assessor which group they belonged to. The intervention groups received intervention from the same therapist. A multi-therapist study is needed to clarify any independent effects of the Armeo®Spring, as opposed to the possibility of therapist effects.

The interviews to gain the opinions of the participants were conducted by the principal investigator, who was not blinded to treatment group allocation. This could have biased the results as participants may not have been truly honest and open about their experiences and feelings, and may have been overly positive. However, honest feedback about experiences of therapy was encouraged.

While the outcome measures used in this study reflected a range of abilities, no measures relating to real world use of the upper limb or participants perceptions of use of the upper limb were utilised. Additionally, within the current study, patient report of ability was generally used to achieve a Barthel score. This could have led to under or over estimating of ability and inaccurate scores being gained. The imbalances between the groups, as discussed above and the ceiling effects of the included outcome measures, further mean that the findings of this study can only be cautiously explored.

6.5.3 Strengths of the study

This pilot study had many elements of a well-designed trial. Attempts were made to screen all consecutive admissions into an acute stroke unit. This is one of few studies investigating the use of a novel device within an acute setting and therefore a feasibility and acceptability design was appropriate. Allocation to treatment groups was completed through a randomisation procedure, with adequate allocation concealment. Furthermore, a blinded outcome assessor was used for the efficacy outcomes and analysis was completed on an intention-to-treat basis at the end of intervention.

6.5.4 Implications for practice

This pilot study has limited implications for practice. The findings of this study suggest that a small number of patients are eligible to receive this intervention in the acute phase post-stroke and that per-protocol levels of intensity are difficult to achieve. Further research is required before definitive conclusions can be made regarding the efficacy of this novel device for improving upper limb outcomes. If such a device is already in place in an acute setting it is reasonable to suggest that this should be used as an adjunct to standard therapy as it was found to be a safe and acceptable intervention in this small-scale study.

6.5.5 Implications for research

Randomised controlled trials with larger numbers of participants should be considered. Larger studies with an additional group matched for therapist attention would be appropriate. However, this again raises the question of the feasibility of increasing direct therapeutic interventions within the current health-care setting. It is therefore suggested that in order for feasibility to be established the intervention should be delivered by ward therapists instead of a researcher in future studies. In order for per-protocol levels of intensity to be achieved alternative health-care settings should be considered i.e. a combined acute and rehabilitation facility. Any replication of this study

should also consider assessing outcomes at 6 months and 12 months post-stroke to assess if differences exist between groups within the chronic stage. Additionally mechanical data, extracted from the Armeo®Spring is advised for future studies to provide objective measures of outcomes. Included in the Armeo®Spring software are tools which allow for accurate, objective monitoring of progress, which in addition to an easily understandable summary of performance after each game and session, include precise assessment of participants ability to move in terms: of active reaching distance, reaction time and movement velocity (A-MOVE), precise, goal orientated movements (A-GOAL), inter-limb coordination during active movements (A-COORD) and range of motion during active and passive movements (A-ROM). All participants (control and intervention participants) should have an assessment using the device at baseline and then at follow-up assessment points.

6.6 Conclusions

This small-scale randomised feasibility study found that implementation of a novel device (Armeo®Spring) within an acute stroke setting was challenging. Only a limited number of patients were eligible for participation in the study and per-protocol levels of intensity of the intervention could not be achieved. However, the intervention was found to be safe with positive findings reported by participants with regard to acceptability of and satisfaction with the intervention. There was a suggestion that those receiving increased intensity of therapy, delivered by the Armeo®Spring achieved greater change scores on measures of upper limb recovery and level of disability between baseline and end of intervention and 3 month follow-up. However, due to the small number of participants and limitations of the study these results must be interpreted with caution. Further larger studies should be conducted to assess the feasibility of use of the Armeo®Spring within additional settings and to determine if any significant effects exist between groups. Since completion of this feasibility study, the experiences encountered have been used to inform the design of two larger scale studies,

which are designed to investigate the use of devices in arm rehabilitation (personal communication).

Chapter 7

Conclusions

Chapter 7 Conclusions

This thesis set out to investigate issues and accumulate information relating to upper limb interventions following stroke. This has been achieved using a number of methods.

Throughout my research I used the Medical Research Council (MRC) complex intervention framework as a guide in order to provide information for a phase III randomised controlled trial (evaluation stage of the framework) that was theoretically-defensible, reproducible and adequately controlled, with adequate statistical power. This thesis focused on the developmental and feasibility/piloting phases of the framework.

In order to identify the relevant evidence base a number of systematic reviews were undertaken to establish what is already known about interventions targeted at the upper limb. Additionally, a systematic review of predictive variables was completed to allow for better understanding of likelihood of recovery and identify potential predictive variables to stratify patients in a planned trial. These reviews contributed to the development of relevant theory within this area. Additionally completion of these reviews, and the other two reviews gave me the opportunity to; further consider upper limb problems and possible aspects associated with recovery, identify an appropriate intervention, understand the characteristics of beneficial interventions and consider important factors such as appropriate outcomes and control intervention. The Cochrane systematic reviews that were undertaken were relevant to the undertaking of a feasilibty study of an electromechanical device as some such devices have a bilateral element and therefore when considering which device to study it was worth investigating if a device with such an element would have added benefit. With a push toward community rehabilitation, instead of prolonged rehabilitation within a hospital setting, devices which can be easily used with outpatients or within the home setting require to be investigated. Currently there are limited devices which can be used at home.

Electromechanical/robotic devices also provide the possibility of providing an adjunct to other types of interventions, as it is unlikely that patients would only receive rehabiltiaiton with a device (patients would usually receive a programme of therapy).

The feasibility trial that was undertaken assessed recruitment rates and feasibility of delivering per-protocol intensity of interventions, acceptability of the intervention and allowed for cautious estimation of sample size to be provided.

Within this conclusions chapter I will outline the main results from each section of this thesis, in relation to the original research objectives. In addition, challenges encountered and areas for future development will be discussed.

7.1 Key Findings

7.1.1 Predictors of upper limb recovery

The first research objective was to identify predictive variables of upper limb recovery after stroke. This was completed using systematic review methodology, with included meta-analysis.

A large number of studies met the inclusion criteria for this review. The most consistent and robust evidence indicated that initial measures of upper limb function and impairment and neurophysiological measures can predict upper limb recovery. Moderate evidence of association was found for the variables of global disability and lower limb impairment.

7.1.2 Interventions targeted at upper limb recovery

This systematic review and accompanying meta-analysis provided a summary of the existing evidence for interventions targeted at upper limb

recovery following stroke. In total thirteen interventions were identified, eight of which suggested beneficial or promise of beneficial effects.

Despite the heterogeneous nature of the evidence available there was consistent evidence to suggest that interventions with elements of intensive, repetitive, task-specific practice are likely to have favourable outcomes in terms of upper limb recovery after stroke.

7.1.3 Effectiveness of two specific interventions

Two Cochrane systematic reviews were completed to contribute high quality evidence to the existing evidence base of upper limb interventions.

The first review investigated bilateral training. Although eighteen trials were included in this review, firm conclusions could not be drawn due to insufficient high quality evidence. The available evidence indicates that bilateral training is no more (or less) effective than usual care or unilateral training for functional or motor impairment outcomes.

The second Cochrane review focused on home-based therapy interventions. This review was completed as increasingly stroke services are being provided in the community. Only four small randomised controlled trials met the inclusion criteria for this review and therefore no conclusions could be drawn regarding the effects of such interventions.

7.1.4 Identify and evaluate a novel, evidence-based intervention

Following completion of a thorough examination of the existing evidence-base I wanted to identify and then evaluate a novel, evidence-based intervention as per my research objectives. From the research evidence I chose a repetitive, task-specific, intensive intervention (Armeo®Spring). Electromechanical/robotic devices had suggested a potential positive effect for upper limb recovery.

A pilot feasibility study of stroke patients with upper limb deficits within an acute stroke unit was undertaken with the primary aim of establishing the feasibility and acceptability of the Armeo®Spring device as a way of providing repetitive, task-specific, intensive practice. Secondary outcomes of safety and efficacy were also considered. This feasibility study demonstrated that recruiting into such a trial, in an acute setting is challenging and that per-protocol levels of intensity of intervention were not feasible to provide. However, increased levels of therapeutic intervention were achieved and this novel intervention was found to be acceptable to participants. This pilot trial also demonstrated a higher change in efficacy outcomes within both intervention groups than in the control group; although this is an indicative finding rather than a statistically significant result. Furthermore, due to small sample size and other confounding factors these findings must be interpreted with caution.

7.2 Challenges encountered

The systematic reviews were all primarily limited by the heterogeneity of the available studies.

In particular, the predictive variable review proved to be complex and challenging, and took longer than originally anticipated. Interpretation of the results was complicated by methodological factors including variations in study populations, upper limb motor outcome scales, timing of baseline and outcome assessments and predictors selected.

The systematic review and meta-analysis of interventions was limited by small numbers of participants and trials and heterogeneous outcome measures and interventions. A larger number of participants, within a larger number of more homogenous trials would obviously have been preferable.

The two Cochrane reviews were mainly limited by the lack of high quality evidence, particularly within the home-based therapy review. Further

limitations of the home-based therapy review, in terms of definition of the intervention are also acknowledged.

Within the feasibility trial the recruitment rate was lower than expected and hoped for. To overcome this, recruitment could have been extended. However, within the constraints of time and funding this would not have been practical, unless recruitment had been started earlier. Unfortunately, due to only having access to one Armeo®Spring device involvement of more than one site was also not practical. Despite these limitations the information gained from this study provides important information for future studies and it served the purpose of a feasibility study, as proposed by the MRC complex intervention framework.

7.3 Future directions

The rehabilitation research community need to consider a number of factors which have been highlighted throughout this thesis.

Adequate reporting of methods undertaken in trials is essential. This thesis has identified that poor reporting is often evident and this makes reviewing and summarising the available evidence problematic.

A consensus on a core set of relevant outcome criteria for upper limb recovery would be useful to allow for more accurate comparison of trials. It is suggested that such a dataset should include outcome measures, which are relevant to all domains of the International Classification of Functioning, Disability and Health (ICF)[19].

With regard to the particular findings of this thesis, trials of upper limb interventions should consider stratifying participants according to appropriate variables and interventions targeted at the upper limb should incorporate elements of intensive, task-specific and repetitive practice.

Interventions targeted at upper limb recovery is an area which is continually growing and it is clear from the work undertaken in this thesis that further research is required for evidence to be applicable and relevant in all clinical settings.

Further developmental, feasibility/piloting work is suggested as this thesis gave limited consideration to the implementation of the Armeo®Spring device, in terms of clinicians' perceptions and likelihood of funding being available for such a device. Such considerations form an important part of the development process (modelling process and outcomes) of the MRC complex intervention.

This thesis used the MRC complex intervention framework as a guide to identify and evaluate a novel intervention for upper limb recovery following stroke. The information gained; appropriate variables to stratify patients, characteristics of beneficial interventions, feasibility of recruiting and providing intensive levels of per-protocol interventions within an acute stroke unit and sample size estimation, would not only be useful to plan a further study of the Armeo®Spring device but also for randomised controlled trials of other upper limb interventions.

Therefore in conclusion a future large scale study of the Armeo®Spring is recommended, once further work (outlined above) is completed. It is recommended that such a study be completed in a setting where patients are not transferred to another location within a short time frame. Furthermore stratification on the basis of clinical baseline measures is suggested. For a future study I would propose only a two group study with the intervention group receiving more toward the low-intensity amount of Armeo®Spring intervention (40 minutes a day 3 times a week) and the control group receiving standard care. In terms of outcome measure I would advocate the use of the Action Research Arm Test as the primary outcome measure, with additional measures incorporating motor impairment of the upper limb, ability in ADL and perceived usage of the upper limb. It is also my suggestion that mechanical data, incorporated within the software of the device be included

as an objective outcome measure. Longer-term follow-up (6-12 months) is also proposed to assess effects of the intervention in the longer term.

Appendices

Appendix A – Upper limb functional outcomes

Table A-1 - Secondary analysis – (ii) Results of association between predictor variables and functional outcomes of upper limb recovery

Variable	Total no. of studies (participants)	Vote counting (significant association)	Strength of evidence analysis	Statistical analysis No. of studies (participants) Odds ratio (95% CI)	Statistical conclusion	Combined assessment of evidence.
Demographic factors						
Age (younger vs. older)	9[65;96;109;119;121;125;126;130;133] (n=766)	1[125] (n=57)	Strong evidence of no association	3[65;96;130] (n=278) 1.31 (0.75 - 2.29)	No significant association	Strong evidence of no association between age and upper limb functional recovery.
Sex (male vs. female)	9[65;96;109;114;119;121;125;130;133] (n=750)	0	Strong evidence of no association	4[65;96;114;130] (n=312) 1.53 (1.02 – 2.32)	Significant association	Inconclusive evidence. Suggestion that males are more likely to have better upper limb functional recovery.
Time since stroke (less vs. more time)	6[65;76;125;130;133;149] (n=1498)	5[65;125;133;141;149] (n=1343)	Moderate evidence of association	2[65;130] (n=256) 1.06 (1.02 – 1.10)	Significant association	Moderate evidence of association. Those less time since stroke more likely to have better upper limb functional recovery.
Social support (yes/no)	1[65] (n=100)	0	Limited evidence of no association	1[65] (n=100) 1.41 (0.84 – 2.38)	No significant association	Limited evidence of no association between level of social support and upper limb recovery.
Severity of stroke – global factors						
Global disability (less vs. more disability)	6[65;96;99;125;131;133] (n=524)	5[65;99;125;131;133] (n=502)	Moderate evidence of association	3[65;96;131] (n=188) 2.47 (0.87 – 7.04)	No significant association	Inconclusive evidence of association between global disability and upper limb functional recovery.
Type/Class of stroke (less vs. more severe)	4[65;119;130;133] (n=533)	2[65;130] (n=256)	Inconclusive evidence	2[65;130] (n=256) 3.54 (0.46 – 27.34) I^2=95%	No significant association	Inconclusive evidence of association between severity of stroke and upper limb functional recovery.

Urinary incontinence (absent vs. present)	4[65;126;130;139] (n=382)	2[65;130] (n=256)	Inconclusive evidence	2[65;130] (n=256) 4.12 (1.82 – 9.32) I^2=55.2%	Significant association	Inconclusive evidence relating to the association between urinary incontinence and upper limb functional recovery.
Global impairment (less vs. more impairment)	2[109;119] (n=113)	2[109;119] (n=113)	Limited evidence of association	0	NA	Limited evidence of association between global impairment and upper limb functional recovery.
Lesion size/volume (smaller vs. larger)	2[101;114] (n=86)	0	Limited evidence of no association	1[114] (n=34) 1.20 (0.70 - 2.05)	No significant association	Limited evidence of no association between infarction size/volume and upper limb functional recovery.
Level of consciousness at onset (GCS)	1[65] (n=100)	1[65] (n=100)	Limited evidence of association	1 (n=100) 1.03 (1.01 – 1.06)	Significant association	Limited evidence of association between level of consciousness at onset and upper limb functional recovery.
7th Cranial nerve	1[109] (n=58)	1[109] (n=58)	Limited evidence of association	0	NA	Limited evidence of association between 7th cranial nerve involvement and upper limb functional recovery.
Bowel function	1[126] (n=50)	0	Limited evidence of no association	0	NA	Limited evidence of no association between bowel function and upper limb functional recovery.
Severity of stroke –focal factors						
UL baseline impairment measures (less vs. more impairment)*	20 (n=1838) [27;65;75;76;89;99;100;102;109;114;119;121;125;130;131;133;135;138;140;142]	14[27;65;75;76;89;99;109;114;125;130;131;133;135;142] (n=1634)	Strong evidence of association	9[27;65;89;100;121;130;131;135;142] (n=1235) 18.66 (9.80 – 35.53)	Significant association	Strong evidence of association. Those with less initial UL impairment are more likely to have better upper limb functional recovery.
UL baseline functional measures (more vs. less function)**	9[101;102;109;119;124;126;133;142;149] (n=1503)	9[101;102;109;119;124;126;133;142;149] (n=1503)	Strong evidence of association	3[101;124;142] (n=149) 51.97 (9.34 – 289.03)	Significant association	Strong evidence of association. Those with more initial upper limb function are more likely to have better upper limb functional recovery.
Lower limb impairment (less vs. more impairment)	3[65;119;130] (n=311)	3[65;119;130] (n=311)	Moderate evidence of association	2[65;130] (n=256) 10.65 (4.94 – 22.94)	Significant association	Moderate evidence of association. Those with less leg impairment more likely to have better upper limb functional recovery.

Co-factors (associated with stroke severity)						
Side of stroke (left vs. right)	9[65;96;99;109;119;121;125;130;133] (n=773)	2[65;130] (n=256)	Moderate evidence of no association	4[65;96;99;130] (n=335) 1.49 (0.82 – 2.71)	No significant association	Moderate evidence of no association between side of stroke and upper limb functional outcomes.
Cognition and perception (no deficit vs. deficit)***	7[65;76;99;109;130;133;139] (n=685)	3[76;109;130] (n=230)	Inconclusive evidence	3[65;99;130] (n=313) 2.01 (0.79 – 5.15) I^2=92.6%	No significant association	Inconclusive evidence relating to the association between cognition and perception and functional upper limb recovery.
UL sensation (no deficit vs. deficit)	5[65;99;109;121;139] (n=337)	3[65;99;109] (n=215)	Inconclusive evidence	1[65] (n=100) 1.89 (1.33 – 2.69)	Significant association	Inconclusive evidence. Suggestion that absence of sensory deficit is associated with better upper limb functional recovery.
Visual disorders (absent vs. present)	3[65;109;130] (n=314)	3[65;109;130] (n=314)	Moderate evidence of association	2[65;130] (n=256) 5.22 (2.40 – 11.36)	Significant association	Moderate evidence of association. Those with absence of a visual disorder more likely to have better upper limb functional recovery.
Sitting balance (no deficit vs. deficit)	3[65;126;130] (n=306)	1[130] (n=156)	Inconclusive evidence	2[65;130] (n=256) 4.75 (0.28 – 80.53) I^2=96.8%	No significant association	Inconclusive evidence. Suggestion of no association between sitting balance and upper limb functional recovery.
Stroke location	2[99;101] (n=109)	2[99;101] (n=109)	Limited evidence of association	Unable to pool data	Unable to pool data	Limited evidence of association between stroke location and upper limb functional recovery.
Shoulder complications (absent vs. present)	2[109;139] (n=134)	2[109;139] (n=134)	Limited evidence of association	0	NA	Limited evidence of association. Those with absent shoulder complications more likely to have better upper limb functional recovery.
Speech disorders (absent vs. present)	1[109] (n=58)	1[109] (n=58)	Limited evidence of association	0	NA	Limited evidence of association. Those with no speech disorders more likely to have better upper limb functional recovery.
Handedness (right vs. left vs. ambidextrous)	1[109] (n=58)	0	Limited evidence of no association	0	NA	Limited evidence of no association between handedness and upper limb functional recovery.

Sensation (no deficit vs. deficit)****	2[130;133] (n=378)	1[130] (n=156)	Inconclusive evidence	1[130] (n=156) 9.15 (3.36 – 24.89)	Significant association	Inconclusive evidence relating to association between sensation and upper limb functional recovery.
No. of comorbid conditions (less vs. more)	2[119;130] (n=211)	0	Limited evidence of no association	1[130] (n=156) 1.96 (0.96 – 3.98)	No significant association	Limited evidence of no association between no. of comorbid conditions and upper limb functional recovery.
Rt-PA (yes/no)	1[130] (n=156)	0	Limited evidence of no association	1[130] (n=156) 1.73 (0.81 – 3.73)	No significant association	Limited evidence of no association between Rt-PA and upper limb recovery.
No. of previous strokes	1[109] (n=58)	1[109] (n=58)	Limited evidence of association	0	NA	Limited evidence of association between number of previous strokes and upper limb functional recovery.
Duration for stroke to develop	1[109] (n=58)	1[109] (n=58)	Limited evidence of association	0	NA	Limited evidence of association between duration for stroke to develop and upper limb functional recovery.
Pain in arm	1[109] (n=58)	1[109] (n=58)	Limited evidence of association	0	NA	Limited evidence of association between pain in arm and upper limb functional recovery.
Sit to stand	1[126] (n=50)	0	Limited evidence of no association	0	NA	Limited evidence of no association between sit to stand and upper limb functional recovery.
Proximal/Distal paresis	1[114] (n=34)	0	Limited evidence of no association	1 (n=34) 9.09 (0.26 – 333.33)	No significant association	Limited evidence of no association between distribution of paresis and upper limb functional recovery.
Neurophysiological factors						
Motor evoked potentials (present vs. absent)	5[96;114;115;135;144] (n=191)	3[96;115;135] (n=136)	Inconclusive evidence	4[96;114;135;144] (n=115) 8.75 (0.94 – 81.80)	No significant association	Inconclusive evidence of association between presence of MEPs and better upper limb recovery.

Somatosensory evoked potentials (present vs. absent)*****	2[122;124] (n=87)	2[122;124] (n=87)	Limited evidence of association.	1[124] (n=68) 35.14 (4.18 – 295.19)	Significant association	Limited evidence of association. Those with present SSEPs are more likely to have better upper limb functional recovery.
Pre-morbid function						
Pre-stroke ability	1[109] (n=58)	0	Limited evidence of no association	0	NA	Limited evidence of no association between pre-stroke ability and upper limb functional recovery.
Pre-stroke mental status	1[109] (n=58)	0	Limited evidence of no association	0	NA	Limited evidence of no association between pre-stroke mental status and upper limb functional recovery.

Footnotes:
0 – no studies able to be included in statistical analysis
NA – no conclusions could be drawn from statistical analysis as no studies were available for inclusion in meta-analysis
Unable to pool data – due to differences in way data presented unable to sensibly combine in a meta-analysis
I^2 data only given if I^2>50%

*Au-Yeung 2009[99] - 2 variables; Motricity Index (MI) and Composite Spasticity Scale. MI (chosen for analysis) significant; Composite Spasticity Scale non-significant association.
*Beebe 2009[100] - 10 variables; NIHSS motor arm and Active range of movement at 9 segments of upper extremity. NIHSS motor arm (chosen for analysis as odds ratios could be calculated for association with ARAT at 3 months) non-significant. All 9 segments of AROM significant association with upper extremity function score.
*Katrak 1998[121] - 3 variables; hand movement scale, shoulder shrug and shoulder abduction. Hand motor scale (chosen for analysis) and shoulder abduction non-significant association. Shoulder shrug had a significant association.
*Park 2008[133] - 4 variables of upper limb impairment; Fugl-Meyer (F-M) UL (chosen for analysis) and spasticity of elbow, flexors and wrist flexors. F-M significant. Other variables non-significant.
*Renner 2009[138] - 5 variables; hand grip, rise of rate of tension of hand grip, wrist extension, rate of rise of tension of wrist extension and isotonic wrist extension acceleration. Hand grip (chosen for analysis) and wrist extension non-significant association. Other variables had a significant association.

**Canning 2004[102] - 2 variables; Motor Assessment Scale (MAS) and dexterity. MAS (chosen for analysis) significant association; dexterity non-significant association.
**Loewen 1990[126] – 2 variables; Modified MAS combined arm score and upper arm function scales. Combined arm score (chosen for analysis) significant; upper arm function non-significant.

***Kwakkel 2003[65] – 2 variables; MMSE and visual inattention (letter cancellation test). MMSE (chosen for analysis) no significant association; visual inattention found to have a significant association.
***De Weerdt 1987[109] – 3 variables; Post stroke mental status, tactile hemi-inattention and stereognosis. Post stroke mental status (chosen for analysis) and tactile hemi-inattention significant association. Stereognosis non-significant association.

****Park 2008[133] - 2 variables; light touch and proprioception. Light touch (chosen for analysis) non-significant association; proprioception significant association.

******Al-Rawi 2009[98] – 3 variables; N_{20} latency, peak to peak amplitude and amplitude ratio. N_{20} latency (chosen for analysis) and peak to peak amplitude positively correlated. No relationship reported for amplitude ratio.

Appendix B – Upper limb impairment outcomes

Table B-1 - Secondary analysis – (iii) Results of association between predictor variables and impairment outcomes of upper limb recovery

Variable	Total no. of studies (participants)	Vote counting (significant association)	Strength of evidence analysis	Statistical analysis No. of studies (participants) Odds ratio (95% CI)	Statistical conclusion	Combined assessment of evidence.
Demographic factors						
Age (younger vs. older)	18[57;70;74;96;106;109;113;121;125;129;132;134;136;141;143;144;146;150] (n=1120)	1[57] (n=108)	Strong evidence of no association	9[96;106;113;129;134;141;143;144;150] (n=334) 1.92 (1.16 – 3.17)	Significant association	Inconclusive evidence. Suggestion that younger people are more likely to have better upper limb recovery in terms of impairment.
Sex (male vs. female)	16[70;74;96;106;109;121;125;129;132;134;136;141;143;144;146;150] (n=804)	0	Strong evidence of no association	8[96;106;129;134;141;143;144;150] (n=134) 1.80 (0.85 – 3.82)	No significant association	Strong evidence of no association between sex and upper limb recovery in terms of impairment.
Time since stroke (less vs. more time)	6[74;113;125;129;132;141] (n=565)	1[125] (n=57)	Moderate evidence of no association	3[113;129;141] (n=230) 2.14 (1.12 – 4.07)	Significant association	Inconclusive evidence of association between time since stroke and upper limb recovery in terms of impairment.
Socioeconomic status	1[63] (n=419)	1[63]	Limited evidence of association	NA	NA	Limited evidence of association between socioeconomic status and upper limb recovery.
Severity of stroke – global factors						
Global disability (less vs. more disability)	12[57;68-70;96;110;125;127;134;137;141;143] (n=474)	6[57;70;96;110;125;134] (n=348)	Inconclusive evidence	7[69;96;127;134;137;141;143] (n=122) 6.11 (2.45 – 15.23)	Significant association	Moderate evidence of association. Those with less initial disability more likely to have better upper limb recovery in terms of impairment.

Global impairment (less vs. more impairment)	4[74;109;113;127] (n=435)	2[74;109] (n=229)	Inconclusive evidence	2[113;127] (n=209) 2.19 (0.35 - 13.90)	No significant association	Inconclusive evidence of association between global impairment and upper limb recovery in terms of impairment.
Type/Class of stroke (less vs. more severe)	3[57;74;110] (n=329)	2[57;74] (n=279)	Limited evidence of association	0	NA	Limited evidence of association. Those with less severe strokes more likely to have better upper limb recovery in terms of impairment.
Lesion size/volume (smaller vs. larger)*	3[106;134;150] (n=46)	0	Limited evidence of no association	2[106;150] (n=31) 2.65 (0.41 – 17.18)	No significant association	Limited evidence of no association between infarction size/volume and upper limb recovery.
Urinary incontinence (absent vs. present)	1[139] (n=76)	0	Limited evidence of no association	0	NA	Limited evidence of no association.
7th Cranial nerve	1[109] (n=58)	1[109] (n=58)	Limited evidence of association	0	NA	Limited evidence of association between 7th cranial nerve involvement and upper limb recovery.
Severity of stroke –focal factors						
UL baseline impairment measures (less vs. more impairment)**	28[27;57;69;70;74;75;97;98;100;106;108-110;121;125;127;129;132;135;138;140;141;143-145;147;148;150] (n=1338)	17[27;57;70;74;75;98;109;125;127;129;132;135;138;144;145;147;148] (n=1055)	Strong evidence of association	16[27;69;75;97;100;106;108;121;127;129;135;141;143;144;147;150] (n=483) 11.46 (6.03 – 21.79)	Significant association	Strong evidence of association. Those with less initial UL impairment are more likely to have better upper limb recovery in terms of impairment.
Lower limb impairment (less vs. more impairment)	3[74;147;150] (n=223)	2[74;147] (n=206)	Limited evidence of association	2[147;150] (n=52) 21.15 (4.29 – 104.16)	Significant association	Limited evidence of association. Those with less LL impairment more likely to have better upper limb recovery in terms of impairment.

UL baseline functional measures (more vs. less function)	1[127] (n=9)	0	Limited evidence of no association	1[127] (n=9) 12.60 (0.45 – 352.78)	No significant association	Limited evidence of no association between initial UL functional measures and upper limb recovery in terms of impairment.
Hand grip asymmetry	1[141] (n=17)	0	Limited evidence of no association	0	NA	Limited evidence of no association between hand grip asymmetry and upper limb recovery in terms of impairment.
Co-factors (associated with stroke severity)						
Side of stroke (left vs. right)	16[70;74;96;106;107;109;113;121;125;129;132;134;141;143;144;146] (n=916)	0	Strong evidence of no association	8[96;106;113;129;134;141;143;144] (n=331) 1.18 (0.73 – 1.90)	No significant association	Strong evidence of no association between side of stroke and upper limb recovery in terms of impairment.
UL sensation (no deficit vs. deficit)	9[57;70;109;113;121;132;139;141;148] (n=702)	4[57;109;113;132] (n=427)	Inconclusive evidence	2[113;141] (n=171) 2.02 (1.06 – 3.84)	Significant association	Inconclusive evidence. Suggestion that absence of sensory deficit is associated with better upper limb recovery in terms of impairment.
Stroke location	6[74;111;134;136;141;150] (n=396)	1[74] (n=171)	Moderate evidence of no association	Unable to pool data	Unable to pool data	Moderate evidence of no association between stroke location and upper limb recovery in terms of impairment.
Cognition and perception (no deficit vs. deficit)***	5[70;74;109;113;139] (n=550)	2[74;109] (n=229)	Inconclusive evidence	1[113] (n=149) 1.53 (0.77 – 3.04)	No significant association	Inconclusive evidence relating to the association between cognition and perception and upper limb recovery in terms of impairment.
Shoulder complications (absent vs. present)****	5[70;109;132;139;148] (n=376)	2[109;139] (n=134)	Inconclusive evidence	0	NA	Inconclusive evidence of association between shoulder complications and upper limb recovery in terms of impairment.

Handedness (right vs. left vs. ambidextrous)	2[74;109] (n=229)	0	Limited evidence of no association	0	NA	Limited evidence of no association between handedness and upper limb recovery in terms of impairment.
Visual disorders (absent vs. present)	2[70;109] (n=154)	1[109] (n=58)	Inconclusive evidence	0	NA	Inconclusive evidence relating to association between visual disorders and upper limb recovery in terms of impairment.
Speech disorders (absent vs. present)	2[70;109] (n=154)	1[109] (n=58)	Inconclusive evidence	0	NA	Inconclusive evidence relating to association between speech disorders and upper limb recovery in terms of impairment.
Length of stay	1[132] (n=107)	0	Limited evidence of no association	0	NA	Limited evidence of no association between length of stay and upper limb recovery in terms of impairment.
Mood	1[70] (n=96)	0	Limited evidence of no association	0	NA	Limited evidence of no association between mood and upper limb recovery in terms of impairment.
No. of previous strokes	1[109] (n=58)	1[109] (n=58)	Limited evidence of association	0	0	Limited evidence of association between number of previous strokes and upper limb recovery in terms of impairment.
Duration for stroke to develop	1[109] (n=58)	1[109] (n=58)	Limited evidence of association	0	NA	Limited evidence of association between duration for stroke to develop and upper limb recovery in terms of impairment.
Pain in arm	1[109] (n=58)	1[109] (n=58)	Limited evidence of association	0	NA	Limited evidence of association between pain in arm and upper limb recovery in terms of impairment.
Neurophysiological factors						

Motor evoked potentials (present vs. absent)*****	18[69;96;103;104;106;107;110;112;115;116;118;120;129;135;137;141;143;147] (n=632)	14[69;103;107;110;112;115-117;120;129;135;137;143;147] (n=529)	Strong evidence of association	13[69;96;104;106;116;118;120;129;135;137;141;143;147] (n=370) 12.40 (5.21 – 29.53)	Significant association	Strong evidence of association. Those with present MEPs are more likely to have better upper limb recovery in terms of impairment.
Somatosensory evoked potentials (present vs. absent)	5[98;112;116;122;124;145] (n=212)	5[98;112;116;122;124;145] (n=212)	Strong evidence of association	1[116] (n=29) 6.66 (1.13 – 39.25)	Significant association	Strong evidence of association. Those with present SSEPs are more likely to have better upper limb recovery in terms of impairment.
Diffusion tensor tractography (DTT) (preserved corticospinal tract or not)	3[105;120;150] (n=125)	3[105;120;150] (n=125)	Limited evidence of association	2[120;150] (n=70) 35.46 (8.97 – 140.10)		Limited evidence of association. Those with preserved corticospinal tract (determined by DTT) more likely to have better upper limb recovery in terms of impairment.
Pre-morbid function						
Pre-stroke ability	1[109] (n=58)	0	Limited evidence of no association	0	NA	Limited evidence of no association between pre-stroke ability and upper limb recovery.
Pre-stroke mental status	1[109] (n=58)	0	Limited evidence of no association	0	NA	Limited evidence of no association between pre-stroke mental status and upper limb recovery.

Footnotes:

0 – no studies able to be included in statistical analysis

NA – no conclusions could be drawn from statistical analysis as no studies were available for inclusion in meta-analysis

Unable to pool data – due to differences in way data presented unable to sensibly combine in a meta-analyses

* Prabhakaran 2008[136] - 2 variables; subcortical lesion volume (significant) cortical lesion volume (non-significant). Not included in any analysis.

**Escuardo 1998[110] reported a negative association between upper limb impairment at baseline and outcome. Not included in analysis.

** Katrak 1990[75] - 2 variables; Hand Movement Scale (HMS) (chosen for analysis) non-significant, significant association for shoulder shrug.

** Katrak 1998[121] - 3 variables; HMS, shoulder shrug and shoulder abduction. HMS (chosen for analysis) and shoulder shrug significant association. Shoulder abduction non-significant.

**Loubinoux 2003[127] – 4 variables; MI, finger tapping test, dynamometer and MI (hand section). MI (chosen for analysis) found to have a significant association. Other three non-significant.
**Paci 2007[132] – 2 variables; Fugl-Meyer (upper limb section), Fugl-Meyer (ROM/pain score). Fugl-Meyer (chosen for analysis) significant association. Other variable non-significant association.
**Smania 2007[140] - 4 variables; active finger extension, shoulder shrug, shoulder abduction and HMS. HMS (chosen for analysis), shoulder shrug and shoulder abduction no significant association reported. Significant association reported for active finger extension.

***De Weerdt 1987[109] - 3 variables; Post stroke mental status, tactile hemi-inattention and stereognosis. Post stroke mental status (chosen for analysis) and tactile hemi-inattention found to have a significant association. Stereognosis found to have non-significant association.
***Feys 2000[70] – 5 variables; Mini mental state examination, body image disturbance, locus of control scale, visual hemi-inattention and tactile hemi-inattention. MMSE (chosen for use in analysis) found to have a non-significant association, 3 others non-significant. Locus of control found to have a significant association.

****Paci 2007[132] – 2 variables; pain (chosen for analysis) not significantly associated, other predictor (subluxation) significantly associated.

*****Rapisarda 1996[137] - 2 variables; present/absent (chosen for use in analysis) significant; other variable (CMCT) variable non-significant.

Appendix C – Details of included studies

Details of included trials for each intervention category as used in the review of interventions

Table C-1 - Approaches to therapy (Bobath)

Trials	Participants recruited; reported at outcome	Interventions	Comparison	Outcome(s)
Other review[168]				
Gelber 1995[169]	27; 19	Neurodevelopmental techniques (Bobath)	Traditional functional retraining approach	Box and Block Test (BBT) Nine Hole Peg Test (NHPT)
Langhammer 2000[170]	61; 53	Bobath physiotherapy	Motor relearning programme	Motor Assessment Scale (MAS) (arm section) MAS (hand section)
Logigian 1983[171] (male and female subgroups)	42	Facilitation approach (Bobath)	Traditional approach	Manual Muscle Test (MMT)
Platz 2005[172]	42	Bobath therapy (augmented Bobath therapy)	Arm BASIS Training (augmented therapy time)	Action Research Arm Test (ARAT)
van Vliet 2005[173]	120; 85	Bobath physiotherapy	Movement science based physiotherapy	MAS (upper arm) MAS (hand movements)

Table C-2 - Bilateral training

Trials	Participants recruited; reported at outcome	Interventions	Comparison	Outcome(s)
Cochrane review[174]				
Cauraugh 2002[175]	20	Bilateral training + EMG triggered stimulation	Unilateral training +EMG triggered stimulation	BBT – no poolable data available
Cauraugh 2008[176]	16	Bilateral training + EMG triggered stimulation	Unilateral training +EMG triggered stimulation	BBT
Desrosiers 2005[177]	41; 33	Bilateral training	Usual care	BBT Purdue Pegboard Test

Lin 2009a[178]	40	Bilateral training	Usual care	Motor Activity Log (MAL) (amount of use (AOU)) Stroke Impact Scale (SIS) (hand function)
Lin 2009b[179]	33	Bilateral training	Usual care	MAL (AOU)
Luft 2004[180]	21	Bilateral training with Rhythmic Auditory Cueing	Usual care	Wolf Motor Arm Test
Lum 2006[181]	14	Robot-bilateral training	Robot-unilateral training	Fugl-Meyer (F-M) (UL proximal section) F-M (UL distal section)
Morris 2008[182]	106; 97	Bilateral training	Unilateral training	ARAT NHPT
Stoykov 2009[183]	24	Bilateral training	Unilateral training	MAS (upper arm function) MAS (hand movement)
Summers 2007[184]	12	Bilateral training	Unilateral training	Modified MAS (upper arm function) Modified MAS (hand movement)

Table C-3 - Constraint-induced movement training (CIMT)

Trials	Participants recruited; reported at outcome	Interventions	Comparison	Outcome(s)
Cochrane review[185]				
Alberts 2004[186]	10	CIMT	No treatment	Wolf Motor Function Test (WMFT) – no poolable data available
Atteya 2004[187]	4	Modified CIMT (mCIMT)	Usual care	ARAT
Boake 2007[188]	23; 20; 18 (hand)	mCIMT	Usual care	MAL Grooved Pegboard Test
Dahl 2008[189]	30	CIMT	Usual care	WMFT SIS (hand function)
Dromerick 2000[190]	23; 20	CIMT	Usual care	ARAT ARAT (pinch)
Lin 2007[191]	34; 32	mCIMT	Usual care	MAL (AOU)
Myint 2008[192]	48; 43; 39 (hand)	CIMT	Usual care	ARAT NHPT
Page 2001[193]	4	mCIMT	Usual care	ARAT

Page 2002[194]	9	mCIMT	Usual care	ARAT - no poolable data available
Page 2004[195]	11	mCIMT	Usual care	ARAT
Page 2005[196]	10	mCIMT	Usual care	ARAT
Page 2008[197]	25	mCIMT	Usual care	ARAT
Ploughman 2004[198]	27; 23	Forced use therapy	Usual care	ARAT Chedoke McMaster Stroke Assessment (CMSA) (hand section)
Taub 1993[199]	9	CIMT	No treatment	Arm Motor Activity Test
Wittenberg 2003[200]	16	CIMT	No treatment	WMFT
Wolf 2006[201]	222; 199	CIMT	Usual care	WMFT
Wu 2007a[202]	30	mCIMT	Usual care	MAL (AOU)
Wu 2007b[203]	47	mCIMT	Usual care	MAL (AOU)
Wu 2007c[204]	26	mCIMT	Usual care	MAL (AOU) SIS (hand function)
Additional trials Dromerick 2009[205]	36; 34	CIMT	Usual care	ARAT
Lin 2008[206]	22	CIMT	Usual care	MAL (AOU)
Lin 2009[178]	40	Distributed form of CIT (dCIT)	Usual care	MAL (AOU) SIS (hand function)
Lin 2010[207]	13	dCIMT	Usual care	MAL (AOU)

Table C-4 - Electromyographic biofeedback (EMG-BFB)

Trials	Participants recruited	Interventions	Comparison	Outcome(s)
Cochrane review[208]				
Armagan 2003[209]	27	Exercise programme + EMG-BFB	Exercise programme + placebo EMG-BFB	Brunnstrom stage of hand recovery
Basmajian 1987[210]	29	Physiotherapy + EMG-BFB	Physiotherapy	Upper Extremity Function Test (UEFT)
Crow 1989[211]	40	Physiotherapy + EMG-BFB	Physiotherapy	ARAT
Inglis 1984[212]	30	Physiotherapy + EMG-BFB	Physiotherapy	Brunnstrom stages of recovery

Table C-5 - Electrostimulation

Trials	Participants recruited; reported at outcome	Interventions	Comparison	Outcome(s)
Cochrane review[213]				
Cauraugh 2000[214]	11	Electrostimulation	No treatment	BBT
Cauraugh 2002[175]	15	Electrostimulation	No treatment	BBT
Cauraugh 2003[215]	16	Electrostimulation	No treatment	BBT
Chae 1998[216]	46; 28	Electrostimulation	Placebo	F-M
Francisco 1998[217]	16; 9	Electrostimulation	Usual care	F-M
Kimberley 2004[218]	16	Electrostimulation	Placebo	BBT Jebsen Hand Function Test (JHFT)
Linn 1999[219]	40	Electrostimulation	No treatment	MAS
Popovic 2003[220]	28	Electrostimulation	No treatment	UEFT
Powell 1999[221]	60; 55	Electrostimulation	No treatment	ARAT NHPT
Sonde 1998[222]	44	Electrostimulation	No treatment	F-M
Additional trials Alon 2007[223]	15	Electrostimulation	Task-specific practice	BBT
Alon 2008[224]	38; 26; 8 (hand)	Electrostimulation	Task-specific practice	BBT Jebsen-Taylor light object lift
Chan 2009[225]	20	Electrostimulation	Placebo	Functional test of the hemiparetic upper extremity Grip power
Gabr 2005[226]	12	Electrostimulation	Home exercise programme	ARAT – no poolable data available
Hara 2006[227]	16; 14	Electrostimulation	Usual care	NHPT – no poolable data available
Hara 2008[228]	22; 20	Electrostimulation	Usual care	NHPT – no poolable data available
Hsu 2010[229]	66	Electrostimulation (high) Electrostimulation (low)	Usual care	ARAT ARAT pinch section
Mangold 2009[230]	23	Electrostimulation	Usual care	CMSA (arm) CMSA (hand)

Ring 2005[41]	22	Electrostimulation	Usual care	BBT JHFT - no poolable data available for both outcomes
Thrasher 2008[231]	21	Electrostimulation	Usual care	Chedoke McMaster Stages of Motor Recovery
Weber 2010[232]	23	Electrostimulation	Usual care	ARAT

Table C-6 – Hands-on therapy interventions

Trials	Participants recruited	Interventions	Comparison	Outcome(s)
Cochrane review[233]				
Carey 1980[234]	24	Manual stretching	No intervention	Joint Moving Tracking Test
Mann 2005[235]	22	Passive extension exercises	Other upper limb intervention	ARAT
Mikulecka 2005[236]	40	Soft tissue stretch, joint mobilisation and pressure to hand	Usual care	Jebsen Taylor Test

Table C-7 - High-intensity therapy

Trials	Participants recruited; reported at outcome	Interventions	Comparison	Outcome(s)
Other review[237]				
Kwakkel 1999[238]	70; 63	Arm training	Immobilisation of arm by inflatable air splint	ARAT
Lincoln 1999[239]	282	- Extra physiotherapy provided by assistant physiotherapist (APT) - Extra physiotherapy provided by qualified physiotherapist (QPT)	Usual care (physiotherapy)	Extended Motricity Index (MI) NHPT
Rodgers 2003[51]	123; 105	Enhanced upper limb therapy	Usual care	ARAT
Sunderland 1992 (mild and severe subgroups)[240]	137; 121	Enhanced therapy	Usual care	ARAT NHPT

Table C-8 - Mental practice

Trials	Participants recruited	Interventions	Comparison	Outcome(s)
Cochrane review[241]				
Muller 2007[242]	12	Mental practice	Motor practice	Jebsen hand function (stacking) (individual items)
Page 2001[243]	13	Mental practice + physical practice of ADL tasks	Control – physical practice of ADL or ambulation tasks + listening to tape of stroke information	ARAT
Page 2005[244]	11	Mental practice + physical practice of ADL tasks	Control – physical practice of ADL tasks + relaxation by audiotape	ARAT
Page 2007[245]	32	Mental practice + physical practice of ADL tasks	Control – physical practice of ADL tasks + relaxation by audiotape	ARAT
Page 2009[246]	10	Mental practice + mCIMT	mCIMT	ARAT
Riccio 2010[247]	36	Mental practice + conventional intervention	Conventional intervention	Arm Functional Test (Functional Ability Scale)

Table C-9 - Mirror therapy

Trials	Participants recruited; reported at outcome	Interventions	Comparison	Outcome(s)
Other review[248]				
Altschuler 1999[249]	9	Parasagittal mirror	Same protocol but with direct observation of affected arm	ROM, speed and accuracy rated by 2 senior neurologists
Dohle 2009[250]	48; 36	Parasagittal mirror	Same protocol but with direct observation of affected arm	ARAT
Rothgangel 2004[251]	16	Parasagittal mirror	Same protocol but with direct observation of affected arm	ARAT – no poolable data available
Yavuzer 2008[252]	40	Parasagittal mirror	Same protocol but with non-reflective side of mirror	Functional Independence Measure (FIM) (self-care) Brunnstrom stage (hand)

Additional trials Michielsen 2011[253]	40; 36	Parasagittal mirror	Same protocol but with direct observation of affected arm	ARAT ABIL-hand

Table C-10 - Repetitive task training

Trials	Participants recruited; reported at outcome	Interventions	Comparison	Outcome(s)
Cochrane review[254]				
Blennerhassett 2004[255]	30	Variety of activities	Attention control	MAS (arm) MAS (hand)
Higgins 2006[256]	91	Functional tasks	Lower extremity training	BBT NHPT
Kwakkel 1999[238]	70; 61	Functional exercises	Immobilisation by splint	ARAT
Langhammer 2000[170]	61; 53	Motor relearning – functional task training	Usual care	MAS (arm) MAS (hand)
Turton 1990[257]	22	Home-based exercises	Usual care	Southern Motor Assessment 10 hole peg test
Winstein 2004[62]	43; 40	Task-specific functional training	Usual care	Functional test of the hemiparetic upper extremity
van Vliet 2005[173]	120; 85	Movement science therapy – functional training	Usual care	Rivermead Motor Assessment (RMA) 10 hole peg test
Yen 2005[258]	30	Shaping training	Usual care	WMFT
Additional trial Harris 2009[259]	103	Self-administered homework based exercise program	Control (education)	ARAT Grip strength

Table C-11 – Electromechanical/Robotic devices

Trials	Participants recruited; reported at outcome	Interventions	Comparison	Outcome(s)
Cochrane review[260]				
Amirabdollahian 2007[261]	31	Robot mediated therapy	Sling suspension	F-M – no poolable data available

Daly 2005[262]	13; 12 (hand)	Robotic training	Functional neuromuscular stimulation	F-M AMAT wrist/hand
Fazekas 2007[263]	30	Robot training	Bobath therapy	F-M
Hesse 2005[264]	44; 43 (hand)	Robotic training	Functional electrical stimulation	F-M F-M (wrist/hand)
Kahn 2006[265]	19	Robot guided therapy	Free-reaching therapy	CMSA (arm)
Lum 2002[266]	30; 27	Robot training	Physiotherapy + 5 min robot training	F-M F-M (wrist/hand)
Lum 2006[181]	30; 16 (hand)	Robot training (3 different groups collapsed into one robot group)	Conventional therapy	F-M F-M (wrist/hand)
Masiero 2007[267]	35; 30 (hand)	Robotic training	Robot exposure	F-M F-M (wrist/hand)
Volpe 2000[268]	56	Robotic training	Robot exposure	F-M F-M (wrist/hand) – no poolable data available
Volpe 2008[269]	21	Robotic therapy	Intensive movement protocol	F-M F-M (wrist/hand)
Additional trials Burgar 2011[270]	54	Robotic therapy (low intensity) Robotic therapy (high intensity)	Intensive conventional therapy	F-M
Conroy 2011[271]	62; 57	Robot assisted reaching (planar and vertical) (A) Robot assisted reaching (planar) (B)	Intensive conventional therapy	F-M SIS hand
Housman 2009[272]	34; 31	Gravity-supported, computer-enhanced arm orthosis	Tabletop exercises	Rancho Los Amigos Grip strength
Lo 2010[273]	53; 52	Robot-assisted therapy	Usual care	WMFT
Masiero 2011[274]	21	Robotic therapy	Conventional therapy	Frenchay Arm Test F-M (wrist/hand)
Rabadi 2008[275]	20	Robotic therapy	Occupational therapy	ARAT F-M (wrist/hand)

Table C-12 - Splinting

Trials	Participants recruited; reported at outcome	Interventions	Comparison	Outcome(s)
Other Review[276]				
Lannin 2003[277]	28; 25	Static palmer resting mitt splint	Usual care	MAS (arm) MAS (hand)
Poole 1990[278]	18	Inflatable splint	Usual care	F-M F-M (wrist/hand)
Additional trial Lannin 2007[279]	63; 62	Neutral splint Extension splint	Usual care	MAS (items 6,7 and 8)

Table C-13 - Virtual reality training

Trials	Participants recruited; reported at outcome	Interventions	Comparison	Outcome(s)
Cochrane review[280]				
Crosbie 2008[281]	18	Virtual reality: reaching and grasping	Bobath therapy	ARAT
Housman 2009[272]	34; 28	Virtual reality training	Upper limb exercises	F-M Grip strength
Jang 2005[282]	10	Virtual reality: whole body	No intervention	BBT
Piron 2007[283]	38	Virtual reality training	Usual care	F-M
Piron 2009[284]	36	Virtual reality training	Upper limb exercises	F-M
Piron 2010[285]	50; 47	Virtual reality training	Upper limb exercises	F-M
Saposnik 2010[286]	22; 16	Virtual reality: Nintendo Wii	Leisure activities	Abbreviated WMFT Grip strength
Sucar 2009[287]	22	Virtual reality training	Upper limb exercises	F-M
Yavuzer 2008[288]	20	Virtual reality: Playstation eyetoy	Watching playstation games	Brunnstrom UE stages Brunnstrom hand stages

Appendix D – Characteristics of included studies (bilateral training)

Table D-1 - Full characteristics of included studies for review of bilateral training

Study	Cauraugh 2002[175]
Methods	Randomised controlled trial. Random assignment with restriction that 20 participants were tested in 2 treatment groups. Method of randomisation and allocation concealment not reported.
Participants	N=25 (only 20 relevant to this review), n=18 included in analysis; M/F: 21/4; Age: 63.7 years; Time since stroke: 39.1 mos; Type of stroke: Not stated Inclusion criteria: diagnosis of CVA and no more than two CVAs on same side of brain, upper limit of 80% motor recovery (EMG activation patterns compared with non-affected upper limb), lower limit of 10°voluntary wrist or finger extension against gravity, no other neurological deficits, no pacemaker, no use of drugs for spasticity, not enrolled in any other rehabilitation protocol.
Interventions	Group 1 (10 participants): unilateral + EMG-triggered stimulation wrist/finger extension Group 2 (10 participants): bilateral + EMG-triggered stimulation wrist/finger extension Each group completed 3 sets of 30 successful EMG-triggered neuromuscular stimulation trials (approximately 1 hour 30 mins); in total 6 hours of training (4 days) were completed in 2 weeks. Profession of individual(s) providing training unclear.
Outcomes	Primary outcome: functional movement: Box and Block Test (BBT) Secondary outcomes: motor impairment – temporal outcomes: reaction time for speed of information processing and rapid muscle onset (simple reaction time, premotor reaction time and chronometic motor reaction time) – premotor reaction time selected; strength outcomes: EMG activity of wrist/fingers extensor muscles.
Notes	Control group (n=5) did not receive the neuromuscular electric stimulation or bilateral assistance for the wrist/fingers extensors therefore not included in any analyses. Unable to use presented data for BBT as no standard deviations presented. Means from graph were estimated and presented in results section. Pre-motor reaction time was chosen for inclusion as temporal outcomes as medians and SDs presented. Medians imputed as mean values. Two participants excluded from analyses due to extreme reaction times; it was unclear which groups these participants were in, therefore analysis for reaction time based on n=18 participants (1 participant removed from each group). For muscle activity (strength) unable to use presented data within analysis as median root mean and square error presented with no SDs. Medians from graph were estimated and presented in results sections. Data for this outcome based on 24 participants but unclear from which group the excluded participant was from.
Study	Cauraugh 2003[289]
Methods	Randomised controlled trial. Participants randomly assigned to 1 of 2 groups. Method of randomisation and allocation concealment not reported.
Participants	N=20; M/F: 16/4; Age: 63.03 years; Time since stroke: 33.86 mos; Type of stroke: Not stated Inclusion criteria: absence of other neurological deficits, able to voluntarily extend wrist or fringes 10°against gravity, upper limit of 80% motor recovery (EMG activation patterns), diagnosis of CVA, sufficient voluntary control to activate the microprocessor, sufficient cognitive function to follow instructions.

Interventions	Group 1 (10 participants): unilateral + EMG-triggered stimulation wrist/finger extension Group 2 (10 participants): bilateral + EMG-triggered stimulation wrist/finger extension Participants completed 3 sessions of 30 successful EMG triggered stimulation trials (approx. 90 minutes) with 5 minute break between sessions. Participants completed 360 trials across 12 sessions of training over 4 days. Profession of individual(s) providing training unclear.
Outcomes	Secondary outcomes: motor impairment – strength outcomes: EMG activity level of wrist and finger extensor muscles
Notes	Number of participants in each group not reported, an equal number in each group was assumed. Data presented in paper as a graph – mean $\log_{10}$ and SE. Means estimated from graph and SD calculated from estimated SE.
Study	Cauraugh 2005[290]
Methods	Randomised controlled trial. Random assignment following a randomisation schedule. No mention of allocation concealment.
Participants	N=21; M/F: 11/10; Age: Unilateral 63.29±10.81 years, Bilateral 69.37±10.14 years, Time since stroke: Unilateral 3.57±2.42 years, Bilateral 4.73±3.52 years, Type of stroke: Not stated Inclusion criteria: diagnosis of no more than 3 strokes, lower limit of 10° voluntary wrist/finger extension starting from 80°w rist and finger flexion, upper limit of 80% motor recovery, no other neurological deficits, not participating in another upper limb programme.
Interventions	Group 1 (10 participants): unilateral + EMG-triggered stimulation wrist/finger extension Group 2 (11 participants): bilateral + EMG-triggered stimulation wrist/finger extension Each group completed 4 days of 90 minutes training/week over 2 weeks. Profession of individual(s) providing training unclear.
Outcomes	Secondary outcomes: motor impairment – temporal outcomes: reaction time (ms), movement time (ms), deceleration time (ms), peak velocity (cm/s) and SD peak velocity (movement time selected). All measured for sing aiming test and recorded by EMG.
Notes	Control group (n=5), no stroke history, not included in participant numbers or analysis. Median values presented in paper, this imputed as mean values. Movement time data inverted for analysis (multiplied by -1).
Study	Cauraugh 2008[176]
Methods	Randomised controlled trial. Randomly assigned to 1 of 2 treatment protocol orders. Method of randomisation and allocation concealment not stated.
Participants	N=16, M/F: 10/6; Age: Unilateral 66.6±12.35 years, Bilateral 65.04±12.47 years, Time since stroke: Unilateral 4.2±9.13 years, Bilateral 1.41±0.89 years, Type of stroke: Not stated Inclusion criteria: diagnosis of no more than 3 strokes, lower limit of 10° voluntary wrist/finger extension starting from 80°w rist and finger flexion, upper limit of 80% motor recovery, no other neurological deficits, not participating in another upper limb programme.
Interventions	Group 1 (8 participants): unilateral + EMG-triggered neuromuscular stimulation wrist/finger extension Group 2 (8 participants): bilateral + EMG-triggered neuromuscular stimulation wrist/finger extension Both groups completed 5 consecutive upper limb protocols. For the purposes of this review we compared the first treatment protocol from each group (as above). Each training session involved 90 successful movement trials; completed in 4 days of 90 minutes training per day over 2 weeks. Consecutive treatment protocols were separated on average by 4 weeks of no rehabilitation. Profession of individual(s) administering training unclear.

Outcomes	Primary outcome: functional movement: (BBT) Secondary outcomes: motor impairment – temporal outcomes: motor reaction time and total reaction time - motor reaction time selected; strength outcomes: maximal isometric contraction of wrist/fingers extensors. No suitable data were available for strength outcome. Outcomes were recorded at the end of each intervention protocol.
Notes	Data presented in paper in graph format - mean and SE for Box and Block Test. Means estimated from graph and SD calculated from estimated SE. Two review authors independently estimated the values from the graphs, the average of the 2 estimates used in the analysis. Motor reaction data also presented in graph format: median and SE. Median value estimated from graph imputed as mean and SD calculated from SE. Motor reaction time score (m/s) inverted (multiplied by -1) for analysis.
Study	Chang 2006[293]
Methods	Randomised cross-over design. Participants each performed 3 tasks in a randomly presented order. Not designed or presented as a traditional RCT.
Participants	N=20; M/F: 17/3; Age: 56±10.54 years; Time since stroke: 404.7±565.06 days, Type of stroke: infarct 17, haemorrhagic 3 Inclusion criteria: CT or MRI imaging evidence of single-hemisphere stroke, arm reaching ability (Fugl-Meyer assessment > 30), no perceptual-cognitive dysfunction limiting comprehension of experimental task, no severe concurrent medical problems, no other neurological or orthopaedic conditions affecting arm/trunk movements.
Interventions	Each participant performed 3 movement tasks: (1) reaching forward with affected limb (unilateral); (2) reaching forward with both limbs simultaneously (bilateral); (3) reaching forward with both limbs simultaneously + load applied to non-affected upper limb (bilateral + load). Each movement condition performed for 5 trials with 5-minute rest between each condition. Typical experimental session lasted approximately 40 minutes. There was no training period - movement and outcome measurement occurred simultaneously. Profession of individual(s) providing training unclear.
Outcomes	Secondary outcomes: motor impairment – temporal outcomes: movement time, movement velocity, number of movement units and normalised jerk score of movement - movement time selected; spatial outcomes: elbow flexion-extension range, shoulder flexion-extension range and trunk linear line value - elbow range selected.
Notes	Data not available for the first phase of this study, and therefore not included in any analyses. The unilateral and bilateral conditions would have been a suitable comparison.
Study	Desrosiers 2005
Methods	Randomised controlled trial. Randomly assigned by block randomisation scheme within each stratum (stratified on impairment level of hand and sensibility of the hand). Randomisation completed in blocks of 4. Allocation concealment completed through the use of sealed envelopes.
Participants	N=41, n=33 included in analysis; M/F: 19/22; Age: Usual care 74.3±10.1 years, Bilateral 72.2±10.8 years, Time since stroke: Usual care 35.4±33.7 days, Bilateral 34.2±34.4 days, Type of stroke: infarct 40, haemorrhagic 1 Inclusion criteria: unilateral stroke > 10 days but < 2 months, cognitive functioning within normal limits, understanding of French or English, minimal upper extremity function (stage 2 for hand and stage 3 for arm on Chedoke-McMaster Stroke Assessment), no severe body neglect or visual perception deficits.

Interventions	Group 1 (21 participants): usual care - functional activities and exercises for the arm Group 2 (20 participants): bilateral training - package of interventions including bilateral and unilateral tasks Both groups received usual therapy interventions. Both groups received 4 x 45-minute sessions per week for 5 weeks, in total receiving between 15 and 20 sessions. Both interventions provided by same occupational therapy research assistant. Note: the descriptions of interventions provided in the full-text paper are confusing; information given in the abstract has been central to the above classifications of the nature of the interventions.
Outcomes	Primary outcome: performance in activities of daily living: measure de l'independence fonctionelle (MIF - French translation of FIM) Primary outcome: functional movement - arm functional movement: BBT, TEMPA - BBT selected; hand functional outcome: Purdue Pegboard Test Secondary outcome: motor impairment - motor impairment scales: Fugl-Meyer (upper limb section); temporal outcomes: co-ordination (finger to nose, number of movements in 20 seconds); strength outcomes: grip strength (vigorimeter). AMPS also used as outcome measures but not relevant to this review
Notes	Control group received usual care; however this may have contained some bilateral tasks. This could be a confounding factor. Descriptions of interventions were unclear and definitions of symmetrical, synchronous and simultaneous were difficult to interpret. Five drop-outs from Group 1 (lack of interest x2, early release, fatigue, death) and 3 drop-outs from Group 2 (death, fracture and refusal).
Study	Dickstein 1993[294]
Methods	Randomised cross-over design. Participants each performed 3 movements in a randomly presented order. Not designed or presented as a traditional RCT.
Participants	N=25; M/F: 14/11; Age: 73±1.45 years; Time since stroke: 2.5±2.22 mos; Type of stroke: infarct 24, head trauma 1 Inclusion criteria: absence of cognitive impairments, unimpaired hearing, absence of movement, disorders in unaffected upper extremity, ability to flex elbow on paretic side at least 30° from partial ext ension of 150°, not bilateral brain damage.
Interventions	Each participant performed 1 familiarisation set of unilateral movements with the unaffected arm, then performed 3 sets of movements presented in a random order (unilateral (unaffected), unilateral (affected) or bilateral). Each set comprised 16 elbow flexion movements which were carried out in response to an auditory signal. There was no training period - movement and outcome measurement occurred simultaneously. Profession of individual(s) providing training unclear (assume physiotherapist).
Outcomes	Secondary outcomes: motor impairment – temporal outcomes: reaction and movement time (movement time selected).
Notes	Data not available for the first phase of this study, and therefore not included in any analyses. The unilateral (affected) and bilateral conditions would have been a suitable comparison.
Study	Harris-Love 2005[295]
Methods	Randomised cross-over design. Participants each performed 4 trials of 6 reaching tasks in a block randomised order. Not designed or presented as a traditional RCT.
Participants	N=32; M/F: 15/17; Age: 57±14 years; Time since stroke: 1.95 years; Type of stroke: Ischemic Inclusion criteria: at least 6 months post-stroke, at least 10° antigravity shoulder flexion and 20° of gravity minimised elbow extension, able to produce at least 5 cm of forward translation of the hand on a table without leaning forward, no orthopaedic conditions and/or pain in paretic arm or shoulder.

Interventions	Each participant performed 4 trials each of unilateral paretic, unilateral non-paretic and bilateral reaching, then 4 trials of 6 reaching tasks (unilateral paretic, unilateral non-paretic, bilateral reaching and 3 bilateral reaching tasks involving different loads added to the non-paretic hand) completed at the fastest possible speed. For all tasks participants were instructed to reach the target (box) as quickly as possible after a verbal go command and come to a complete stop. There was no training period - movement and outcome measurement occurred simultaneously. Profession of individual(s) providing training unclear (assume physiotherapist).
Outcomes	Secondary outcomes: motor impairment – temporal outcomes: movement time, peak velocity and peak acceleration -movement time selected.
Notes	Data not available for the first phase of this study, and therefore not included in any analyses. The unilateral (paretic) and bilateral conditions would have been a suitable comparison.
Study	Kilbreath 2006[296]
Methods	Randomised cross-over design. Participants each performed 3 tasks in randomly presented order. Not designed or presented as a traditional RCT.
Participants	N=13; M/F: 8/5; Age: 67.9±8.3 years; Time since stroke: 36.1±18 mos; Type of stroke: Not stated Inclusion criteria: no significant musculotendinous or bony restrictions of upper limbs, no chronic disease independently causing significant disability or significant weakness of the upper limbs, sufficient strength in affected arm to move the arm forward at the shoulder and elbow and grasp with affected hand, score >= 1 on Frenchay upper limb test, comprehend simply instructions. Note: it is unclear whether or not these were pre-stated inclusion criteria, or whether these criteria are descriptors of the participants who were eventually included.
Interventions	Each participant performed 2 bimanual and 1 unimanual tasks. Each task involved participant reaching, grasping and transporting a tray with either affected arm (unimanual task), reaching for a large tray with both arms or 2 small trays (bimanual tasks). There was no training period - movement and outcome measurement occurred simultaneously. Each task was performed 5 times. Profession of individual(s) providing training unclear (assume physiotherapist).
Outcomes	Secondary outcome: motor impairment – temporal outcomes: movement duration for hand to reach tray and for tray transport – movement time for hand to reach tray selected; spatial outcomes: lateral deviation of the hands, synchrony of hand movements and relative phase angle - lateral deviation of the hand selected.
Notes	Study included another 13 participants with no stroke history; not included in participant numbers or analysis. Data are not available for the first phase only of this study and it is therefore not included in any analyses. The unilateral and bilateral conditions would have been a suitable comparison.
Study	Lin 2009a[178]
Methods	Randomised controlled trial using a stratified block allocation scheme. Computerised (block) randomisation, with per-stratification according to participating hospital. Allocation concealment ensured by use of opaque, numbered envelopes (each hospital site had a pre-prepared set of envelopes with cards indicating allocation).
Participants	N=60; M/F: 34/26; Age: Usual care 50.7±13.93 years, CIT 55.28±9.34, Bilateral 51.58±8.67 years; Time since stroke: Usual care 21.9±20.51 mos, CIT 21.25±21.59 mos Bilateral 18.50±17.40 mos; Type of stroke: Not stated Inclusion criteria: > 6 months post CVA, > Stage III Brunnstrom stage for proximal and distal parts of upper limb, considerable non-use of the affected upper limb (Motor activity log, amount of use < 2.5), no serious cognitive deficits (24 on MMSE), no excessive spasticity in any joints of upper limb (Modified Ashworth Scale 2), lack of participation in any experimental rehabilitation or drug study within past 6 months, no balance problems sufficient to compromise safety when wearing constraint mitt.

Interventions	Group 1 (20 participants): usual care – training for hand function, co-ordination, balance and movements of the affected upper limb and compensatory practice with affected or both upper limbs Group 2 (20 participants): other upper limb intervention - constraint-induced therapy: restriction of movement of the unaffected hand by placement in a mitt for 6 hours/day and intensive training of the affected upper limb in functional tasks; level of ability adapted based on patient ability and improvement during training Group 3 (20 participants): bilateral training - simultaneous movements of both affected and unaffected upper limb in functional tasks in symmetric or alternating patterns All groups completed therapy for 2 hours/day, 5 days per week for 3 weeks. All other interdisciplinary rehabilitation continued. Occupational therapists undertook the training in each group.
Outcomes	Primary outcome: performance in activities of daily living: Functional Independence Measure Primary outcome: functional movement – arm functional movement: Motor Activity Log amount of use and quality of movement scales - amount of use scale selected; hand functional outcome: Stroke Impact Scale – hand function section Secondary outcome: performance in extended activities of daily living: Stroke Impact Scale (ADL/IADL section); motor impairment- motor impairment scales: Fugl-Meyer scale.
Notes	Overall and sub-scores for the Functional Independence Measure and Fugl-Meyer were presented. Only the overall scores were used.
Study	Lin 2009b[179]
Methods	Randomised controlled trial. Method of randomisation and allocation concealment not reported.
Participants	N=33; M/F: 19/14; Age: Usual care 55.5±13.17 years, Bilateral 52.08±9.60 years; Time since stroke: Usual care 13.12±8.13 mos, Bilateral 13.940±12.73 mos; Type of stroke: Not stated Inclusion criteria: clinical diagnosis of a first or recurrent unilateral stroke; ability to reach Brunnstrom stage III or above in the proximal and distal part of the arm; no serious cognitive deficits (MMSE ≥24); no excessive spasticity in the affected arm (Modified Ashworth Scale score ≤2 in any joint); no other neurologic, neuromuscular or orthopaedic disease; lack of participation in any experimental rehabilitation or drug studies.
Interventions	Group 1 (17 participants): usual care –dose-matched standard occupational therapy that also focused on upper extremity training and included neurodevelopmental techniques, trunk-arm control, weight bearing by the affected arm, fine motor tasks practice and practice on compensatory strategies Group 2 (16 participants): bilateral training – both upper extremities moving simultaneously in functional tasks with symmetric patterns Both groups received training for 2 hours per day, 5 days a week for 3 weeks. Occupational therapists provided the interventions.
Outcomes	Primary outcome: performance in activities of daily living: Functional independence measure Primary outcome: functional movement - Motor Activity Log amount of use and quality of movement scales - amount of use scale selected Secondary outcome: motor impairment - motor impairment scales: Fugl-Meyer scale; temporal outcomes: movement time and percentage of movement time at which peak velocity occurs for unilateral and bilateral reaching task – movement time for unilateral task selected; spatial outcomes: normalised total distance

Notes	Adjusted means (controlling for pre-treatment differences) and post-treatment means were presented and used for all outcomes. SDs were taken from the post-treatment columns. Movement time and spatial outcome data inverted for analysis (multiplied by -1). Sub-categories of the Functional Independence Measure presented. Only total scores were used.
Study	Luft 2004[180]
Methods	Randomised controlled trial using a stratified block allocation scheme (variable block size, allocation 1:1). Allocation concealment not reported.
Participants	N=21, M/F: 12/9; Age: DMTE 59.6±10.5 years, BATRAC 63.3±15.3 years; Time since stroke: DMTE median 45.5 (IQR 22.6-66.3) mos, BATRAC 75 (IQR 37.9-84.5) mos; Type of stroke: Not stated Inclusion criteria: residual upper extremity spastic hemiparesis following single cortical or subcortical ischaemic stroke; ability to move affected limb (at least partial range movement against gravity); completed 3 to 6 months of rehabilitation therapy; adequate language and neurocognitive function to understand instructions; no multiple strokes, history of other neurological disease, chronic pain or emotional disorders.
Interventions	Group 1 (12 participants): usual care –Dose matched therapeutic exercises (DMTE) based on neurodevelopmental principals. Group 2 (9 participants): bilateral training- bilateral training with auditory cueing (BATRAC). This consisted of pushing and pulling bilaterally, either in synchrony or alternation, 2 independent handles sliding in the traverse plane. Training time consisted of hour-long therapy sessions (4 x 5-minute movement periods interspersed with 10-minute rest periods) 3 times per week for 6 weeks. Profession of individual(s) providing training unclear (assume physiotherapist).
Outcomes	Primary outcome: functional movement – arm functional movement: Wolf Motor Arm Test (time to complete 14 functional tasks with affected arm and hand), University of Maryland Arm Questionnaire for stroke - WMAT selected Secondary outcome: motor impairment - motor impairment scales: Fugl-Meyer Motor Performance Test (upper limb section); strength outcomes WMAT (strength) and dynamometry (elbow and shoulder strength) - WMAT strength selected fMRI and EMG variables also recorded – these were not relevant to this review.
Notes	Bilateral training group also received rhythmic auditory cueing, to guide the speed of the movements. Discussion amongst review authors led to the conclusion that the rhythmic auditory cueing could be viewed as an adjunct or guide to the bilateral training and that therefore this study was relevant to this review (i.e. the rhythmic auditory cueing has not been considered as another intervention). This study is a substudy of a larger study designed to investigate the effect of BATRAC. SEM presented in paper, this was converted into SD units and entered into the analysis. Change scores presented in paper and used in analysis. WMFT (time) data inverted for analysis (multiplied by -1).
Study	Lum 2006[181]
Methods	Restricted randomised controlled trial. Patients were stratified by initial Fugl-Meyer score and side of stroke and randomly assigned to 1 of 4 groups. Following interim analysis the randomisation schedule was changed from providing the same number of participants to each group so that subsequent participants could only be allocated to 2 of the groups, therefore participants did not have an equal chance of entering 1 of the 4 groups. The change in randomisation during the trial may have introduced bias.

Participants	N=30 (only 14 relevant to this review); M/F: 7/7; Age: Unilateral 69.8(SEM 4) years, Bilateral 72.2(SEM 11.7) years; Time since stroke: Unilateral 10(SEM 1.9) wks, Bilateral 6.2 (SEM 1) wk; Type of stroke: Not stated Inclusion criteria: single CVA, 1 to 5 months post-stroke, no upper-limb joint pain or ROM limitation that would limit ability to complete training, no unstable cardiovascular, orthopaedic or neurological conditions, > 21 on MMSE
Interventions	Group 1 (9 participants): robot-unilateral training group, 12 reaching tasks progressing from easiest robotic-mode to most challenging mode Group 2 (5 participants): robot-bilateral training group, practiced same 12 reaching tasks but in bilateral mode. Rhythmic circular movements also performed. Training lasted 1 hour per session for 15 sessions over 4 weeks. Training was supervised by an occupational therapist.
Outcomes	Primary outcome: performance in activities of daily living: Functional independence measure (self-care and transfer sections only) Secondary outcome: motor impairment - motor impairment scales: Fugl-Meyer (proximal and distal upper limb sections), Motor Status Score (movement scale and synergy scale) and Modified Ashworth scale (proximal and distal cores) - Fugl-Meyer (proximal upper limb section); strength outcomes: Motor power examination (several joints across proximal upper limb)
Notes	This study included assistive technology, however it compared a bilateral and unilateral group both receiving robotic assistance, therefore we decided that this was relevant to include as bilateral training versus unilateral training. Four groups were included in this trial: robot-unilateral, robot-bilateral, robot-combined and control. Only robot-unilateral and robot-bilateral relevant to this review. Participants in the other 2 groups (16 participants) not included in any analysis. Average gains data presented in paper and used in analysis. SDs calculated from presented SE of the mean.
Study	Morris 2008[182]
Methods	Randomised controlled trial. Randomly allocated using concealed web-based randomisation. Stratified according to side of hemiplegia, stroke classification and baseline ARAT.
Participants	N=106, n=97 included in analysis; M/F: 61/55; Age: Unilateral 67.8±9.9 years, Bilateral 67.9±13.1 years; Time since stroke: Unilateral 23.2±5.7 days, Bilateral 22.6±5.6 days; Type of stroke: Reported as ischaemic 9, haemorrhagic 97 Inclusion criteria: acute unilateral stroke confirmed by CT; persistent upper limb impairment (< 6 on each upper limb sections of Motor Assessment Scale); ability to participate in 30-minute physiotherapy sessions; ability to sit unsupported for 1minute; no severe neglect, aphasia or cognitive impairment that would limit participation; no previous stroke resulting in residual disability; no premorbid arm impairment; no hemiplegic shoulder pain; ability to provide informed consent.
Interventions	Group 1 (50 participants): unilateral training Group 2 (56 participants): bilateral training Each group performed 4 tasks (moving dowelling peg, moving block, grasp empty glass and take to mouth and point to targets). Intervention protocol was progressive and standardised. Systematic feedback was provided on performance. Training lasted 20 minutes a session 5 days a week over 6 weeks in addition to usual therapy. As many trials as possible were completed in each session with a maximum of 30 trials of each task, per session. Two senior stroke rehabilitation physiotherapists conducted the intervention.

Outcomes	Primary outcome: performance in activities of daily living: Barthel Index Primary outcome functional movement – arm functional movement: ARAT; hand functional movement: NHPT Secondary outcome: motor impairment - motor impairment scales: Rivermead Motor Assessment (upper limb section). Hospital Anxiety and Depression Scale and Nottingham Health Profile also used as outcome measures but not relevant to this review.
Notes	End of intervention outcome assessment (6 weeks) used in analysis. Outcome measures also recorded after 18 weeks (97 participants). At 6 weeks: 4 drop-outs from Group 1 (died, moved away, requested withdrawal) and 5 drop-outs from Group 2 (died, moved away, requested withdrawal). Change and final outcome scores presented. Outcome scores used in analysis.
Study	Mudie 2001[291]
Methods	Randomised controlled trial. Randomly assigned to 1 of 2 groups. Method of randomisation or allocation concealment not reported.
Participants	N=36; M/F: 26/10; Age: Unilateral acute 77.9±9.2 years, Unilateral chronic 65.7±13.1 years, Bilateral acute 71.98±5.8 years, Bilateral chronic 64.6±10.9 years; Time since stroke: Unilateral acute 1.8±0.6 mos, Unilateral chronic 90±117 mos, Bilateral acute 1.9±1.1 mos, Bilateral chronic 34.2±37.2 mos; Type of stroke: ischaemic 35 , after clipped aneurysm 1 Inclusion criteria: dense hemiplegia (less than or equal to 2 on Motor Assessment Scale items 6 and 7), able to understand instructions; produce a response with non-hemiplegic arm during bilateral trials, no other strokes or confounding co-morbidities.
Interventions	Group 1 (18 participants): unilateral training Group 2 (18 participants): bilateral training Each group completed 5 trials, including 5 repetitions of 5 seconds each (of isometric contractions for 2 tasks (shoulder abduction and wrist extension)). 15 seconds rest between each of the 5 trials, and 5 minutes rest between the 2 tasks. For Group 1, trials 1, 2, 3 and 5 were performed unilaterally and trial 4 bilaterally. For Group 2, trials 1, 3 and 5 were performed unilaterally and trials 2 and 4 bilaterally. Therefore, data from trial 2 only was extracted for this review. There was no training period: movement and outcome measurement occurred simultaneously. Profession of individual(s) providing training unclear (assume occupational therapist).
Outcomes	Secondary outcome: motor impairment –strength outcomes: muscle activity (EMG) for shoulder abduction and wrist extension - wrist extension activity selected.
Notes	Results for acute and chronic patients presented separately, therefore 2 subgroups of this trial are included in the relevant analysis.
Study	Platz 2001[292]
Methods	Randomised controlled trial. Random allocation to 1 of 2 groups, with block randomisation according to side of stroke. Details of allocation concealment not reported.
Participants	N=14; M/F: 9/5; Age: 55.9±11.6 years; Time since stroke: Not stated; Type of stroke: all ischaemic Inclusion criteria: CT-proven stroke in middle cerebral artery territory, sub-acute phase, clinically complete or almost complete recovery from hemiparesis, no cognitive impairment. Note: it is unclear whether or not these were pre-stated inclusion criteria, or whether these criteria are descriptors of the included participants written following patient assessment.

Interventions	Group 1 (7 participants): unilateral training Group 2 (7 participants): bilateral training Each group completed 3 training tasks (fast and accurate aiming movements, fast tapping movements with index finger, picking up and placing small wooden sticks). Each participant completed training comprising of 10 practice blocks, each lasting 2.5 minutes. Tasks were completed in a repetitive way and serial order. Total training time was approximately 30minutes per session, performed on 5 consecutive weekdays. Training was supervised by an occupational therapist.
Outcomes	Secondary outcome: motor impairment - temporal outcomes: total movement time (ms), MT/ first phase, MT/second phase, MT coefficient of variation (total movement time selected); spatial outcomes: spatial error (mm), spatial error/first phase (spatial error selected). All outcomes assessed for aiming movements during single task and dual task. Outcome data for single task aiming movement used for analysis.
Notes	Data extracted comprised least square means. Standard deviation for outcomes not provided. SDs extracted from baseline data.
Study	Stoykov 2009[183]
Methods	Randomised controlled trial. Stratified into 2 impairment levels based on Fugl-Meyer upper extremity scores (19 to 28 or 29 to 40). Within each group of 12 participants a randomised computer-generated list provided group assignment.
Participants	N=24; M/F: 16/8; Age: Unilateral 64.75±11.1 years, Bilateral 63.8±12.6 years; Time since stroke: Unilateral 10.2±10.1 years, Bilateral 9.5±5.4 years; Type of stroke: all ischaemic Inclusion criteria: Fugl-Meyer upper extremity score 19 to 40, >6 months post-stroke, cortical or subcortical lesion, ability to follow 2-step commands, 18 to 80 years of age, no evidence of cerebellum or brainstem involvement, no evidence of field cut, no evidence of neglect, ability to give informed consent, no symptomatic cardiac failure or unstable angina, no uncontrolled hypertension, no significant orthopaedic or pain conditions in affected upper extremity, no severe obstructive pulmonary disease.
Interventions	Group 1 (12 participants): unilateral training Group 2 (12 participants): bilateral training Training consisted of 6 training tasks that incorporated both discrete movements (2 tasks) and rhythmic movements (4 tasks), paced by a metronome. Initially most tasks completed for 20 repetitions, which was gradually increased to 40 repetitions. Therapeutic challenge was increased throughout the training period. Three training sessions of 1 hour duration completed each week for 8 weeks. Profession of individual(s) administering training not reported.
Outcomes	Primary outcome: functional movement – arm functional movement: Motor Assessment Scale upper arm and combined upper limb movements - upper arm function scores selected; hand functional movement: Motor Assessment Scale hand movements and advanced hand movements - hand movement scores selected. Secondary outcome: motor impairment – motor impairment scales: Motor Status Score (total score, shoulder/elbow scale and wrist/hand scale; total scale selected for use in analysis); strength outcomes: muscle strength comparator dynamometer fro arm strength and Jamar dynamometer for grip strength (arm strength outcome selected for use in analysis).

Notes	Data presented in paper in graph format - mean and SE for Motor Assessment Scale and Motor Status Score. Means estimated from graph and SDs calculated from estimated SE. Two review authors independently estimated the values from the graphs; the average of the 2 estimates was used in the analysis. Unable to include strength outcome in analysis as separate results for the 2 groups (unilateral and bilateral) not presented. A non-significant result between the groups reported in the paper on these measures and this indicated in the results section.
Study	Summers 2007[184]
Methods	Randomised controlled trial. Randomly allocated to 1 of 2 groups. Method of randomisation and allocation concealment not stated.
Participants	N=12, M/F: 5/7; Age: Unilateral 60±14 years, Bilateral 63.16±16 years, Time since stroke: Unilateral 4±3.1 years, Bilateral 6.3±5.2 years, Type of stroke: Various Inclusion criteria: first stoke at least 3 months prior to intervention, no multiple infarctions, most components of movement present in the affected extremity but impairment of function relative to unaffected side, intact cognitive functions, no other neurological disorders.
Interventions	Group 1 (6 participants): unilateral training Group 2 (6 participants): bilateral training Participants performed 50 training trials of a dowel placement task (lifting a wooden dowel from a table and placing it on a shelf) and 2 warm up reaching trials during each session. Six sessions completed over a period of 6 days. Profession of individual(s) administering training not reported.
Outcomes	Primary outcome: functional movement – arm functional movement: Modified Motor Assessment Scale upper arm function and combined upper limb movements - upper arm function scores selected; hand functional movement: Modified Motor Assessment scale hand movements and advanced hand movements - hand movement scores selected. Secondary outcome: motor impairment – temporal outcomes: movement time and velocity profile - movement time selected; spatial outcomes: elbow angle and curvature of arm trajectories - elbow angle selected. TMS recorded but not relevant to this review.
Notes	SD for bilateral group equals 0 for upper arm function on Modified Motor Assessment Scale, therefore effect size not estimable. Imputed control group SD. No SD presented for movement kinematics and therefore unsuitable for inclusion in statistical pooling. Two participants excluded from movement time and elbow angle due to technical difficulties within the trial.

Appendix E – Characteristics of included studies (home-based therapy programmes)

Table E-1 - Full characteristics of included studies for review of home-based therapy programmes

Study	Duncan 1998[336]
Methods	RCT. Participants randomly assigned to control or intervention group using a random list generated by group assignments. Randomisation completed in blocks of 10. Random list generated prior to the beginning of the study. Only a laboratory technician who had no input into participant selection or recruitment was aware of group assignment.
Participants	N=20 selected from local participating hospitals and Kansas City Stroke Registry. M/F: Not reported; Age: Usual care (67.8±7.2 years), Home therapy (67.3±9.6 years); Time since stroke: Usual care (56 days), Home therapy (66 days); Type of stroke: Ischaemic 18, Haemorrhage 2, Brain stem 1; Initial UL impairment: Usual care (F-M 36.4), Home therapy (F-M 38.1) Inclusion criteria: 30 to 90 days after stroke; minimal or moderately impaired sensorimotor function (Fugl-Meyer 40 to 90, Oprington Prognostic Scale score 2.0 to 5.2); ambulatory with supervision and/or assistive device; living at home; living within 50 miles of the University of Kansas Medical Center; no medical condition that interfered with outcome assessments or limited participation in submaximal exercise programme; MMSE > 18; and no receptive aphasia that interfered with ability to follow a 3-step command
Interventions	Group 1 (10 participants): usual care. Usual care as prescribed by physicians. The therapy programmes received by the control group varied in intensity, frequency and duration. Group 2 (10 participants): home therapy programme. This involved an exercise programme designed to improve strength, balance and endurance and to encourage more use of the affected extremity. The programme was a home-based exercise programme provided by a physical therapist. Exercise sessions were divided into the following 4 blocks (preceded by a 10-minute warm-up session of stretching and flexibility exercises) (1) Assistive and resistive exercises using PNF patterns or theraband exercises to the major muscle groups of the upper and lower extremities (2) Balance exercises (3) Encouraged to use the affected upper extremity in functional activities (4) Progressive walking programme or progressive exercise on a bicycle ergometer. The programme included 3 visits per week for 8 weeks, and the patients were instructed to continue the exercise programme for an additional 4 weeks. Each session lasted approximately 1.5 hours.
Outcomes	Primary outcome: Performance in ADL: Barthel Index (0 to 100) Primary outcome: Functional movement: Jebsen Test of Hand Function (dexterity measure). Data for this outcome could not be included in the data analysis as total scores and SD were not reported. Secondary outcome: Performance in extended ADL: Lawton Instrumental ADL Secondary outcome: Motor impairment: Fugl-Meyer Upper Extremity Scale (0 to 66) Oprington Prognositc Scale, Fugl-Meyer Lower Extremity Scale (0 to 34), Medical Outcomes study- 36 Health Status Measurement, 10 metre walk, 6 minute walk and Berg Balance Scale were also reported, but not relevant to this review. Outcome measures completed at the end of intervention period only.
Notes	SDs not included in the paper. However SDs were calculated from data gained from the study authors. Data gained from study authors was also used to enter mean values for Barthel Index. This data gained from personal communication with the author differs from those presented in the published paper.

Study	Duncan 2003[337]
Methods	Prospective RCT. Participants were randomly assigned to intervention or control group using a random-number generator with a block size of 6. Allocation concealment ensured through the use of sealed envelopes.
Participants	N=100 selected from Kansas City Stroke Registry. M/F:56/44; Age: Usual care (70.2±11.4 years), Home therapy (68.5±9.0 years), Drop-outs (74.6±9.8 years)); Time since stroke: Usual care (73. 5±27.1 days), Home therapy (77.5±28.7 days), Drop-outs (84±27.2 days); Type of stroke: Ischaemic 90; Initial UL impairment: Usual care (F-M 43.3±11.9), Home therapy (F-M 45.8±12.8), Drop-outs (F-M 50.6±7.4) Inclusion criteria: stroke within 30 to 150 days; ability to ambulate 25 feet independently; mild to moderate stroke deficits (Fugl-Meyer Upper and Lower Extremity Scales 27 to 90, Orpington Prognositc Score 2 to 5.2, palpable wrist extension on involved side); MMSE ≥16; no serious cardiac conditions; not oxygen dependent; no severe weight-bearing pain; no other serious organ system disease; and life expectancy > 1 year
Interventions	Group 1 (50 participants): usual care. Usual care as prescribed by physicians. Two-thirds were provided with an unsupervised exercise programme. Those who did receive therapy received an average of 8.7 ∓ 5.3 physical therapy visits and 10.4 ∓ 7 occupational therapy visits. Physical and occupational therapy were received separately, as prescribed by participants' physicians. Duration of combined physical therapy and occupational therapy visits comparable to those in intervention group (approximately 90 minutes). There was much variation in the types of exercises received. Group 2 (50 participants): home therapy programme. This involved an exercise programme designed to improve strength, balance and endurance and to encourage more use of the affected extremity. The programme was a home-based exercise programme provided by a physical therapist. Exercise sessions were divided into the following 4 blocks (preceded by a 10-minute warm-up session of stretching and flexibility exercises) (1) Assistive and resistive exercises using PNF patterns or theraband exercises to the major muscle groups of the upper and lower extremities (2) Balance exercises (3) Encouraged to use the affected upper extremity in functional activities (4) Progressive walking programme or progressive exercise on a bicycle ergometer. Physical and occupational therapists supervised the programme, at participants home and included 36 sessions of 90-minute duration over 12 to 14 weeks. There were structured protocols for the exercise tasks, criteria for progression and guidelines for reintroducing therapy after intercurrent illness. Each participant received an average of 33.4 ∓ 2.3 visits, and the average duration of a visit was 91 ∓ 4.5 minutes. For both groups, treating therapists completed a treatment log to capture type of exercises and frequency and duration of therapy visits.
Outcomes	Primary outcome: Performance in ADL: Barthel Index (0 to 100). Data for this outcome were extracted from the associated paper[339] (n=93 post-treatment, n=80 6 month follow-up). Primary outcome: Functional movement: Wolf Motor Function Test. The data for this outcome were presented for patients above and below median at baseline. It was assumed that 25 participants were in each group. Secondary outcome: Performance in extended ADL: Lawton Instrumental ADL. Data for this outcome were extracted from the associated paper[339] Secondary outcome: Motor impairment: Fugl-Meyer Upper Extremity Scale (0 to 66) and grip strength (Jamar dynamometer) Orpington Prognositc Scale, Fugl-Meyer Lower Extremity Scale (0 to 34), isometric strength testing for ankle dorsiflexion and knee extension, 10-metre walk test, 6 minute walk and Berg Balance Scale were also reported but are not relevant to this review. The associated paper further reported Medical Outcomes Study short-form 36-item questionnaire (SF-36) and Stroke Impact Scale (SIS) which are also not relevant.

Notes	Change scores only reported and therefore used in the analysis For performance in ADL and extended ADL outcomes, data from another paper[339] was used. These data had been adjusted for age, pre-stroke physical function, stroke severity and baseline measurement of outcome and analysis was completed with multiple imputations; however data was entered not including drop-outs, therefore data only available for 93 participants. Follow-up data (6 months post-treatment) only available for 80 participants For other outcomes 8 drop-outs reported. 6 participants from intervention arm (significant renal insufficiency detected after randomisation, subclavian steal syndrome diagnosed after randomisation, 1 withdrew after 18 visits, 3 experienced a second stroke) and 2 from usual care group (1 withdrew after randomisation, 1 did not return for 3-month assessment). ITT analysis was completed and therefore analysis based on 100 participants Wolf Motor Function Test time for completion was used in the analysis. The data was inverted for use in the analysis (multiplied x-1). To increase availability of included data presented SEs were converted into SDs (SD = SE$\sqrt{n}$).
Study	Piron 2008[338]
Methods	RCT. Participants were randomly assigned using simple randomisation to 1 of 2 treatment groups of 5 patients. Details of any allocation concealment were not reported.
Participants	N=10. M/F: 5/5; Age: VR 65±11 years, VR with telerehabilitation 53±15 years; Time since stroke: VR 364±56 days, VR with telerehabilitation 280±56 days; Type of stroke: Ischaemic; Initial UL impairment: (F-M) 50.3. Inclusion criteria: mild to intermediate arm motor impairment; ischaemic stroke in the area of the middle cerebral artery; and no cognitive problems that could interfere with comprehension.
Interventions	Group 1 (5 participants): virtual reality training with therapist. A 3D motion tracking system recorded participants' arm movements and a virtual environment created in which the participants' movements were represented. A sequence of virtual tasks was performed whilst participants watched their movement trajectory on screen compared with an ideal trajectory. The virtual reality system thus provided visual feedback, i.e. knowledge of performance and knowledge of results. Treatment occurred in hospital with a therapist present. Group 2 (5 participants): virtual reality with telerehabilitation at home. The same practice as group 1 was performed but via a computer in the participants' homes, with a videoconferencing system and a remote link to the therapist in the hospital. Both groups received 1 hour of daily training for 1 month. Same physical therapist managed the rehabilitation sessions for both groups.
Outcomes	Secondary outcome: Motor impairment: Fugl-Meyer Upper Extremity Scale Multidimensional disease and treatment specific satisfaction questionnaire was also reported as an outcome but this was not relevant to this review. Outcome measures were completed at the end of the intervention period only.
Notes	No details given as to the training or experience of the therapist delivering the intervention. No SDs were included in the paper. In order to include this study in the meta-analysis, we used the SD reported by Piron 2009, which included participants with similar levels of initial upper limb motor impairment. The largest SD reported by Piron 2009 (7.7) was used in order to be conservative.
Study	Piron 2009[284]
Methods	RCT. Simple randomisation using sequentially numbered, opaque, sealed envelopes. Allocation to 1 of 2 treatment groups was performed by the therapist co-ordinator of the hospital who was not involved in the participants rehabilitation programme.

Participants	N=36. M/F: 21/15; Age: Usual care 64.4±7.9 years, VR with telerehabilitation 66±7.9 years; Time since stroke: Usual care 333±11.9 days, VR with telerehabilitation 412±184.8 days; Type of stroke: Ischaemic; Initial UL impairment: Usual care (F-M) 47.3±4.5, VR with telerehabilitation 48.4±7.2 Inclusion criteria: mild to intermediate arm motor impairment on Fugl-Meyer Upper Extremity Scale; single ischaemic stroke in the area of middle cerebral artery; no apraxia (< 62 points on the de Renzi Test); and no clinical evidence of cognitive impairment that could interfere with verbal comprehension, such as neglect and language disturbances (more than 40 errors in the Token Test).
Interventions	Group 1 (18 participants): conventional physiotherapy in the local health district. Participants performed specific exercises for the upper limb with a strategy of progressive complexity. First, they were requested to control isolated motions without postural control, then postural control was included, and finally complex motions with postural control were practiced. Examples of tasks were to touch different targets arranged in front, manipulate different objects, follow trajectories displayed on a plane and to recognise different arm positions Group 2 (18 participants): telerehabilitation system at home. This consisted of 2 dedicated personal computer-based workstations; 1 at the participant's home; and 1 at the hospital. This generated a virtual environment in which participants executed motor tasks. This was combined with video-conferencing which permitted the remote control of the participant's video camera mobility in order to observe the participants movements during the rehabilitation tasks. The virtual reality system incorporated a 3D motion tracking system to record arm movements. 5 virtual tasks comprising simple arm movements were practised whilst participants watched their movement trajectory on screen compared to an ideal trajectory. Participants received verbal feedback from the therapist about the exactness of the movements Both groups received 1 hour of daily training, 5 days per week for 1 month.
Outcomes	Primary outcome: Functional movement: ABILHAND Scale Secondary outcome: Motor impairment scale: Fugl-Meyer Upper Extremity Subscore and Ashworth Scale. Fugl-Meyer selected for analysis. Outcome measures performed 1 month before treatment began, at baseline, immediately after 1 month treatment and at 1 month after treatment ceased (follow-up).
Notes	No details given as to the training or experience of the therapist delivering the intervention.

Appendix F – Armeo®Spring device

Pictures taken from Hocoma website:
http://www.hocoma.com/products/armeo/armeospring 2011

Appendix G - Consent form

CONSENT FORM

Title of Project: Arm intervention after stroke: A feasibility study (AIAS)

Name of Researcher: Fiona Coupar

Please initial box

1. I confirm that I have read and understand the information sheet dated ……. (version……) for the above study. I have had the opportunity to consider the information and ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that if I withdraw from the study that any data collected may be used for analysis. I give permission for this data to be used. ☐

4. I understand that relevant sections of my medical notes and data collected during the study may be looked at by researchers involved in this study. I give permission for these individuals to have access to my records. ☐

5. I understand that I will be asked to take part in an informal interview about the treatment I receive. I agree for this interview to be recorded. ☐

6. I understand that the study treatments will not continue after the study period but standard care will continue, as required. ☐

6. I agree to participate in this study. ☐

7. I agree for my G.P to be informed of my participation in this study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

Appendix H – Interview topic guide

Introduction

The aim of this part of the research is to find out your opinions about the therapy you received, targeted at your arm.

To facilitate the process we would like to audio-tape our conversation today. Only researchers on the project will have access to the tapes and the tapes will be destroyed after the research is finished. I will also be taking notes to help in the analysis process. All interviews will be treated as confidential. All information gained will be anonyomised and no identifiable data will be used. All information gained will be allocated a unique identification number.

We have planned for the interview to last approximately 30 minutes. During this time I will ask you a number of questions and seek your opinions about different aspects of the therapy you received. I will be specifically looking for your opinions about the types of things that were done to improve your arm movement. I am interested in hearing your opinions and feelings as you are the expert in the therapy you received.

Background

When did you have your stroke?
How did the stroke affect you?
    Possible probe: What did this mean for you?
        How does this make you feel?
In particular how was your arm affected?
    Possible probe: What did this mean for you?
        What affect(s) did this have?

Therapy

What therapy did you receive to improve you arm abilities?
    Possible probe: Tell me more about what this involved?
What were your hopes for the intervention?
How important was therapy targeted at your arm?

Opinions of therapy

Did you find the therapy you received acceptable?
    Possible probe: Why was this?
Were you satisfied with the therapy you received?
    Possible probe: Why do you feel like this?

Did the therapy you received meet your expectations?
    Possible probe: Why do you think that was?
What did you like about the therapy?
What did you not like about the therapy?
Do you think it made a difference to your arm?
    Possible probe: What makes you say that?
How do you think the therapy for your arm could have been better?
Would you recommend this therapy?

End of interview
Thank you for your time and participation. Other closing comments/remarks.

Appendix I – Safety Checklist: End of intervention period

Patient number: Date:

Safety outcomes/Adverse events

(a) Arm pain scale (includes shoulder)

In the last 2 weeks have you had any pain in your affected arm?

Yes ☐

No ☐

How would you describe this pain (mark only one)?

Excruciating (very severe) ☐

Severe ☐

Moderate ☐

Mild ☐

None ☐

If 0 (zero) is not pain at all and the number 10 (ten) means as painful as it could be, then how painful was it? (Please give a number between one and ten): **Number** ☐

(b) Borg Perceived Exertion scale (exertion of therapy)

The 15-point scale is illustrated below as an example:

6 would be the equivalent of sitting down doing nothing,
9 would be walking gently, 13 a steady exercising pace and 19/20 the hardest exercise you have ever done.

6
7 - Very, very light **Number:** ☐
8
9 - Very light
10
11 - Fairly light
12
13 - Moderately hard
14
15 - Hard
16
17 - Very hard
18
19 - Very, very hard
20 – Exhaust

(c) Subluxation (clinical report)	**No**	☐	**Yes**	☐
(d) Increased spasticity (clinical report)	**No**	☐	**Yes**	☐
(e) Skin breakdown on affected arm (observation)	**No**	☐	**Yes**	☐
(f) Adverse events (clinical report)				
Chest infection	**No**	☐	**Yes**	☐
UTI	**No**	☐	**Yes**	☐
DVT/PTE	**No**	☐	**Yes**	☐
Falls **Number of falls:**	**No**	☐	**Yes**	☐
Recurrent stroke	**No**	☐	**Yes**	☐

Other (please specify)……

Appendix J – Action Research Arm Test

Patient identifier ☐

Instructions

There are four subtests: Grasp, Grip, Pinch and Gross Movement. If the participant passes the first task in each subset then they score top marks and move onto next subtest. If a subject fails the first and the second tasks in a subtest, then they score 0 for that subtest and move onto the next. The patient must be able to sit unaided to complete the test. If not they score 0.

Score: 0 = can perform no part of the test 1 = performs tasks partially
2 = completed test, but takes abnormally long time 3 = performs test normally

Start with the least impaired arm first

a) Grasp	**R**	**L**
1. Pick up a 10 cm block (If score = 3 then total = 18 & go to Grip)	☐	☐
2. Pick up 2.5 cm block (If Grasp score = 0 so far then grasp total = 0 & go to Grip)	☐	☐
3. 5 cm cube	☐	☐
4. 7.5 cm cube	☐	☐
5. Ball (Cricket)	☐	☐
6. Stone	☐	☐
Grasp total:	☐	☐

b) Grip		
1. Pour water glass to glass (if score = 3 then total =12 & go to Pinch)	☐	☐
2. 2.25 cm tube (If grip score = 0 so far then Grip total = 0 & go to Pinch)	☐	☐
3. 1 cm tube	☐	☐
4. Washer over bolt	☐	☐
Grip total:	☐	☐

c) Pinch		
1. 6 mm bearing 3rd finger & thumb (if score = 3, total = 18 & go to Gross)	☐	☐
2. Marble index & thumb (If Pinch score = 0 then Pinch total = 0 & go to Gross)	☐	☐
3. 6mm bearing 2nd finger and thumb	☐	☐
4. 6mm bearing 1st finger and thumb	☐	☐
5. Marble 3rd finger and thumb	☐	☐

6. Marble 2nd finger and thumb		
Pinch total:		

d) Gross

1. Place hand behind head (If score = 3 then total = 9 & finish)		
2. Place hand on top of head (If score = 0 then total = 0 & finish)		
3. Hand to mouth		
Gross total:		
ARAT total:		

Appendix K – Fugl-Meyer Assessment

Patient Identifier			
1 Shoulder / elbow / forearm Score			
1.1 Reflex activity			
1.1.1 Flexors (biceps and finger flexors)	0		2
1.1.2 Extensors (triceps)	0		2
1.2 Flexor synergy – volitional movement within synergy			
1.2.1 Shoulder retraction	0	1	2
1.2.2 Shoulder elevation	0	1	2
1.2.3 Shoulder abduction to 90º	0	1	2
1.2.4 Shoulder external rotation	0	1	2
1.2.5 Elbow flexion	0	1	2
1.2.6 Forearm supination	0	1	2
1.3 Extensor synergy – volitional movement within synergy			
1.3.1 Shoulder adduction/internal rotation	0	1	2
1.3.2 Elbow extension	0	1	2
1.3.3 Forearm pronation	0	1	2
1.4 Volitional movement mixing the dynamic flexor and extensor			
1.4.1 Hand on lumbar spine	0	1	2
1.4.2 Shoulder flexion 0º -90º	0	1	2
1.4.3 Forearm pronation/supination elbow at 90º	0	1	2
1.5 Volitional movement are performed with little or no synergy dependence			
1.5.1 Shoulder abduction	0	1	2
1.5.2 Shoulder flexion 90º-180º	0	1	2
1.5.3 Forearm pronation-supination elbow at 0º	0	1	2
1.6 Normal reflex activity	0	1	2
2 Wrist			
2.1 Wrist stability – elbow 90º	0	1	2
2.2 Wrist flexion/extension – elbow 90 º	0	1	2
2.3 Wrist stability – elbow 0º	0	1	2
2.4 Wrist flexion/extension – elbow 0º	0	1	2
2.5 Circumduction	0	1	2
3 Hand			
3.1 Mass flexion – finger flexion	0	1	2
3.2 Mass extension – finger extension	0	1	2
3.3 Grasp A – distal finger grasp	0	1	2
3.4 Grasp B – thumb adduction grasp - paper	0	1	2
3.5 Grasp C – thumb to index finger grasp - opposition	0	1	2
3.6 Grasp D – cylinder grasp	0	1	2
3.7 Grasp E – spherical grasp- ball	0	1	2
4. Co-ordination/speed			
4.1 Tremor – finger to nose	0	1	2
4.2 Dysmetria- finger to nose	0	1	2
4.3 Speed – finger to nose	0	1	2
Upper limb score			

Appendix L – Barthel Index

Participant number: _____ Date: _____

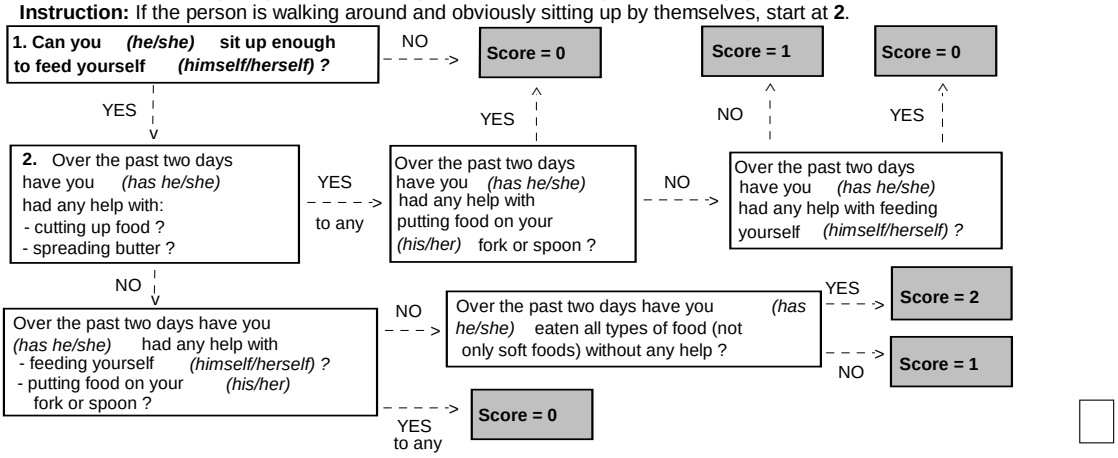
Barthel Index

If the participant indicates that they are not independent in any of these activities, ask "Who helps you with these tasks?", and note which person is the chief carer.

FEEDING

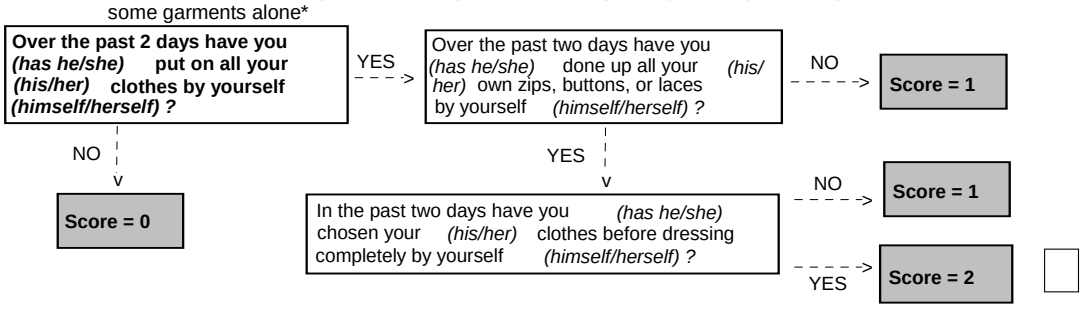
** Independent = Able to eat any normal food (not only soft food*). Food cooked and served by others (food provided in reach). But not cut up. Help = food cut up, patient feeds self*.

Instruction: If the person is walking around and obviously sitting up by themselves, start at **2**.



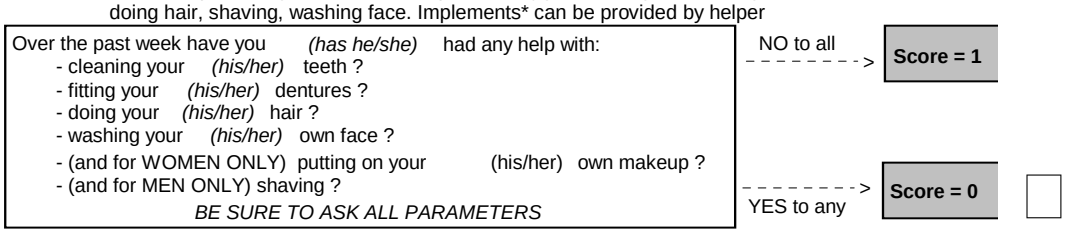
DRESSING

** Independent = Should be able to select and put on all clothes (including buttons, zips, laces etc), which may be adapted. Half = help with buttons, zips etc (CHECK!), but can put on some garments alone*



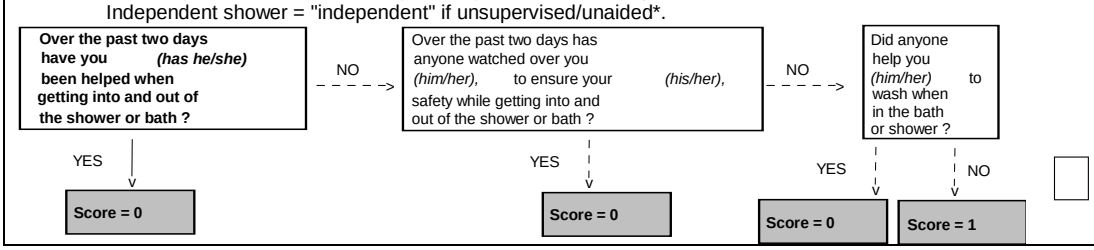
GROOMING

** Refers to preceding week. Refers to personal hygiene: doing teeth, fitting false teeth, doing hair, shaving, washing face. Implements* can be provided by helper



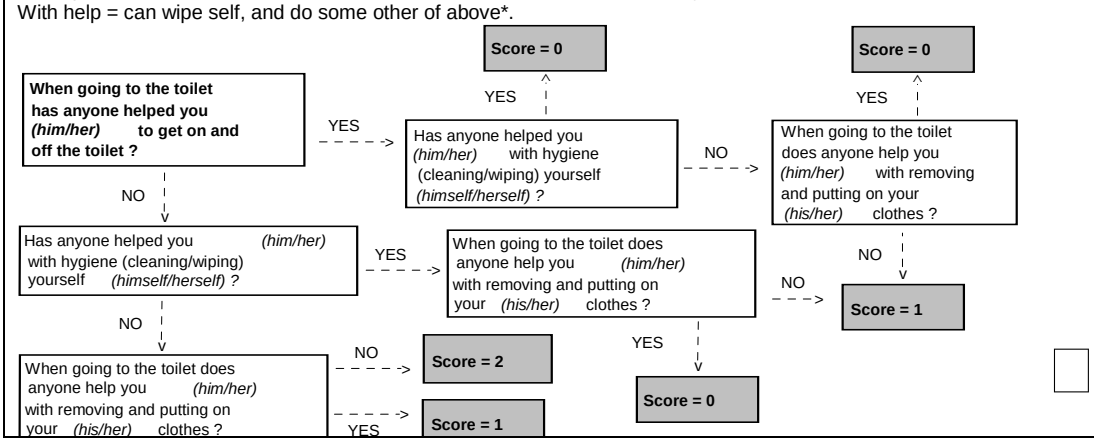
BATHING

** Usually the most difficult activity. Must get in and out unsupervised, and wash self.
Independent shower = "independent" if unsupervised/unaided*.



TOILET USE

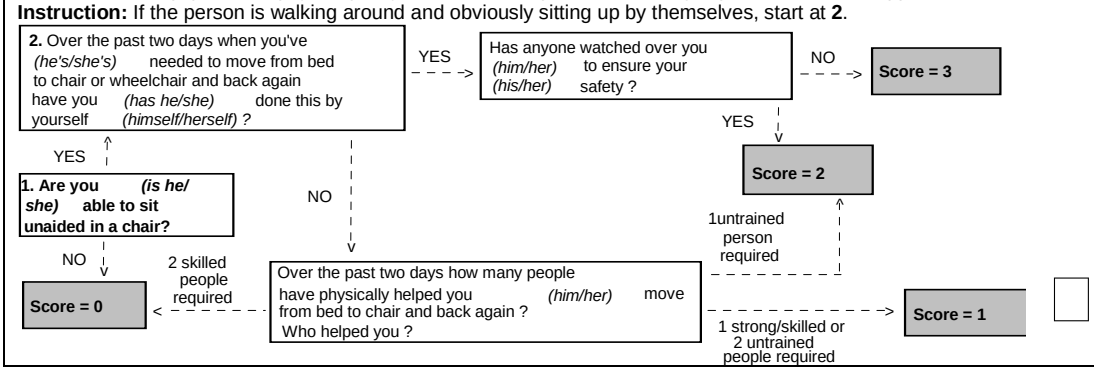
**Independent = Should be able to reach toilet/commode, undress sufficiently, clean self, dress and leave.
With help = can wipe self, and do some other of above*.



TRANSFER

** Independent = From bed to chair and back.
Dependent = no sitting balance (unable to sit); two people to lift.
Major help = one strong/skilled, or two normal people. Can sit up.
Minor help (verbal or physical) = by one, untrained person, including supervision/ moral support.

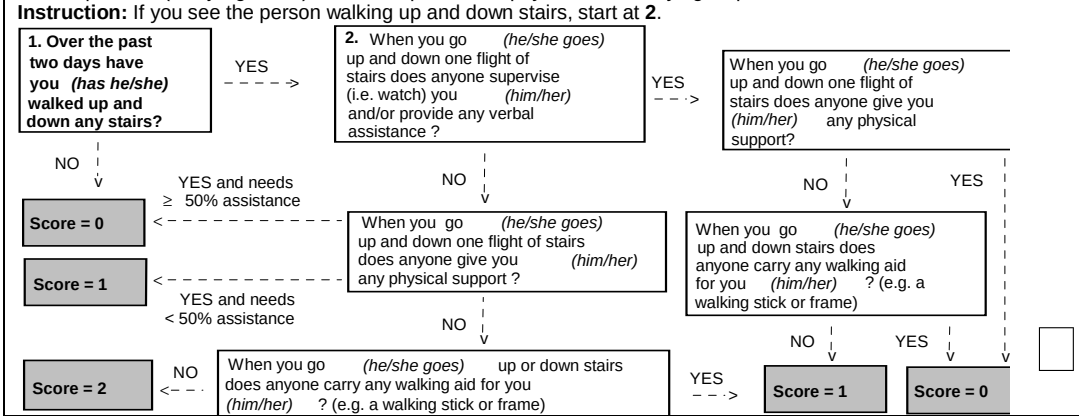
Instruction: If the person is walking around and obviously sitting up by themselves, start at **2**.



STAIRS

**Independent = Must carry any walking aid used (if used). If patient hasn't walked up or down stairs because there are no stairs at home but usually does use them while shopping, etc, score as independent (use judgement). Needs help = verbal, physical, and carrying help

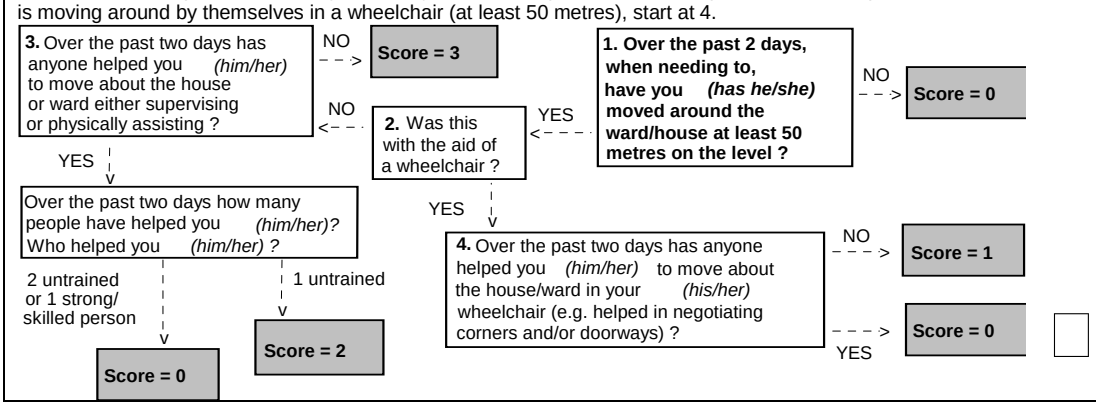
Instruction: If you see the person walking up and down stairs, start at **2**.



MOBILITY

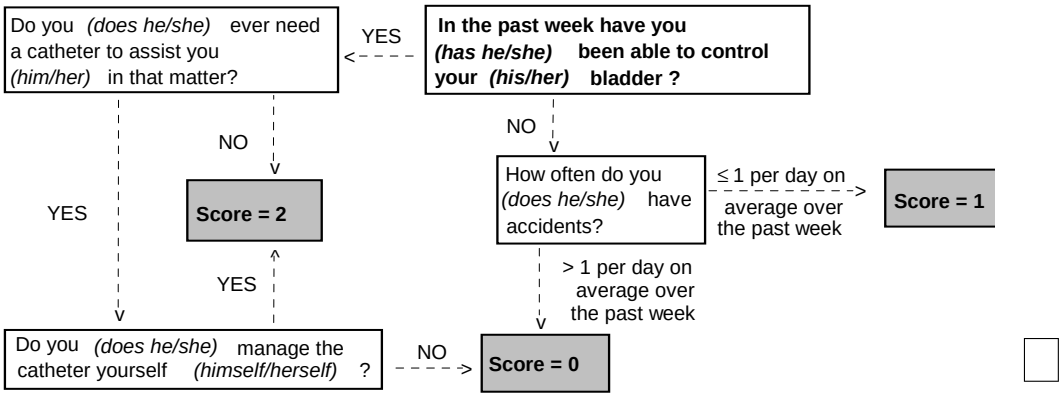
** Refers to mobility about house or ward, indoors.
Independent = May use aid (stick, frame). If in a wheelchair, must negotiate doors/corners unaided.
Help (physical/verbal) = by one, untrained person, including supervision/moral support.

Instruction: If the person is walking around by themselves (at least 50 metres), start at 3. If the person is moving around by themselves in a wheelchair (at least 50 metres), start at 4.



BLADDER

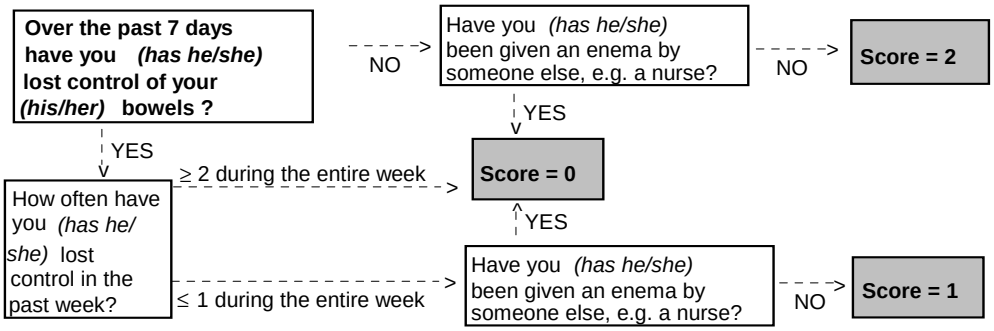
** Refers to preceding week. Occasional = less than once a day (max once per 24 hours).
A catheterised patient who can manage the catheter alone is registered as continent.



BOWELS

** Refers to preceding week.

If needs enema from nurse, then "incontinent". Occasional accident = once/week.



Reference List

1. Hatano S. Experience from a multicenter stroke register: a preliminary report. *Bull World Health Organization* 1976;**54**:541-53.

2. Warlow C, Sudlow C, Dennis M, Wardlaw J, Sandercock P. Stroke. *Lancet* 2003;**362**:1211-24.

3. Sudlow C, Warlow C. Comparable studies of the incidence of stroke and its pathological types - Results from an international collaboration. *Stroke* 1997;**28**:491-9.

4. Feigin V, Lawes C, Bennett D, Anderson C. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *Lancet Neurol* 2003;**2**:43-53.

5. Warlow C, van Gijn J, Dennis M, Wardlaw J, Bamford J, Hankey G *et al*. Stroke; practical management. Oxford: Blackwell Publishing, 2008.

6. World Health Organization. The atlas of heart disease and stroke. www.who.int/cardiovascular.diseases/resources/atlas/en/. Last accessed July 2008.

7. Mant J, Wade C, Winner S. Health care needs assessment: Stroke. In Stevens A, Raftery J, Mant J, Simpson S, eds. *Health care needs assessment; the epidemiologically based needs assessment reviews*, Oxford: Radcliffe Medical Press, 2004.

8. Adamson J, Beswick A, Ebrahim S. Is stroke the most common cause of disability? *J Stroke Cerebrovasc* 2004;**13**:171-7.

9. National Audit Office. Department of Health - Reducing brain damage: Faster access to better stroke care (online). 2005. www.nao.org.uk/publications/0506/reducing_brain_damage.aspx. Last accessed July 2008.

10. Wolfe C. The impact of stroke. *Brit Med Bull* 2000;**56**:275-86.

11. Rothwell P. The high cost of not funding stroke research: a comparison with heart disease and cancer. *Lancet* 2001;**357**:1612-6.

12. Bonita R. Epidemiology of Stroke. *Lancet* 1992;**339**:342-4.

13. Scottish Executive. Coronary Heart Disease and Stroke Strategy for Scotland (online). 2002. www.scotland.gov.uk/publications/2002/10/15530. Last accessed July 2008.

14. Department of Health. National Stroke Strategy (online). 2007. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_081062. Last accessed July 2008.

15. Wolfe, C and Rudd, T. The burden of stroke of stroke white paper: Raising the awareness of the global toll of stroke related disability and death. 2007. www.safestroke.org/resources/the-burden-of-stroke-white-paper.aspx. Last accessed July 2008.

16. Department of Health. Stroke rehabilitation. *Effective Health care* 1992;**2**:1-11.

17. Langhorne P, Stott D, Robertson L, MacDonald J, Jones L, McAlpine C *et al*. Medical complications after stroke - Multicenter study. *Stroke* 2000;**31**:1223-9.

18. Arganoff, A. Stroke motor impairment (online). http://emedicine.medscape.com/articles/324386-overview. Last accessed July 2008.

19. World Health Organization. International classification of functioning, disability and health (online). 2001. www.who.int/classification/icf/en/ Last accessed July 2008.

20. Wade D, Langton Hewer R, Skilbeck C, David R. Stroke: a critical approach to diagnosis, treatment and management. London: Chapman & Hall, 1985.

21. Nakayama H, Jorgensen H, Raaschou H, Olsen T. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. *Arch Phys Med Rehab* 1994;**75**:394-8.

22. Wade D. Measuring upper limb impairment and disability after stroke. *Int Disabil Stud* 1989;**11**:89-92.

23. Fregni F, Pascual-Leone A. Hand motor recovery after stroke: Tuning the orchestra to improve hand motor function. *Cog Behav Neurol* 2006;**19**:21-33.

24. Goulding R, Thompson D, Beech C. Caring for patients with hemiplegia in an arm following stroke. *Br J Nurs* 2004;**13**:534-9.

25. Wyller T, Sveen U, Sodring K, Pettersen A, BautzHolter E. Subjective well-being one year after stroke. *Clin Rehabil* 1997;**11**:139-45.

26. Feys H, De Weerdt W, Selz B, Steck G, Spichiger R, Vereeck L *et al*. Effect of a therapeutic intervention for the hemiplegic upper limb in the acute phase after stroke - A single-blind, randomized, controlled multicenter trial. *Stroke* 1998;**29**:785-92.

27. Parker V, Wade D, Langton Hewer R. Loss of arm function after stroke: measurement, frequency, and recovery. *Int Rehabil Med* 1986;**8**:69-73.

28. Wardlaw J, Murray V, Berge E, del Zoppo G. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2009;**4**:CD000213.

29. Scottish Intercollegiate Guidelines Network. Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary preventation: a national clinical guideline (online). 2008. www.sign.ac.uk/guidelines/fulltext/108/index.html. Last accessed January 2012.

30. Quaba O, Robertson C. Thrombolysis and its implications in the management of stroke in the accident and emergency department. *Scot Med J* 2002;**47**.

31. O'Connor R, McGraw P, Edelsohn L. Thrombolytic therapy for acute ischemic stroke: Why the majority of patients remain ineligible for treatment. *Ann Emerg Med* 1999;**33**:9-14.

32. Royal College of Physicians. National clinical guidelines for stroke (online). 2008. www.rcplondon.ac.uk/resources/stroke-guidelines. Last accessed January 2012.

33. Scottish Intercollegiate Guidelines Network. Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning (online). 2010. www.sign.ac.uk/guidelines/fulltext/118/index.html. Last accessed January 2012.

34. The European Stroke Organization (ESO) Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. www.eso-stroke.org/pdf/ESO08-Guidelines.original.english.pdf. Last accessed February 2012.

35. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database of Syst Rev* 2012;**4**:CD000197.

36. Langhorne P, Pollock A. What are the components of effective stroke unit care? *Age Ageing* 2002;**31**:365-71.

37. Young J, Forster A. Rehabilitation after stroke. *BMJ* 2007;**334**:86-90.

38. Wade D. Evidence relating to assessment in rehabilitation. *Clin Rehabil* 1998;**12**:183-6.

39. Young J. Caring for older people - Rehabilitation and older people. *BMJ* 1996;**313**:677-81.

40. Bohannon R, Andrews A, Smith M. Rehabilitation Goals of Patients with Hemiplegia. *Int J Rehabil Res* 1988;**11**:181-3.

41. Ring H, Rosenthal N. Controlled study of neuroprosthetic functional electrical stimulation in sub-acute post-stroke rehabilitation. *J Rehabil Med* 2005;**37**:32-6.

42. Sackett D, Rosenberg W, Gray J, Haynes R, Richardson W. Evidence based medicine: What it is and what it isn't - It's about integrating individual clinical expertise and the best external evidence. *BMJ* 1996;**312**:71-2.

43. Medical Research Council. A framework for development and evaluaion of RCTs for complex interventions to improve health. London: Medical Research Council, 2000.

44. McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D. Randomised trials in surgery: problems and possible solutions. *BMJ* 2002;**324**:1448-51.

45. Pollock C, Freemantle N, Sheldon T, Song F, Mason J. Methodological difficulties in rehabilitation research. *Clin Rehabil* 1993;**7**:63-72.

46. Wolfe C, Rudd A, Tilling K. Trials of community rehabilitation need to be of adequate sample size. *Stroke* 1998;**29**:1737-8.

47. Campbell N, Murray E, Darbyshire J, Emery J, Farmer A, Griffiths F *et al*. Designing and evaluating complex interventions to improve health care. *BMJ* 2007;**334**:455-9.

48. Pomeroy V, Tallis R. Need to focus research in stroke rehabilitation. *Lancet* 2000;**355**:836-7.

49. Day S, Altman D. Statistics Notes - Blinding in clinical trials and other studies. *BMJ* 2000;**321**:504.

50. Schulz K, Chalmers I, Hayes R, Altman D. Evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408-12.

51. Rodgers H, Mackintosh J, Price C, Wood R, McNamee P, Fearon T *et al*. Does an early increased-intensity interdisciplinary upper limb therapy programme following acute stroke improve outcome? *Clin Rehabil* 2003;**17**:579-89.

52. Legg L, Drummond AE, Langhorne P. Occupational Therapy for patients with problems of activities of daily living after stroke. *Cochrane Database Syst Rev* 2006;**4**:CD003585.

53. van Peppen R, Kwakkel G, Wood-Dauphinee S, Hendriks H, Van der Wees P, Dekker J. The impact of physical therapy on functional

outcomes after stroke: what's the evidence? *Clin Rehabil* 2004;**18**:833-62.

54. Pomeroy V, Tallis R. Need to focus research in stroke rehabilitation. *Lancet* 2000;**355**:836-7.

55. Scottish Executive. Allied Health Professions Research and Development Action Plan. Edinburgh: Scottish Executive (Astron), 2004.

56. Pomeroy V, Tallis R. Physical therapy to improve movement performance and functional ability poststroke. Part 2. A research direction. *Rev Clin Gerontol* 2000;**10**:381-7.

57. Meldrum D, Pittock S, Hardiman O, Ni Dhuill C, O'Regan M. Recovery of the upper limb post ischaemic stroke and the predictive value of the Orpington Prognostic Score. *Clin Rehabil* 2004;**18**:694-702.

58. Campbell M, Fitzpatrick R, Haines A, Kinmonth A, Sandercock P, Spiegelhalter D *et al*. Framework for design and evaluation of complex interventions to improve health. *BMJ* 2000;**321**:694-6.

59. Medical Research Council. Developing and evaluating complex interventions: new guidance. 2008. www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC004871. Last accessed April 2012.

60. Craig P, Dieppe P, MacIntyire S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008;**337**:979-83.

61. Wyller T, Holmen J, Laake P, Laake K. Correlates of subjective well-being in stroke patients. *Stroke* 1998;**29**:363-7.

62. Winstein C, Rose D, Tan S, Lewthwaite R, Chui H, Azen S. A randomized controlled comparison of upper-extremity rehabilitation strategies in acute stroke: A pilot study of immediate and long-term outcomes. *Arch Phys Med Rehab* 2004;**85**:620-8.

63. Putman K, De Wit L, Schoonacker M, Baert I, Beyens H, Brinkmann N *et al*. Effect of socioeconomic status on functional and motor recovery after stroke: a European multicentre study. *J Neurol Neurosurg Psychiatry* 2007;**78**:593-9.

64. Wade D, Langton Hewer R, Wood V, Skilbeck C. The hemiplegic arm after stroke: measurement and recovery. *J Neurol Neurosurg Psychiatry* 1983;**46**:521-4.

65. Kwakkel G, Kollen B, van der GJ, Prevo A. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. *Stroke* 2003;**34**:2181-6.

66. Van der Lee J, Snels I, Beckerman H, Lankhorst G, Wagenaar R, Bouter L. Exercise therapy for arm function in stroke patients: a systematic review of randomized controlled trials. *Clin Rehabil* 2001;**15**:20-31.

67. Basmajian J, Gowland C. The Many Hidden Faces of Stroke - A Call for Action. *Arch Phys Med Rehab* 1987;**68**:319.

68. Shelton F, Reding M. Effect of lesion location on upper limb motor recovery after stroke. *Stroke* 2001;**32**:107-12.

69. Nascimbeni A, Gaffuri A, Imazio P. Motor evoked potentials: prognostic value in motor recovery after stroke. *Funct Neurol* 2006;**21**:199-203.

70. Feys H, De Weerdt W, Nuyens G, van de Winckel A, Selz B, Kiekens C. Predicting motor recovery of the upper limb after stroke rehabilitation: value of a clinical examination. *Physiother Res Int* 2000;**5**:1-18.

71. Altman D. Systematic reviews in health care - Systematic reviews of evaluations of prognostic variables. *BMJ* 2001;**323**:224-8.

72. Dennis M. Predictions models in acute stroke - Potential uses and limitations. *Stroke* 2008;**39**:1665-6.

73. Hendricks H, Zwarts M, Plat E, van Limbeek J. Systematic review for the early prediction of motor and functional outcome after stroke by using motor-evoked potentials. *Arch Phys Med Rehab* 2002;**83**:1303-8.

74. Shelton F, Volpe B, Reding M. Motor impairment as a predictor of functional recovery and guide to rehabilitation treatment after stroke. *Neurorehabil Neural Repair* 2001;**15**:229-37.

75. Katrak P. Shoulder shrug--a prognostic sign for recovery of hand movement after stroke. *Med J Australia* 1990;**152**:297-301.

76. Barreca S, Finlayson M, Gowland C, Basmajian J. Use of the Halstead Category Test as a cognitive predictor of functional recovery in the hemiplegic upper limb: a cross-validation study. *Clin Neuropsyc* 1999;**13**:171-81.

77. Chen S-Y, Winstein C. A systematic review of voluntary arm recovery in hemiparetic stroke. *J Neurol Phys Ther* 2009;**33**:2-13.

78. Stinear C. Prediction of recovery of motor function after stroke. *Lancet Neurol* 2010;**9**:1228-32.

79. Egger M, Davey Smith G, Altman DG. Systematic reviews in health-care: Meta-analysis in context. London: BMJ, 2001.

80. Greenhalgh T. How to read a paper: Papers that summarise other papers (systematic reviews and meta-analyses). *BMJ* 1997;**372**:672-5.

81. Stroup D, Berlin J, Morton S, Olkin I, Williamson G, Rennie D *et al*. Meta-analysis of observational studies in epidemiology - A proposal for reporting. *JAMA* 2000;**283**:2008-12.

82. Mahoney F, Barthel D. Functional evaluation: The Barthel Index. *Maryland State Med J* 1965;**39**:56-61.

83. Bonita R, Beaglehole R. Modification of Rankin Scale: Recovery of motor function after stroke. *Stroke* 1988;**19**:1497-500.

84. Keith R, Granger C, Hamitlon B, herwin F. The Functional Independence Measure: a new tool for rehabilitation. *Adv Clin Rehabil* 1987;**1**:6-18.

85. Lyle R. A performance-test for assessment of upper limb function in physical rehabilitation treatment and research. *Int J Rehabil Res* 1981;**4**:483-92.

86. Carr J, Shepherd R. Investigation of a new Motor Assessment Scale for stroke patients. *Phys Ther* 1985;**65**:175-80.

87. Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the Box and Block Test of manual dexterity. *Am J Occup Ther* 1985;**39**:386-91.

88. Fugl-Meyer A, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. I. A method for evaluation of physical performance. *Scand J Rehabil* 1975;**7**:13-31.

89. Jorgensen H, Nakayama H, Pedersen P, Kammersgaard L, Otto H, Tom R *et al*. Epidemiology of stroke-related disability: The Copenhagen Stroke Study. *Clin Geriatr Med* 1999;**15**:785-99.

90. Sandercock P, Algra A, Anderson C, et al. Cochrane Stroke Group. About the Cochrane Colloboration (Cochrane Review Groups). *The Cochrane Library* 2009;**2**.

91. Wells G, Shea B, O'Connell D, Peterson J, Welch V Losos M et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2008 http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Last accessed January 2012.

92. Belo J, Berger M, Reijman M, Koes B, Bierma-Zeinstra S. Prognostic factors of progression of osteoarthritis of the knee: A systematic review of observational studies. *Arthrit Care Res* 2007;**57**:13-26.

93. Hayden J, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006;**144**:427-37.

94. Scholten-Peeters G, Verhagen A, Bekkering G, van der Windt D, Barnsley L, Oostendorp R *et al*. Prognostic factors of whiplash-associated disorders: A systematic review of prospective cohort studies. *Pain* 2003;**104**:303-22.

95. Clarke M, Oxman Ae. Cochrane reviewers handbook version 4.2.0 (Updated March 2003). Chichester: John Wiley & Sons, 2003.

96. Alagona G, Delvaux V, Gerard P, De Pasqua V, Pennisi G, Delwaide P *et al*. Ipsilateral motor responses to focal transcranial magnetic stimulation in healthy subjects and acute-stroke patients. *Stroke* 2001;**32**:1304-9.

97. Delaux V, Alagona G, Gerard P, De Pasqua V, Pennisi G, de Noordhout A. Post-stroke reorganization of hand motor area: a 1-year prospective follow-up with focal transcranial magnetic stimulation. *Clin Neurophysiol* 2003;**114**:1217-25.

98. Al-Rawi M, Hamdan F, Abdul-Muttalib A. Somatosensory evoked potentials as a predictor for functional recovery of the upper limb in patients with stroke. *J Stroke Cerebrovasc* 2009;**18**:262-8.

99. Au-Yeung S, Hui-Chan C. Predicting recovery of dextrous hand function in acute stroke. *Disabil Rehabil* 2009;**31**:394-401.

100. Beebe J, Lang C. Active range of motion predicts upper extremity function 3 months after stroke. *Stroke* 2009;**40**:1772-9.

101. Binkofski F, Seitz R, Hacklander T, Pawelec D, Mau J, Freund H. Recovery of motor functions following hemiparetic stroke: a clinical and magnetic resonance-morphometric study. *Cerebrovasc Dis* 2001;**11**:273-81.

102. Canning C, Ada L, Adams R, O'Dwyer N. Loss of strength contributes more to physical disability after stroke than loss of dexterity. *Clin Rehabil* 2004;**18**:300-8.

103. Catano A, Houa M, Caroyer J, Ducarne H, Noel P. Magnetic transcranial stimulation in non-haemorrhagic sylvian strokes: interest of facilitation for early functional prognosis. *Electromyogr Motor C* 1995;**97**:349-54.

104. Catano A, Houa M, Noel P. Magnetic transcranial stimulation: clinical interest of the silent period in acute and chronic stages of stroke. *Electromyogr Motor C* 1997;**105**:290-6.

105. Cho S-H, KIm D, Kim D-S, Kim Y-H, Lee C-H, Jang S-H. Motor outcome according to the integrity of the corticospinal tract

determined by diffusion tensor tractography in the early stages of corona radiata infarct. *Neurosci Lett* 2007;**426**:123-7.

106. Cruz MA, Tejada J, Diez TE. Motor hand recovery after stroke. Prognostic yield of early transcranial magnetic stimulation. *Electromyogr Clin Neurophysiol* 1999;**39**:405-10.

107. Dachy B, Biltiau E, Bouillot E, Dan B, Deltenre P. Facilitation of motor evoked potentials in ischemic stroke patients: prognostic value and neurophysiologic correlations. *Clin Neurophysiol* 2003;**114**:2370-5.

108. De Souza L, Hewer R, Miller S. Assessment of recovery of arm control in hemiplegic stroke patients. 1. Arm function tests. *Int Rehabil Med* 1980;**2**:3-9.

109. De Weerdt W, Lincoln N, Harrison M. Prediction of arm and hand function recovery in stroke patients. *Int J Rehabil Res* 1987;**10**:110-2.

110. Escudero J, Sancho J, Bautista D, Escudero M, Lopez-Trigo J. Prognostic value of motor evoked potential obtained by transcranial magnetic brain stimulation in motor function recovery in patients with acute ischemic stroke. *Stroke* 1998;**29**:1854-9.

111. Feys H, Hetebrij J, Wilms G, Dom R, De Weerdt W. Predicting arm recovery following stroke: value of site of lesion. *Acta Neurol Scand* 2000;**102**:371-7.

112. Feys H, Van Hees J, Bruyninckx F, Mercelis R, De Weerdt W. Value of somatosensory and motor evoked potentials in predicting arm recovery after a stroke. *J Neurol Neurosurg Psychiatry* 2000;**68**:323-31.

113. Gowland C. Recovery of motor function following stroke profile and predictors. *Physiother Can* 1982;**34**:77-84.

114. Hatakenaka M, Miyai I, Sakoda S, Yanagihara T. Proximal paresis of the upper extremity in patients with stroke. *Neurology* 2007;**69**:348-55.

115. Heald A, Bates D, Cartlidge N, French J, Miller S. Longitudinal study of central motor conduction time following stroke. 2. Central motor conduction measured within 72 h after stroke as a predictor of functional outcome at 12 months. *Brain* 1993;**116**:1371-85.

116. Hendricks H, Hageman G, van Limbeek J. Prediction of recovery from upper extremity paralysis after stroke by measuring evoked potentials. *Scand J Rehabil Med* 1997;**29**:155-9.

117. Hendricks H, Pasman J, Mulder T, Notermans S, Schoonderwaldt H. Value of somatosensory evoked potentials for the prediction of

motor recovery of the upper extremity after cerebral infarction. *J Rehabil Sci* 1994;**7**:3-8.

118. Hendricks H, Pasman J, van Limbeek J, Zwarts M. Motor evoked potentials in predicting recovery from upper extremity paralysis after acute stroke. *Cerebrovasc Dis* 2003;**16**:265-71.

119. Higgins J, Mayo NE, Desrosiers J, Salbach NM, Ahmed S. Upper-limb function and recovery in the acute phase poststroke. *J Rehabil Res Dev* 2005;**42**:65-76.

120. Jang S, Ahn S, Sakong J, Byun W, Choi B, Chang C *et al*. Comparison of TMS and DTT for predicting motor outcome in intracerebral hemorrhage. *J Neurol Sci* 2010;**290**:107-11.

121. Katrak P, Bowring G, Conroy P, Chilvers M, Poulos R, McNeil D. Predicting upper limb recovery after stroke: the place of early shoulder and hand movement. *Arch Phys Med Rehab* 1998;**79**:758-61.

122. Keren O, Ring H, Solzi P, Pratt H, Groswasser Z. Upper limb somatosensory evoked potentials as a predictor of rehabilitation progress in dominant hemisphere stroke patients. *Stroke* 1993;**24**:1789-93.

123. Keren O, Ring H, Pratt H, Groswasser Z. Dynamic changes in upper limb short latency somatosensory-evoked potentials following stroke in the dominant hemisphere. *Clin Rehabil* 1995;**9**:52-60.

124. La Joie W, Reddy N, Melvin J. Somatosensory evoked potentials: their predictive value in right hemiplegia. *Arch Phys Med Rehab* 1982;**63**:223-6.

125. Lin K-C, Huang Y-H, Hsieh Y-W, Weu C-Y. Potential predictors of motor and functional outcomes after distributed constraint-induced therapy for patients with stroke. *Neurorehab Neural Re* 2009;**23**:336-42.

126. Loewen S, Anderson B. Predictors of stroke outcome using objective measurement scales. *Stroke* 1990;**21**:78-81.

127. Loubinoux I, Carel C, Pariente J, Dechaumont S, Albucher J, Marque P *et al*. Correlation between cerebral reorganization and motor recovery after subcortical infarcts. *Neuroimage.* 2003;2166-80.

128. Meldrum D, Barrett A, O'Regan M, Pittock S, Moroney J, Hardiman O. Predicting upper limb recovery after ischemic stroke: role of the Orpington Prognostic Score. *Physiother Ireland* 2000;**21**:28-32.

129. Nagao S, Kawai N. Prediction of motor function by magnetic brain stimulation in patients with intracerebral hematoma. *Neurol Med-Chir* 1992;**32**:268-74.

130. Nijland R, van Wegen E, Harmeling-van der Wel B, Kwakkel G, Investigators EPOS. Presence of finger extension and shoulder abduction within 72 hours after stroke predicts functional recovery: early prediction of functional outcome after stroke: the EPOS cohort study. *Stroke* 2010;**41**:745-50.

131. Olsen T. Arm and leg paresis as outcome predictors in stroke rehabilitation. *Stroke* 1990;**21**:247-51.

132. Paci M, Nannetti L, Taiti P, Baccini M, Rinaldi L. Shoulder subluxation after stroke: relationships with pain and motor recovery. *Physiother Res Int* 2007;**12**:95-104.

133. Park S, Wolf S, Blanton S, Winstein C, Nichols-Larsen D. The EXCITE trial: Predicting a clinically meaningful Motor Activity Log outcome. *Neurorehab Neural Re* 2008;**22**:486-93.

134. Pennisi G, Rapisarda G, Bella R, Calabrese V, Maertens De Noordhout A, Delwaide P. Absence of response to early transcranial magnetic stimulation in ischemic stroke patients: prognostic value for hand motor recovery. *Stroke* 1999;**30**:2666-70.

135. Pizzi A, Carrai R, Falsini C, Martini M, Verdesca S, Grippo A. Prognostic value of motor evoked potentials in motor function recovery of upper limb after stroke. *J Rehabil Med* 2009;**41**:654-60.

136. Prabhakaran S, Zarahn E, Riley C, Speizer A, Chong J, Lazar R *et al*. Inter-individual variability in the capacity for motor recovery after ischemic stroke. *Neurorehab Neural Re* 2008;**22**:64-71.

137. Rapisarda G, Bastings E, de Noordhout A, Pennisi G, Delwaide P. Can motor recovery in stroke patients be predicted by early transcranial magnetic stimulation? *Stroke* 1996;**27**:2191-6.

138. Renner C, Bungert-Kahl P, Hummelsheim H. Change of strength and rate of rise of tension relate to functional arm recovery after stroke. *Arch Phys Med Rehab* 2009;**90**:1548-56.

139. Roy C, Sands M, Hill L, Harrison A, Marshall S. The effect of shoulder pain on outcome of acute hemiplegia. *Clin Rehabil* 1995;**9**:21-7.

140. Smania N, Paolucci S, Tinazzi M, Borghero A, Manganotti P, Fiaschi A *et al*. Active finger extension - A simple movement predicting recovery of arm function in patients with acute stroke. *Stroke* 2007;**38**:1088-90.

141. Stinear C, Barber P, Smale P, Coxon J, Fleming M, Byblow W. Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain* 2007;**130**:170-80.

142. Sunderland A, Tinson D, Bradley L, Hewer R. Arm function after stroke. An evaluation of grip strength as a measure of recovery and a prognostic indicator. *J Neurol Neurosurg Psychiatry* 1989;**52**:1267-72.

143. Trompetto C, Assini A, Buccolieri A, Marchese R, Abbruzzese G. Motor recovery following stroke: a transcranial magnetic stimulation study. *Clin Neurophysiol* 2000;**111**:1860-7.

144. Turton A, Wroe S, Trepte N, Fraser C, Lemon R. Contralateral and ipsilateral EMC responses to transcranial magnetic stimulation during recovery of arm and hand function after stroke. *Electromyogr Motor C* 1996;**101**:316-28.

145. Tzvetanov P, Rousseff R, Atanassova P. Prognostic value of median and tibial somatosensory evoked potentials in acute stroke. *Neurosci Lett* 2005;**380**:99-104.

146. Tzvetanov P, Milanov I, Rousseff R, Christova P. Can SSEP results predict functional recovery of stroke patients within the "therapeutic window"? *Electromyogr Clin Neurophysiol* 2004;**44**:43-9.

147. van Kuijk A, Pasman J, Hendricks H, Zwarts M, Geurts A. Predicting hand motor recovery in severe stroke: the role of motor evoked potentials in relation to early clinical assessment. *Neurorehab Neural Re* 2009;**23**:45-51.

148. Wagner J, Lang C, Sahrmann S, Edwards D, Dromerick A. Sensorimotor impairments and reaching performance in subjects with poststroke hemiparesis during the first few months of recovery. *Phys Ther* 2007;**87**:751-65.

149. Yagura H, Miyai I, Seike Y, Suzuki T, Yanagihara T. Benefit of inpatient multidisciplinary rehabilitation up to 1 year after stroke. *Arch Phys Med Rehab* 2003;**84**:1687-91.

150. Yoshioka H, Horikoshi T, Aoki S, Hori M, Ishigame K, Uchida M *et al*. Diffusion tensor tractography predicts motor functional outcome in patients with spontaneous intracerebral hemorrhage. *Neurosurgery* 2008;**62**:97-103.

151. Easterbrook P, Berlin J, Gorpalan R, Matthews D. Publication bias in clinical research. *Lancet* 1991;**337**:867-72.

152. Deeks J, Higgins J, Altman D, (editors). Chapter 9: Analysing data and undertaking meta-analyses. In Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*

Version 5.1.0. The Cochrane Collaboration, 2011. www.cochrane-handbook.org. Last accessed January 2012.

153. COMET Initiative. www.comet-initiative.org/. Last accessed April 2012.

154. Wade D. Measurement in neurological rehabilitaiton. Oxford: Oxford University Press, 1992.

155. Ballinger C, Ashburn A, Low J, Roderick P. Unpacking the black box of therapy - a pilot study to describe occupational therapy and physiotherapy interventions for people with stroke. *Clin Rehabil* 1999;**13**:301-9.

156. De Wit L, Putman K, Lincoln N, Baert I, Berman P, Beyens H *et al*. Stroke rehabilitation in Europe - What do physiotherapists and occupational therapists actually do? *Stroke* 2006;**37**:1483-9.

157. Cirstea C, Ptito A, Levin M. Feedback and cognition in arm motor skill reacquisition after stroke. *Stroke* 2006;**37**:1237-42.

158. Barnes M, Dobkin B, Bogousslavsky J. Recovery after stroke. Cambridge: Cambridge University Press, 2005.

159. Legg L, Langhorne P, Pollock A, Sellars C. A multidisciplinary research agenda for stroke rehabilitation. *Br J Ther Rehabil* 2000;**797**:319-24.

160. Sackett D, Strauss S, Richardson W. Evidence-based medicine: How to practice and teach EBM. Philadelphia: Churchill Livingstone, 2000.

161. Heller A, Wade D, Wood V, Sunderland A, Hewer R, Ward E. Arm function after stroke - Measurement and recovery over the first three months. *J Neurol Neurosurg Psychiatry* 1987;**50**:714-9.

162. Kellor M, Frost J, Silberbe N, Iversen I, Cummings R. Norms for clinical use - Hand strength and dexterity. *Am J Occup Ther* 1971;**25**:77-83.

163. Demeurisse G, Demol O, Robaye E. Motor evaluation in vascular hemiplegia. *Euro Neurol* 1980;**19**:382-9.

164. Higgins J, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration, 2011. www.cochrane-handbook.org. Last accessed January 2012.

165. RevMan. The Nordic Cochrane Centre. The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

166. Cohen J. Statistical power analysis for the behavioural sciences. USA: Lawerence Erlbaum Associates, 1988.

167. Clinical Evidence. BMJ Publishing Group. 2009. http://clinicalevidence.bmj.com/ceweb/about/guide.jsp. Last accessed April 2009.

168. Luke C, Dodd K, Brock K. Outcomes of the Bobath concept on upper limb recovery following stroke. *Clin Rehabil* 2004;**18**:888-98.

169. Gelber D, Josefczyk P, Herrman D, Good D, Verhulst S. Comparison of two therapy approaches in the rehabilitation of the pure motor hemiparetic stroke patient. *J Neurol Rehabil* 1995;**9**:191-6.

170. Langhammer B, Stanghelle J. Bobath or motor relearning programme? A comparison of two different approaches of physiotherapy in stroke rehabilitation: a randomized controlled study. *Clin Rehabil* 2000;**14**:361-9.

171. Logigian M, Samuels M, Falconer J, Zagar R. Clinical exercise trial for stroke patients. *Arch Phys Med Rehab* 1983;**64**:364-7.

172. Platz T, Eickhof C, van Kaick S, Engel U, Pinkowski C, Kalok S *et al*. Impairment-oriented training or Bobath therapy for severe arm paresis after stroke: a single-blind, multicentre randomized controlled trial. *Clin Rehabil* 2005;**19**:714-24.

173. van Vliet P, Lincoln N, Foxall A. Comparison of bobath based and movement science based treatment for stroke: a randomised controlled trial. *J Neurol Neurosurg Psychiatry* 2005;**76**:503-8.

174. Coupar F, Pollock A, van Wijck F, Morris J, Langhorne P. Simultaneous bilateral training for improving arm function after stroke. *Cochrane Database Syst Rev* 2010;**4**:CD006432.

175. Cauraugh J, Kim S. Two coupled motor recovery protocols are better than one. Electromyogram-triggered neuromuscular stimulation and bilateral movements. *Stroke* 2002;**33**:1589-94.

176. Cauraugh J, Kim S, Summers J. Chronic stroke longitudinal motor improvements: cumulative learning evidence found in the upper extremity. *Cerebrovasc Dis* 2008;**25**:115-21.

177. Desrosiers J, Bourbonnais D, Corriveau H, Gosselin S, Bravo G. Effectiveness of unilateral and symmetrical bilateral task training for arm during the subacute phase of stroke: a randomised controlled trial. *Clin Rehabil* 2005;**19**:581-93.

178. Lin K-C, Chang Y-F, Wu C-Y, Chen Y-A. Effects of constraint-induced therapy versus bilateral arm training on motor performance,

daily functions and quality of life in stroke survivors. *Neurorehab Neural Re* 2009;**23**:441-8.

179. Lin K-C, Chen S-Y, Wu C-Y, Chen Y-A. The effects of bilateral arm training on motor control and functional performance in chronic stroke: a randomised controlled study. *Neurorehab Neural Re* 2009;**24**:42-51.

180. Luft A, McCombe-Waller S, Whitall J, Forrester L, Macko R, Sorkin JD *et al*. Repetitive bilateral arm training and motor cortex activation in chronic stroke. *JAMA* 2004;**292**:1853-61.

181. Lum P, Burgar D, van der Loos M, Shor P, 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**:631-42.

182. Morris J, van Wijck F, Joice S, Ogston S, Cole I, MacWalter A. Effectiveness of unilateral and symmetrical bilateral task training for arm during the subacute phase of stroke: a randomised controlled trial. *Clin Rehabil* 2008;**19**:581-93.

183. Stoykov M, Lewis G, Corcos D. Comparison of bilateral and unilateral training for upper extremity hemiparesis in stroke. *Neurorehab Neural Re* 2009;945-53.

184. Summers J, Kagere F, Garry M, Hiraga C, Loftus A, Cauraugh J. Bilateral and unilateral movement training on upper limb function in chronic stroke patients: A TMS study. *J Neurol Sci* 2007;**252**:76-82.

185. Sirtori V, Corbetta D, Moja L, Gatti R. Constraint-induced movement therapy for upper extremities in stroke patients. *Cochrane Database Syst Rev* 2009;**4**:CD004433.

186. Alberts J, Butler A, Wolf S. The effects of constraint-induced therapy on precision grip: a preliminary study. *Neurorehab Neural Re* 2004;**18**:250-8.

187. Atteya A.. Effects of modified constraint induced movement therapy on upper limb function in subacute stroke patients. *Neurosciences* 2004;**9**:24-9.

188. Boake C, Noser E, Ro T, Baraniuk S, Gaber M, Johnson R *et al*. Constraint-induced movement therapy during early stroke rehabilitation. *Neurorehab Neural Re* 2007;**21**:14-24.

189. Dahl A, Askim T, Stock R, Langorgen E, Lydersen S, Indredavik B. Short- and long-term outcome of constraint-induced movement therapy after stroke: a randomized controlled feasibility trial. *Clin Rehabil* 2008;**22**:436-47.

190. Dromerick A, Edwards D, Hahn M. Does the application of constraint-induced movement therapy during acute rehabilitation reduce arm impairment after ischemic stroke? *Stroke* 2000;**31**:2984-8.

191. Lin K, Wu C, Wei T, Lee C, Liu J. Effects of modified constraint-induced movement therapy on reach-to-grasp movements and functional performance after chronic stroke: a randomized controlled study. *Clin Rehabil* 2007;**21**:1075-86.

192. Myint J, Yuen G, Yu T, Kng C, Wong A, Chow K *et al*. A study of constraint-induced movement therapy in subacute stroke patients in Hong Kong. *Clin Rehabil* 2008;**22**:112-24.

193. Page S, Sisto S, Levine P, Johnston M, Hughes M. Modified constraint induced therapy: A randomized feasibility and efficacy study. *J Rehabil Res Dev* 2001;**38**:583-90.

194. Page S, Sisto S, Johnston M, Levine P. Modified constraint-induced therapy after subacute stroke: A preliminary study. *Neurorehab Neural Re* 2002;**16**:290-5.

195. Page S, Sisto S, Levine P, McGarth R. Efficacy of modified constraint-induced movement therapy in chronic stroke: a single-blinded randomized controlled trial. *Arch Phys Med Rehab* 2004;**85**:14-8.

196. Page S, Levine P, Leonard A. Modified constraint-induced therapy in acute stroke: A randomized controlled pilot study. *Neurorehab Neural Re* 2005;**19**:27-32.

197. Page S, Levine P, Leonard A, Szaflarski J, Kissela B. Modified constraint-induced therapy in chronic stroke: Results of a single-blinded randomized controlled trial. *Phys Ther* 2008;**88**:333-40.

198. Ploughman M, Corbett D. Can forced-use therapy be clinically applied after stroke? An exploratory randomized controlled trial. *Arch Phys Med Rehab* 2004;**85**:1417-23.

199. Taub E, Miller N, Novack T, Cook E, Fleming W, Nepomuceno C *et al*. Technique to improve chronic motor deficit after stroke. *Arch Phys Med Rehab* 1993;**74**:347-54.

200. Wittenberg G, Chen R, Ishii K, Bushara K, Taub E, Gerber L *et al*. Constraint-induced therapy in stroke: Magnetic-stimulation motor maps and cerebral activation. *Neurorehab Neural Re* 2003;**17**:48-57.

201. Wolf S, Winstein C, Miller J, Taub E, Uswatte G, Morris D *et al*. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA* 2006;**296**:2095-104.

202. Wu C, Lin K, Chen H, Chen I, Hong W. Effects of modified constraint-induced movement therapy on movement kinematics and daily function in patients with stroke: A kinematic study of motor control mechanisms. *Neurorehab Neural Re* 2007;**21**:460-6.

203. Wu C, Chen C, Tang, Lin K, Huang Y. Kinematic and clinical analyses of upper-extremity movements after constraint-induced movement therapy in patients with stroke: A randomized controlled trial. *Arch Phys Med Rehab* 2007;**88**:964-70.

204. Wu C, Chen C, Tsai W, Lin K, Chou S. A randomized controlled trial of modified constraint-induced movement therapy for elderly stroke survivors: Changes in motor impairment, daily functioning, and quality of life. *Arch Phys Med Rehab* 2007;**88**:273-8.

205. Dromerick A, Lang C, Birkenmeier R, Wagner J, Miller J, Videen T *et al*. Very early constraint-induced movement during Stroke Rehabilitation (VECTORS) A single-center RCT. *Neurology* 2009;**73**:195-201.

206. Lin K-C, Wu C-Y, Liu J-S. A randomized controlled trial of constraint-induced movement therapy after stroke. *Act Neur S* 2008;**101**:61-4.

207. Lin K-C, Chung H-Y, Wu C-Y, Liu H-L, Hsieh Y-W, Chen I-H *et al*. Constraint-induced therapy versus control intervention in patients with stroke: A functional magnetic resonance imaging study. *Am J Phys Med Rehab* 2010;**89**:177-85.

208. Woodford H, Price C. EMG biofeedback for the recovery of motor function after stroke. *Cochrane Database Syst Rev* 2007;**2**:CD004585.

209. Armagan O, Tascioglu F, Oner C. Electromyographic biofeedback in the treatment of the hemiplegic hand - A placebo-controlled study. *Am J Phys Med Rehab* 2003;**82**:856-61.

210. Basmajian J, Gowland C, Finlayson M, Hall A, Swanson L, Stratford P *et al*. Stroke treatment: comparison of integrated behavioral-physical therapy vs traditional physical therapy programs. *Arch Phys Med Rehab* 1987;**68**:267-72.

211. Crow J, Lincoln N, Nouri F, de Weerdt W. The eff ectiveness of EMG biofeedback in the treatment of arm function after stroke. *Int Disabil Stud* 1989;**11**:155-60.

212. Inglis J, Donald M, Monga T, Sproule M, Young M. Electromyographic Biofeedback and Physical Therapy of the Hemiplegic Upper Limb. *Arch Phys Med Rehab* 1984;**65**:755-9.

213. Pomeroy V, King L, Pollock A, Baily-Hallam A, Langhorne P. Electrostimulation for promoting recovery of movement or functional ability after stroke. *Cochrane Database Sys Rev* 2006;**2**:CD003241.

214. Cauraugh J, Light K, Kim S, Thigpen M, Behrman A. Chronic motor dysfunction after stroke - Recovering wrist and finger extension by electromyography-triggered neuromuscular stimulation. *Stroke* 2000;**31**:1360-4.

215. Cauraugh J, Kim S. Chronic stroke motor recovery: duration of active neuromuscular stimulation. *J Neurol Sci* 2003;**215**:13-9.

216. Chae J, Bethoux F, Bohinc T, Dobos L, Davis T, Friedl A. Neuromuscular stimulation for upper extremity motor and functional recovery in acute hemiplegia. *Stroke* 1998;**29**:975-9.

217. Francisco G, Chae J, Chawla H, Kirshblum S, Zorowitz R, Lewis G *et al*. Electromyogram-triggered neuromuscular stimulation for improving the arm function of acute stroke survivors: A randomized pilot study. *Arch Phys Med Rehab* 1998;**79**:570-5.

218. Kimberley T, Lewis S, Auerbach E, Dorsey L, Lojovich J, Carey J. Electrical stimulation driving functional improvements and cortical changes in subjects with stroke. *Exp Brain Res* 2004;**154**:450-60.

219. Linn S, Granat M, Lees K. Prevention of shoulder subluxation after stroke with electrical stimulation. *Stroke* 1999;**30**:963-8.

220. Popovic M, Popovic D, Sinkjaer T, Stefanovic A, Schwirtlich L. Clinical evaluation of Functional Electrical Therapy in acute hemiplegic subjects. *J Rehabil Res Dev* 2003;**40**:443-53.

221. Powell J, Pandyan A, Granat M, Cameron M, Stott D. Electrical stimulation of wrist extensors in poststroke hemiplegia. *Stroke* 1999;**30**:1384-9.

222. Sonde L, Gip C, Fernaeus S, Nilsson C, Viitanen M. Stimulation with low frequency (1.7Hz) transcutaneous electric nerve stimulation (Low-TENS) increases motor function of the post-stroke paretic arm. *Scand J Rehabil Med* 1998;**30**:95-9.

223. Alon G, Levitt A, McCarthy P. Functional electrical stimulation enhancement of upper extremity functional recovery during stroke rehabilitation: A pilot study. *Neurorehab Neural Re* 2007;**21**:207-15.

224. Alon G, Levitt A, McCarthy P. Functional electrical stimulation (FES) may modify the poor prognosis of stroke survivors with severe motor loss of the upper extremity - A preliminary study. *Am J Phys Med Rehab* 2008;**87**:627-36.

225. Chan M, Tong R, Chung K. Bilateral upper limb training with functional electric stimulation in patients with chronic stroke. *Neurorehab Neural Re* 2009;**23**:357-65.

226. Gabr U, Levine P, Page S. Home-based electromyography-triggered stimulation in chronic stroke. *Clin Rehabil* 2005;**19**:737-45.

227. Hara Y, Ogawa S, Muraoka Y. Hybrid power-assisted functional electrical stimulation to improve hemiparetic upper-extremity function. *Am J Phys Med Rehab* 2006;**85**:977-85.

228. Hara Y, Ogawa S, Tsujiuchi K, Muraoka Y. A home-based rehabilitation program for the hemiplegic upper extremity by power assisted functional electrical stimulation. *Disabil Rehabil* 2008;**30**:296-304.

229. Hsu S, Hu M, Wang Y, Yip P, Chiu J, Hsieh C. Dose-response relation between neuromuscular electrical stimulation and upper-extremity function in patients with stroke. *Stroke* 2010;**41**:821-4.

230. Mangold S, Schuster C, Keller T, Zimmermann-Schlatter A, Ettlin T. Motor training of upper extremity with functional electrical stimulation in early stroke rehabilitation. *Neurorehab Neural Re* 2009;**23**:184-90.

231. Thrasher T, Zivanovic V, McIlroy W, Popovic M. Rehabilitation of reaching and grasping function in severe hemiplegic patients using functional electrical stimulation therapy. *Neurorehab Neural Re* 2008;**22**:706-14.

232. Weber D, Skidmore E, Niyonkuru C, Chang C-L, Huber L, Munin M. Cyclic functional electrical stimulation does not enhance gains in hand grasp function when used as an adjunct to onabotulinumtoxinA and task practice therapy: A single-blind, randomized controlled pilot study. *Arch Phys Med Rehab* 2010;**91**:679-86.

233. Winter J, Hunter S, Sim J, Crome P. Hands-on therapy interventions for upper limb motor dysfunction following stroke. *Cochrane Database Syst Rev* 2011;**6**:CD006609.

234. Carey J. Manual stretch - effect on finger movement control and force control in stroke subjects with spastic extrinsic finger flexor muscles. *Arch Phys Med Rehab* 1990;**71**:888-94.

235. Mann G, Burridge J, Malone L, Strike P. A pilot study to investigate the effects of electrical stimulation on recovery of hand function and sensation in subacute stroke patients. *Neuromodulation* 2005;**8**:193-202.

236. Mikulecka E, Petruskava L, Mayer M, Vlachova I. Differentiated manual treatment of the hand and forearm in early rehabilitation of stroke patients (a controlled study). *Rehabilitacia* 2005;**42**:52-61.

237. Kwakkel G, van Peppen R, Wagenaar R, Dauphinee S, Richards C, Ashburn A *et al*. Effects of augmented exercise therapy time after stroke - a meta-analysis. *Stroke* 2004;**35**:2529-36.

238. Kwakkel G, Wagenaar R, Twisk J, Lankhorst G, Koetsier J. Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. *Lancet* 1999;**354**:191-6.

239. Lincoln N, Parry R, Vass C. Randomized, controlled trial to evaluate increased intensity of physiotherapy treatment of arm function after stroke. *Stroke* 1999;**30**:573-9.

240. Sunderland A, Tinson D, Bradley E, Fletcher D, Hewer R, Wade D. Enhanced physical therapy improves recovery of arm function after stroke - a randomized controlled trial. *J Neurol Neurosurg Psychiatry* 1992;**55**:530-5.

241. Barclay-Goddard R, Stevenson T, Poluha W, Thalman L. Mental practice for treating upper extremity deficits in individuals with hemiparesis after stroke. *Cochrane Database Syst Rev* 2011;**5**:CD005950.

242. Muller K, Butefisch C, Seitz R, Homberg V. Mental practice improves hand function after hemiparetic stroke. *Restor Neurol Neuros* 2007;**25**:501-11.

243. Page S, Levine P, Sisto S, Johnston M. A randomized efficacy and feasibility study of imagery in acute stroke. *Clin Rehabil* 2001;**15**:233-40.

244. Page S, Levine P, Leonard A. Effects of mental practice on affected limb use and function in chronic stroke. *Arch Phys Med Rehab* 2005;**86**:399-402.

245. Page S, Levine P, Leonard A. Mental practice in chronic stroke - results of a randomized, placebo-controlled trial. *Stroke* 2007;**38**:1293-7.

246. Page S, Levine P, Khoury J. Modified constraint-induced therapy combined with mental practice. Thinking through better motor outcomes. *Stroke* 2009;**40**:551-4.

247. Riccio I, Iolascon G, Barillari M, Gimigliano R, Gimigliano F. Mental practice is effective in upper limb recovery after stroke: a randomized single-blind cross-over study. *Eur J Phys Rehab Med* 2010;**46**:19-25.

248. Rothgangel A, Braun S, Beurskens A, Seitz R, Wade D. The clinical aspects of mirror therapy in rehabilitation: a systematic review of the literature. *Int J Rehabil Res* 2011;**34**:1-13.

249. Altschuler E, Wisdom S, Stone L, Foster C, Galasko D, Llewellyn D *et al*. Rehabilitation of hemiparesis after stroke with a mirror. *Lancet* 1999;**353**:2035-6.

250. Dohle C, Pullen J, Nakaten A, Kust J, Rietz C, Karbe H. Mirror therapy promotes recovery from severe hemiparesis: a randomized controlled trial. *Neurorehab Neural Re* 2009;**23**:209-17.

251. Rothgangel A, Morton A, Van den Hout J, Beurskens A. Phantoms in the brain: mirror therapy in chronic stroke patients; a pilot study. *Ned Tijdschr Fys.* 2004;**114**:36-40.

252. Yavuzer G, Selles R, Sezer N, Sutbeyaz S, Bussmann J, Koseoglu F *et al*. Mirror therapy improves hand function in subacute stroke: a randomized controlled trial. *Arch Phys Med Rehab* 2008;**89**:393-8.

253. Michielsen M, Selles R, van der Geest J, Eckhardt M, Yavuzer G, Stam H *et al*. Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: a phase II randomized controlled trial. *Neurorehab Neural Re* 2011;**25**:223-33.

254. French B, Thomas L, Leathley M, Sutton C, McAdam J, Forster A *et al*. Repetitive task training for improving functional ability after stroke. *Cochrane Database Syst Rev* 2007;**4**:CD006073.

255. Blennerhassett J, Dite W. Additional task-related practice improves mobility and upper limb function early after stroke: A randomised controlled trial. *Aust J Physiother* 2004;**50**:219-24.

256. Higgins J, Salbach N, Wood-Dauphinee S, Richards C, Cote R, Mayo N. The effect of a task-oriented intervention on arm function in people with stroke: a randomized controlled trial. *Clin Rehabil* 2006;**20**:296-310.

257. Turton A, Fraser C. The use of home therapy programmes for improving recovery of the upper limb following stroke. *Br J Occup Ther* 1990;**53**:457-62.

258. Yen J, Wang R, Chen H, Hong C. Effectiveness of modified constraint-induced movement therapy on upper limb function in stroke subjects. *Acta Neurol Taiwan* 2005;**14**:16-20.

259. Harris J, Eng J, Miller W, Dawson A. A self-administered graded repetitive arm supplementary program (GRASP) improves arm function during inpatient stroke rehabilitation: a multi-site randomized controlled trial. *Stroke* 2009;**40**:2123-8.

260. Mehrholz J, Platz T, Kugler J, Pohl M. Electromechanical and robot-assisted arm training for improving arm function and activities of daily living after stroke. *Cochrane Database Syst Rev* 2008;**4**:CD006876.

261. Amirabdollahian F, Loureiro R, Gradwell E, Collin C, Harwin W, Johnson G. Multivariate analysis of the Fugl-Meyer outcome measures assessing the effectiveness of GENTLE/S robot-mediated stroke therapy. *J Neuroeng Rehabil* 2007;**4**.

262. Daly J, Hogan N, Perepezko E, Krebs H, Rogers J, Goyal K *et al*. Response to upper-limb robotics and functional neuromuscular stimulation following stroke. *J Rehabil Res Dev* 2005;**42**:723-36.

263. Fazekas G, Horvath M, Troznai T, Toth A. Robot-mediated upper limb physiotherapy for patients with spastic hemiparesis: a preliminary study. *J Rehabil Med* 2007;**39**:580-2.

264. Hesse S, Werner C, Pohl M, Rueckriem S, Mehrholz J, Lingnau M. Computerized arm training improves the motor control of the severely affected arm after stroke - a single-blinded randomized trial in two centers. *Stroke* 2005;**36**:1960-6.

265. Kahn L, Zygman M, Rymer W, Reinkensmeyer D. Robot-assisted reaching exercise promotes arm recovery in chronic hemiparetic stroke: a randomized controlled pilot study. *Journal of Neuroeng and Rehabil* 2006;**3**:12.

266. Lum P, Burgar C, Shor P, 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 Rehab* 2002;**83**:952-9.

267. Masiero S, Celia A, Rosati G, Armani M. Robotic-assisted rehabilitation of the upper limb after acute stroke. *Arch Phys Med Rehab* 2007;**88**:142-9.

268. Volpe B, Krebs H, Hogan N, Edelstein L, Diels C, Aisen M. A novel approach to stroke rehabilitation - Robot-aided sensorimotor stimulation. *Neurology* 2000;**54**:1938-44.

269. Volpe B, 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. *Neurorehab Neural Re* 2008;**22**:305-10.

270. Burgar C, Lum P, Scremin A, Garber S, Van der Loos H, Kenney D *et al*. Robot-assisted upper-limb therapy in acute rehabilitation setting following stroke: Department of Veterans Affairs multisite clinical trial. *J Rehab Res Dev* 2011;**48**:445-58.

271. Conroy S, Whitall J, Dipietro L, Jones-Lush L, Zhan M, Finley M *et al*. Effect of gravity on robot-assisted motor training after chronic stroke: a randomized trial. *Arch Phys Med Rehab* 2011;**92**:1754-61.

272. Housman S, Scott K, Reinkensmeyer D. A randomized controlled trial of gravity-supported, computer-enhanced arm exercise for individuals with severe hemiparesis. *Neurorehab Neural Re* 2009;**23**:505-14.

273. Lo A, Guarino P, Richards L, Haselkorn J, Wittenberg G, Federman D *et al*. Robot-assisted therapy for long-term upper-limb impairment after stroke. *New Engl J Med* 2010;**362**:1772-83.

274. 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 Rehab Res Dev* 2011;**48**:355-66.

275. Rabadi M, Galgano M, Lynch D, Akerman M, Lesser M, Volpe BT. A pilot study of activity-based therapy in the arm motor recovery post stroke: a randomized controlled trial. *Clin Rehabil* 2008;**22**:1071-82.

276. Lannin N, Herbert R. Is hand splinting effective for adults following stroke? A systematic review and methodological critique of published research. *Clin Rehabil* 2003;**17**:807-16.

277. Lannin N, Horsley S, Herbert R, McCuskey A, Cusiek A. Splinting the hand in the functional position after brain impairment: a randomized, controlled trial. *Arch Phys Med Rehab* 2003;**84**:297-302.

278. Poole J, Whitney S, Hangeland N, Baker C. The effectiveness of inflatable pressure splints on motor function in stroke patients. *Occup Ther J Res* 1990;**10**:360-6.

279. Lannin N, Cusick A, McCluskey A, Herbert R. Effects of splinting on wrist contracture after stroke - a randomized controlled trial. *Stroke* 2007;**38**:111-6.

280. Laver K, George S, Thomas S, Deutsch J, Crotty M. Virtual reality for stroke rehabilitation. *Cochrane Database Syst Rev* 2011;**9**:CD008349.

281. Crosbie J. Virtual reality in the rehabilitation of the upper limb following stroke. 2008. University of Ulster.

282. Jang S, You S, Cho Y, Park C, Cho S, et al. Cortical reorganization and associated functional motor recovery after virtual reality in patients with chronic stroke: an experimenter-blind preliminary study. *Arch Phys Med Rehab* 2005;**86**:2218-23.

283. Piron L, Tombolini P, Turolla A, Zucconi C, Agostini M, Dam M *et al*. Reinforced feedback in virtual environment facilitates the arm motor recovery in patients after a recent stroke. *International Workshop of Virtual Reality* 2007;121-3.

284. Piron L, Turolla A, Agostini M, Zucconi C, Cortese F, Zampolini M *et al*. Exercises for paretic upper limb after stroke: a combined virtual-reality and telemedicine approach. *J Rehabil Med* 2009;**41**:1016-20.

285. Piron L, Turolla A, Agostini M, Zucconi C, Ventura L, Tonin P *et al*. Motor learning principles for rehabilitation: a pilot randomized controlled study in poststroke patients. *Neurorehabilitation and Neural Repair* 2010;**24**:501-8.

286. Saposnik G, Teasell R, Mamdani M, Hall J, McIlroy W, Cheung D *et al*. Effectiveness of virtual reality using Wii gaming technology in

stroke rehabilitation: a pilot randomized clinical trial and proof of principle. *Stroke* 2010;**41**:1477-84.

287. Sucar L, Leder R, Hernandez J, Sanchez I, Azcarate G. Clinical evaluation of a low-cost alternative for stroke rehabilitation. *International Conference on Rehabilitation Robotics* 2009;863-6.

288. Yavuzer G, Senel A, Atay M, Stam HJ. "Playstation eyetoy games" improve upper extremity-related motor functioning in subacute stroke: a randomized controlled clinical trial. *Eur J Phys Rehab Med* 2008;**44**:237-44.

289. Cauraugh J, Kim S. Progress toward motor recovery with active neuromuscular stimulation: muscle activation pattern evidence after a stroke. *J Neurol Sci* 2003;**207**:25-9.

290. Cauraugh J, Kim S, Duley A. Coupled bilateral movements and active neuromuscular stimulation: intralimb transfer evidence during bimanual aiming. *Neurosci Lett* 2005;**382**:39-44.

291. Mudie M, Matyas T. Responses of the densely hemiplegic upper extremity to bilateral training. *Neurorehab Neural Re* 2001;**15**:129-40.

292. Platz T, Bock S, Prass K. Reduced skilfulness of arm motor behaviour among motor stroke patients with good clinical recovery: does it indicate reduced automaticity? Can it be improved by unilateral or bilateral training? A kinematic motion analysis study. *Neuropsychologia* 2001;**39**:687-98.

293. Chang J, Tung W, Wu W, Su F. Effect of bilateral reaching on affected arm motor control in stroke - with and without loading on unaffected arm. *Disabil Rehabil* 2006;**28**:1507-16.

294. Dickstein R, Hocherman S, Amdor G, Pillar T. Reaction and movement times in patients with hemiparesis for unilateral and bilateral elbow flexion. *Phys Ther* 1993;**73**:374-85.

295. Harris-Love M, Waller S, Whitall J. Exploiting interlimb coupling to improve paretic arm reaching performance in people with chronic stroke. *Arch Phys Med Rehab* 2005;**86**:2131-7.

296. Kilbreath S, Crosbie J, Canning C, Lee M. Inter-limb coordination in bimanual reach-to-grasp following stroke. *Disabil Rehabil* 2006;**28**:1435-43.

297. Fasoli S, Krebs H, Stein J, Frontera W, Hogan N. Effects of robotic therapy on motor impairment and recovery in chronic stroke. *Arch Phys Med Rehab* 2003;**84**:477-82.

298. Hao Z, Wang D, Zeng Y, Liu M. Repetitive transcranial magnetic stimulation for improving function after stroke (Protocol). *Cochrane Database Syst Rev* 2010;**12**:CD008862.

299. Rabadi M, Rabadi F. Comparison of the action research arm test and the Fugl-Meyer assessment as measures of upper-extremity motor weakness after stroke. *Archives of Physical Medicine and Rehabilitation* 2006;**87**:962-6.

300. Mudie M, Matyas T. Can simultaneous bilateral movement involve the undamaged hemisphere in reconstruction of neural networks damaged by stroke? *Disabil Rehabil* 2000;**22**:23-37.

301. Kelso J, Southard D, Goodman D. Nature of Human Inter-Limb Coordination. *Science* 1979;**203**:1029-31.

302. Swinnen S. Intermanual coordination: From behavioural principles to neural-network interactions. *Nature Reviews Neuroscience* 2002;**3**:350-61.

303. Stinear C, Barber P, Coxon J, Fleming M, Byblow W. Priming the motor system enhances the effects of upper limb therapy in chronic stroke. *Brain* 2008;**131**:1381-90.

304. Cauraugh J, Summers J. Neural plasticity and bilateral movements: a rehabilitation approach for chronic stroke. *Prog Neurobiol* 2005;**75**:309-20.

305. Stewart K, Cauraugh J, Summers J. Bilateral movement training and stroke rehabilitation: a systematic review and meta-analysis. *J Neurol Sci* 2006;**244**:89-95.

306. McCombe Waller S, Whitall J. Bilateral arm training: why and who benefits? *Neurorehabilitation* 2008;**23**:29-41.

307. Higgins J. and Green S editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration, 2011. www.cochrane-handbook.org. Last accessed January 2012.

308. Whiting S, Lincoln N. An ADL assessment for stroke patients. *Br J Occup Ther* 1980;**43**:44-6.

309. Wolf S, Catlin P, Ellis M, Archer A, Morgan B, Piacentino A. Assessing Wolf Motor function Test as outcome measure for research in patients after stroke. *Stroke* 2001;**32**:1635-9.

310. Wilson D, Baker L, Craddock J. Functional test for the hemiparetic upper extremity. *Am J Occup Ther* 1984;**38**:159-64.

311. Desrosiers J, Herbert R, Dutil E, Bravo G. Development and reliability of an upper extemity function test for the elderly: the TEMPA. *Can J Occup Ther* 1993;**60**:9-16.

312. Barreca S, Stratford P, Lambert C, Masters L, Streiner D. Test-retest reliability, validity, and sensitivity of the Chedoke Arm and Hand Activity Inventory: a new measure of upper-limb function for survivors of stroke. *Arch Phys Med Rehab* 2005;**86**:1616-22.

313. Sodring K, BautzHolter E, Ljunggren A, Wyller T. Description and validation of a test of motor function and activities in stroke patients - The Sodring Motor Evaluation of stroke patients. *Scan J Rehabil Med* 1995;**27**:211-7.

314. Jebsen R, Taylor N, Trieschmann R, Howard LA. An objective and standardised test of hand function. *Arch Phys Med Rehab* 1969;**50**:311-9.

315. Tiffin J, Asher E. The Purdue Pegboard: norms and studies of reliability and validity. *J Appl Psychol* 1948;**32**:234-47.

316. Nouri F, Lincoln N. An Extended Activities of Daily Living Index for stroke patients. *Clinical Rehabilitation* 1987;**1**:305.

317. Rossier P, Wade D, Murphy M. An initial investigation of the reliability of the Rivermead Extended ADL index in patients presenting with neurological impairment. *J Rehabil Med* 2001;**33**:61-70.

318. Holbrook M, Skilbeck C. An activities index for use with stroke patients. *Age Ageing* 1983;**12**:166-70.

319. Lincoln N, Leadbetter D. Assessment of motor function in stroke function. *Physiotherapy* 1979;**65**:48-51.

320. Ashburn A. A physical assessment for stroke patients. *Physiotherapy* 1982;**68**:109-13.

321. Ashworth B. Preliminary Trial of Carisoprodol in Multiple Sclerosis. *Practitioner* 1964;**192**:540-&.

322. Bohannon R, Smith M. Interrater reliability of a modified Ashworth Scale of muscle spasticity. *Phys Ther* 1987;**67**:206-7.

323. Medical Research Council. Aids to the investigation of peripheral nerve injuries. London: HMSO, 1975.

324. Bohannon R, Andrews A. Interrater reliability of hand-held dynamometry. *Phys Ther* 1987;**67**:931-3.

325. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer I* 1959;**22**:719-48.

326. Dersimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials* 1986;**7**:177-88.

327. Deeks J, Altman D, Bradburn M. Statistical methods for examining heterogenity and combining results from several studies in meta-analysis. *Systematic Reviews in Health Care: Meta-analysis in Context*, London: BMJ Publication Group, 2001.

328. Lewis G, Byblow W. Neurophysiological and behavioural adaptations to a bilateral training intervention in individuals following stroke. *Clin Rehabil* 2004;**18**:48-59.

329. McCombe Waller S, Whitall J. Fine motor control in adults with and without chronic hemiparesis: baseline comparison to nondisabled adults and effects of bilateral arm training. *Arch Phys Med Rehab* 2004;**85**:1076-83.

330. Mudie H, Matays T. Upper extremity retraining following stroke: effects of bilateral practice. *Neurorehab Neural Re* 1996;**10**:184.

331. Stinear J, Byblow W. Rhythmic bilateral movement training modulates corticomotor excitability and enhances upper limb motricity poststroke: a pilot study. *J Clin Neurophysio* 2004;**21**:124-31.

332. Whitall J, Waller S, Silver K, Macko RF. Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke. *Stroke* 2000;**31**:2390-5.

333. Early Supported Discharge Trialists. Services for reducing duration of hospital care for acute stroke patients. *Cochrane Database Syst Rev* 2005;**2**:CD000443.

334. Outpatient Service Trialists. Therapy-based rehabilitation services for stroke patients at home. *Cochrane Database Syst Rev* 2006;**4**:CD002925.

335. Review Manager (RevMan). Version 5.1 Copenhagen. The Nordic Cochrane Centre. The Cochrane Collaboration. 2011.

336. Duncan P, Richards L, Wallace D, Stoker-Yates J, Pohl P, Luchies C *et al*. A randomized, controlled pilot study of a home-based exercise program for individuals with mild and moderate stroke. *Stroke* 1998;**29**:2055-60.

337. Duncan P, Studenski S, Richards L, Gollub S, Lai S, Reker D *et al*. Randomized clinical trial of therapeutic exercise in subacute stroke. *Stroke* 2003;**34**:2173-80.

338. Piron L, Turolla A, Tonin P, Piccione F, Lain L, Dam M. Satisfaction with care in post-stroke patients undergoing a telerehabilitation programme at home. *J Telemed Telecare* 2008;**14**:257-60.

339. Studenski S, Duncan P, Perera S, Reker D, Lai SM, Richards L. Daily functioning and quality of life in a randomized controlled trial of

therapeutic exercise for subacute stroke survivors. *Stroke* 2005;**36**:1764-70.

340. Baskett J, Broad J, Reekie G, Hocking C, Green G. Shared responsibility for ongoing rehabilitation: a new approach to home-based therapy after stroke. *Clin Rehabil* 1999;**13**:23-33.

341. Hocoma. www.hocoma.com/en/products/armeo/armeo-spring. Last accessed March 2012.

342. Kwakkel G, Kollen B, Krebs H. Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. *Neurorehab Neural Re* 2008;**22**:111-21.

343. Borg G, Linderholm H. Exercise Performance and Perceived Exertion in Patients with Coronary Insufficiency, Arterial Hypertension and Vasoregulatory Asthenia. *Acta Medica Scandinavica* 1970;**187**:17-&.

344. Gladstone D, Danells C, Black S. The Fugl-Meyer assessment of motor recovery after stroke: a critical review of its measurement properties. *Neurorehab Neural Re* 2002;**16**:232-40.

345. Lang C, Wagner J, Dromerick A, Edwards D. Measurement of upper-extremity function early after stroke: properties of the action research arm test. *Arch Phys Med Rehab* 2006;**87**:1605-10.

346. Wade D, Collin C. The Barthel ADL Index: a standard measure of physical disability. *Int Disabil Stud* 1988;**10**:64-7.

347. Wolfe C, Taub N, Woodrow E, Burney P. Assessment of Scales of Disability and Handicap for Stroke Patients. *Stroke* 1991;**22**:1242-4.

348. Strauss A, Corbin J. Basics of qualitative research: techniques and procedures for developing grounded theory. Newbury Park: Sage, 1998.

349. SPSS. SPSS version 19. 1-8-2010. Chicago, IL, USA, IBM.

350. Elashoff, J. nQuery Advisor Version 7.0. 1-1-2007. Cork, Ireland, Statistical Solutions.

351. van der Lee J, Wagenaar R, Lankhorst G, Vogelaar T, Deville W, Bouter L. Forced use of the upper extremity in chronic stroke patients - results from a single-blind randomized clinical trial. *Stroke* 1999;**30**:2369-75.

352. Dobkin B. Interpreting the randomized clinical trial of constraint-induced movement therapy. *Arch Neurol-Chicacgo* 2007;**64**:336-8.

353. van der Lee J, De Groot V, Beckerman H, Wagenaar R, Lankhorst G, Bouter L. The intra- and interrater reliability of the action research

arm test: a practical test of upper extremity function in patients with stroke. *Arch Phys Med Rehab* 2001;**82**:14-9.

354. Lang C, Edwards D, Birkenmeier R, Dromerick A. Estimating minimal clinically important differences of upper-extremity measures early after stroke. *Arch Phys Med Rehab* 2008;**89**:1693-700.