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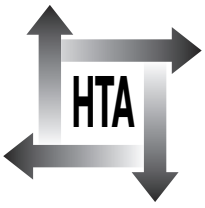

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A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness

B French,[1] M Leathley,[1] C Sutton,[1] J McAdam,[1] L Thomas,[1] A Forster,[2] P Langhorne,[3] C Price,[4] A Walker[3] and C Watkins[1*]

[1] University of Central Lancashire, Preston, UK
[2] University of Leeds, UK
[3] Faculty of Medicine, University of Glasgow, UK
[4] Northumbria Healthcare NHS Trust, Newcastle University, Newcastle upon Tyne, UK

* Corresponding author

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The research reported in this issue of the journal was commissioned by the HTA Programme as project number 05/17/04. The contractual start date was in November 2005. The draft report began editorial review in February 2007 and was accepted for publication in February 2008. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness

B French,[1] M Leathley,[1] C Sutton,[1] J McAdam,[1] L Thomas,[1] A Forster,[2] P Langhorne,[3] C Price,[4] A Walker[3] and C Watkins[1*]

[1] University of Central Lancashire, Preston, UK
[2] University of Leeds, UK
[3] Faculty of Medicine, University of Glasgow, UK
[4] Northumbria Healthcare NHS Trust, Newcastle University, Newcastle upon Tyne, UK
* Corresponding author

Objectives: To determine whether repetitive functional task practice (RFTP) after stroke improves limb-specific or global function or activities of daily living and whether treatment effects are dependent on the amount of practice, or the type or timing of the intervention. Also to provide estimates of the cost-effectiveness of RFTP.
Data sources: The main electronic databases were searched from inception to week 4, September 2006. Searches were also carried out on non-English-language databases and for unpublished trials up to May 2006.
Review methods: Standard quantitative methods were used to conduct the systematic review. The measures of efficacy of RFTP from the data synthesis were used to inform an economic model. The model used a pre-existing data set and tested the potential impact of RFTP on cost. An incremental cost per quality-adjusted life-year (QALY) gained for RFTP was estimated from the model. Sensitivity analyses around the assumptions made for the model were used to test the robustness of the estimates.
Results: Thirty-one trials with 34 intervention–control pairs and 1078 participants were included. Overall, it was found that some forms of RFTP resulted in improvement in global function, and in both arm and lower limb function. Overall standardised mean difference in data suitable for pooling was 0.38 [95% confidence interval (CI) 0.09 to 0.68] for global motor function, 0.24 (95% CI 0.06 to 0.42) for arm function and 0.28 (95% confidence interval 0.05 to 0.51) for functional ambulation. Results suggest that training may be sufficient to have an impact on activities of daily living. Retention effects of training persist for up to 6 months, but whether they persist beyond this is unclear. There was little or no evidence that treatment effects overall were modified by time since stroke or dosage of task practice, but results for upper limb function were modified by type of intervention. The economic modelling suggested that RFTP was cost-effective. Given a threshold for cost-effectiveness of £20,000 per QALY gained, RFTP is cost-effective so long as the net cost per patient is less than £1963. This result showed some sensitivity to the assumptions made for the model. The cost-effectiveness of RFTP tends to stem from the relatively modest cost associated with this intervention.
Conclusions: The evidence suggests that some form of RFTP can be effective in improving lower limb function at any time after stroke, but that the duration of intervention effect is unclear. There is as yet insufficient good-quality evidence to make any firm recommendations for upper limb interventions. If task-specific training is used, adverse effects should be monitored. While the effectiveness of RFTP is relatively modest, this sort of intervention appears to be cost-effective. Owing to the large number of ongoing trials, this review should be updated within 2 years and any future review should include a comparison against alternative treatments. Further research should evaluate RFTP upper limb interventions and in particular constraint-induced movement therapy, address practical ways of delivering RFTP interventions, be directed towards the evaluation of suitable methods to maintain functional gain, and be powered to detect whether RFTP interventions are cost-effective.

Contents

List of abbreviations

ADL	activity of daily living
ARAT	Action Research Arm Test
BBT	Box and Block Test
BI	Barthel Index
CI	confidence interval
CIMT	constraint-induced movement therapy
df	degrees of freedom
EQ-5D	EuroQol-5 Dimensions
FAC	Functional Ambulation Classification
FIM	Functional Independence Measure
FM	Fugl–Meyer Assessment
FTHUE	Functional Test of the Hemiparetic Upper Extremity
9HPT	Nine Hole Peg Test
10HPT	Ten Hole Peg Test
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
MAL	Motor Activity Log
MAS	Motor Assessment Scale
mCIMT	modified constraint-induced movement therapy
5MWS	Five Metre Walk Speed
6MWS	Six Metre Walk Speed
6MWT	Six Minute Walk Test
10MWS	Ten Metre Walk Speed
NHP	Nottingham Health Profile
PSS	Personal Social Services
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RFTP	repetitive functional task practice
RMA	Rivermead Motor Assessment
RTT	repetitive task training
SD	standard deviation
SMD	standardised mean difference
SMES	Sodring Motor Evaluation Scale
TEMPA	Test Evaluant des Membres Superieurs des Personnes Agées
TM	treadmill training
TUG	Timed Up and Go
WMD	weighted mean difference
WMFT	Wolf Motor Function Test

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

The repetitive practice of functional tasks is a component of current approaches to stroke rehabilitation. Practice may be augmented by strategies to enhance learning as used in movement science approaches, by mechanical means such as treadmills, or by strategies to encourage use of the affected limb in daily life by restraining the unaffected limb.

All these approaches have a core mechanism based on the repeated practice of functional tasks. This has the potential to be a resource-efficient component of stroke rehabilitation, including delivery in a group setting, or instructed practice in the home environment. This review considers the effectiveness and cost-effectiveness of all forms of repetitive functional task practice (RFTP).

Objectives

The aims of this study were:

- to determine whether RFTP after stroke improves limb-specific or global function or activities of daily living
- to determine whether treatment effects are dependent on the amount of practice, or the type or timing of the intervention
- to provide cost-effectiveness estimates for RFTP.

Methods

Data sources

The following searches were undertaken:

- electronic searches of Cochrane Stroke Trials Register, the Cochrane Library, MEDLINE, EMBASE, CINAHL, AMED, SportDiscus, ISI Science Citation Index, Index to Theses, ZETOC, PEDro and OT Seeker (all from inception to week 4, September 2006)
- electronic searches on non-English-language databases and for unpublished trials on MetaRegister, BioMed Central, CRISP, Centerwatch, National Research Register, ReFeR, Stroke Trials Directory, REHABDATA and CIRRIE (to May 2006)
- searches of conference proceedings, reference lists of existing systematic reviews, citation searching, publication on bulletin boards and author contact for all relevant trials.

Study selection

The review included randomised and quasi-randomised trials in adults after stroke, which included an intervention where an active motor sequence was performed repetitively within a single training session, where the practice aimed towards a clear functional goal and where the amount of task practice could be quantified. Studies using mechanical or behavioural strategies to facilitate or encourage functional task practice were also included. Primary outcomes included limb-specific or global functional measures. Secondary outcomes included measures of activities of daily living and adverse events.

Data extraction

Two reviewers independently screened titles and abstracts, extracted data and critically appraised the trials. Assessment of methodological quality was undertaken for allocation concealment, blinding, loss to follow-up, trial size and equivalence of treatment. Trialists were contacted for additional information.

Data synthesis

Standard Cochrane quantitative systematic review methods were used. A fixed-effect model was used, and results were expressed as weighted or standardised mean differences, with 95% confidence interval. Subgroup analyses were conducted for amount, timing and type of intervention, and for adequacy of allocation concealment, type of comparison group, equivalence of therapy time and trial size.

The measures of efficacy of RFTP from the data synthesis were used to inform an economic model. The model used a pre-existing data set and tested the potential impact of RFTP on cost. From the model an incremental cost per quality-adjusted life-year (QALY) gained for RFTP was estimated. Sensitivity analyses around the assumptions made for the model were used to test the robustness of the estimates.

Results

Thirty-one trials with 34 intervention–control pairs and 1078 participants were included. Overall, it was found that some forms of RFTP resulted in improvement in global function, and in both arm and lower limb function. Overall standardised mean difference in data suitable for pooling was 0.38 [95% confidence interval (CI) 0.09 to 0.68] for global motor function, 0.24 (95% CI 0.06 to 0.42) for arm function and 0.28 (95% confidence interval 0.05 to 0.51) for functional ambulation. Results suggest that training may be sufficient to have an impact on activities of daily living. Retention effects of training persist for up to 6 months, but whether they persist beyond this is unclear. There was little or no evidence that treatment effects overall were modified by time since stroke or dosage of task practice, but results for upper limb function were modified by type of intervention. The economic modelling suggested that RFTP was cost-effective. Given a threshold for cost-effectiveness of £20,000 per QALY gained, RFTP is cost-effective so long as the net cost per patient is less than £1963. This result showed some sensitivity to the assumptions made for the model. The cost-effectiveness of RFTP tends to stem from the relatively modest cost associated with this intervention.

Conclusions

Implications for practice

The evidence suggests that some form of RFTP can be effective in improving lower limb function at any time after stroke, but that the duration of intervention effect is unclear. There is as yet insufficient good-quality evidence to make any firm recommendations for upper limb interventions. If task-specific training is used, adverse effects should be monitored. While the effectiveness of RFTP is relatively modest, this sort of intervention appears to be cost-effective.

Recommendations for future research

Owing to the large number of ongoing trials, this review should be updated within 2 years. Any future review should include a comparison against alternative treatments. Further research should:

- evaluate RFTP upper limb interventions and in particular constraint-induced movement therapy
- address practical ways of delivering RFTP interventions
- be directed towards the evaluation of suitable methods to maintain functional gain
- be powered to detect whether RFTP interventions are cost-effective, include a baseline activities of daily living measure, include indirect costs and use quality of life as an outcome measure to facilitate economic analysis.

Chapter 1
Introduction

Description of the condition

The annual incidence of first ever stroke in the UK is approximately 100,000 people per year.[1] Although the incidence of stroke is falling,[2] stroke is still the major cause of long-term neurological disability in adults.[3] The prevalence of disability and impairment varies according to sampling of cohorts, but approximately half of all stroke survivors are left with severe functional problems,[4] and 53% are dependent on others for help with daily activities at 6 months after their stroke.[5] Only 5–20% of people with initial upper limb impairment fully regain arm function, and 30–66% regain no functional use at 6 months.[6–9] At 3 weeks and 6 months after stroke, 40% and 15% of people are unable to walk independently indoors,[5] with only 18% regaining unrestricted walking ability.[10] Initial grade of paresis is the most important predictor for motor recovery, with a longer recovery period for people with severe stroke.[11]

Stroke is thus a leading cause of disability, and as such contributes to 4% of NHS costs.[12] While stroke is a costly condition in the acute stage, over 40% of the 5-year cost of stroke is likely to be incurred subsequent to discharge, with 18% of the total cost being due to institutional care.[13] If the disability and subsequent need for institutional care can be reduced, there is a potential for the long-term care costs to be substantially lowered.

Description of the intervention

Systematic reviews of treatment interventions for the paretic upper limb suggest that patients benefit from exercise programmes in which functional tasks are directly trained, with less benefit if the intervention is focused on the impairment, such as muscle strengthening.[14] Although individual studies do not agree whether increased therapy intensity improves overall outcome, a recent meta-analysis[15] has shown that more intensive therapy may at least improve the rate of recovery of activities of daily living (ADLs), particularly if a direct functional approach is adopted.[16]

Repetitive practice of goal-directed, functional movement under varying conditions for procedural learning is a feature of many forms of intervention in stroke rehabilitation. The use of intensive repetition is grounded in neurophysiological hypotheses about the reasons for loss of movement after stroke. Repeated motor practice enhances motor strength, speed and endurance, while sensorimotor coupling contributes to the adaptation and recovery of neuronal pathways.[17] Repetitive task training (RTT) is common as a specific rehabilitation technique, but it is often combined with techniques to enhance cognitive involvement in the relearning of motor skills, such as functional relevance and knowledge of performance, thereby forming the underlying principles in the motor relearning or movement science physiotherapy approach.[18]

Intensive periods of task practice using shaping techniques (progressively increasing the difficulty of a task in small steps and providing frequent feedback and positive encouragement) to build up to completion of a functional task are also a major feature of constraint-induced movement therapy,[19] where they are combined with restricted use of the unaffected limb to overcome learned non-use or adaptive strategies.

Intensive practice of functional movement can also be assisted by treadmills,[20] gait trainers[21] or robotics.[22] Mechanical assistance is used to overcome impairment which restricts the ability to participate, but also serves to deliver an intensity of training sufficient to develop the amount and power of movement required for functional performance.

Scope of the review

This study will consider the impact and cost-effectiveness of all three of the major forms of therapy that have repeated, functional task practice as a major component, namely repetitive task training (RTT), constraint-induced movement therapy (CIMT) and treadmill training (TM). In combination, these three forms of therapy will be referred to as repetitive functional task practice (RFTP).

Systematic reviews of TM[20] and CIMT[23] have already been published. To provide an overall picture of the relative effectiveness and cost-effectiveness of all the common forms of RFTP, the references from the systematic reviews for TM and CIMT were followed up and data were extracted from those primary studies that also met the inclusion criteria for this study. A systematic review of RTT studies has already been submitted to The Cochrane Collaboration by the authors of this report. This review therefore presents the results of these three interventions combined. The characteristics, quality and results of the trials for each intervention are reviewed and presented separately to ensure clarity, until combined in subgroup analysis to present a between-intervention overall estimate of efficacy and comparison of effect.

Scope of the cost-effectiveness analysis

An economic model will be developed from an existing data set. The data set contains information on the natural recovery and resource use of a cohort of stroke patients, which allows estimates to be made on outcomes and costs. The efficacy of RFTP and hence its potential impact on outcomes will be obtained from the review; the cost of RFTP will be estimated by considering staff and equipment costs. Using certain assumptions, which will be clearly outlined in the methods, the model data and the efficacy of RFTP from the review will be used to estimate the cost-effectiveness of RFTP. Uncertainty in the estimate will be considered by varying the parameters of any assumptions that are made.

Objectives

The objectives of this study were to carry out a systematic review and cost-effectiveness analysis to determine:

- whether RFTP improves global or limb-specific functional ability and ADL function in adults after stroke
- the factors that could influence primary outcome measures for RFTP, including the effect of amount, type and timing of intervention
- estimates of the cost-effectiveness of RFTP.

Chapter 2

Review methods

Search strategy for identification of studies

Electronic searches

The Cochrane Stroke Group Trials Register was searched in October 2006, using the following parameters: Intervention Type: "Physiotherapy" or "Occupational Therapy", without restriction of intervention code.

In addition, the following databases were searched as follows: The Cochrane Library (2006 Issue 3), MEDLINE (1966 to September week 4, 2006), EMBASE (1980 to week 40, 2006), CINAHL (1982 to October week 1, 2006), AMED (1985 to week 40, 2006), SportDiscus (1980 to October week 1, 2006), ISI Science Citation Index (1973 to 14 October 2006), Index to Theses (1970 to September 2006), ZETOC (to 14 October 2006), PEDro (to 3 October 2006), OT Seeker (to 21 April 2006) and OT Search (to March 2006).

The main search design was reviewed by the Cochrane Stroke Group Trials Search Co-ordinator. The MEDLINE search given below was used and adapted for other databases.

MEDLINE (OVID)

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 hemorrhage/ 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 or/1-6
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 hemorrhage/rh or *vasospasm, intracranial/rh or *vertebral artery dissection/rh
9 *hemiplegia/rh or exp *paresis/rh
10 exp *gait Disorders, neurologic/rh or *motor skills disorders/rh
11 rehabilitation/ or "activities of daily living"/ or exercise therapy/ or occupational therapy/
12 Physical Therapy Modalities/
13 Exercise Movement Techniques/ or exercise therapy/ or walking/
14 Robotics/
15 exp Psychomotor Performance/
16 movement/ or gait/ or exp locomotion/ or exp motor activity/
17 "Range of Motion, Articular"/ or "Task Performance and Analysis"/ or "Practice (Psychology)"/
18 "Recovery of Function"/
19 ((motor or movement$ or task$ or skill$ or performance) adj5 (repetit$ or repeat$ or train$ or re?train$ or learn$ or re?learn$ or practic$ or practis$ or rehears$ or rehers$)).tw.
20 ((motor or movement$ or task$ or skill$ or performance) adj5 (schedule$ or intervention or therap$ or program$ or regim$ or protocol$)).tw.
21 (functional adj5 (task$ or movement)).tw.
22 or/8-21
23 7 and 22

The search above was combined with the Cochrane Stroke Review Group search for randomised controlled trials.

A similar search (Search 2), given below, was conducted without limits of study type and/or client group, to check for trials incorrectly

indexed, and to trace trials of RFTP in other client groups for citation tracking.

MEDLINE OVID

1 *hemiplegia/rh or exp *paresis/rh
2 exp *gait Disorders, neurologic/rh or *motor skills disorders/rh
3 1 or 2
4 Physical Therapy Modalities/
5 Exercise Movement Techniques/ or exercise therapy/ or walking/
6 Robotics/
7 rehabilitation/ or "activities of daily living"/ or occupational therapy/
8 exp Psychomotor Performance/
9 "Task Performance and Analysis"/ or "Practice (Psychology)"/
10 ((motor or movement$ or task$ or skill$ or performance) adj5 (repetit$ or repeat$ or train$ or re?train$ or practic$ or practis$ or rehears$ or rehers$)).tw.
11 (functional adj5 (task$ or movement)).tw.
12 or/4-11
13 movement/ or gait/ or exp locomotion/ or exp motor activity/
14 "Recovery of Function"/
15 13 and 14
16 3 and (12 or 15)

Unpublished trial data were searched for on national and international databases to May 2006 as follows: MetaRegister of Controlled Trials, BioMed Central, CRISP, Centerwatch, National Research Register, ReFeR, Stroke Trials Directory, REHABDATA and CIRRIE, using simple terms for stroke and rehabilitation or physical therapy.

Physiotherapy, occupational therapy and robotics conference proceedings were searched as follows:

- Australian Physiotherapy Association Conference 2000, 2002, 2004
- Australian Physiotherapy Association Neurology and Gerontology Physiotherapy Conference 2005
- American Physical Therapy Congress Annual Conference 2005
- Canadian Physiotherapy Conference 2005
- UK College of Occupational Therapists Conference 2002, 2003, 2005
- National Association of Neurological Occupational Therapists Conference 2005
- World Confederation for Physical Therapy 1st International Congress 1953, 4th International Congress 1963
- World Confederation of Physiotherapy Europe: First Congress, Copenhagen 1994: Physiotherapy in Stroke Management
- Chartered Society of Physiotherapy Annual Congress 2000, 2001, 2002, 2003, 2004, 2005
- ICORR Rehabilitation Robotics International Conferences 1999, 2001, 2005

Non-English-language literature was identified by searching Chinese, Russian and Indian databases via Eastview, Panteleimon and Indmed, using broad descriptors for stroke, rehabilitation and physical therapy. The China National Knowledge database was searched in both English and Chinese. Searching and translation of Chinese abstracts were undertaken by personnel from the Second Military Medical University, Shanghai.

Other sources

RTT

The reference lists of systematic reviews relevant to physical or occupational therapy in stroke rehabilitation were searched.[11,14–16,24–45] Reference lists of publications and literature reviews relevant to RTT identified by the search were combed to identify further relevant trials.[46–48] In addition, forward citation searching was undertaken on ISI Web of Knowledge for all included trials, and the authors were contacted to ask for details of any other possible relevant trials, either published or unpublished. A request for information was also posted to the bulletin boards of World Congress of Physical Therapy and PHYSIO JISCmail.

CIMT and TM

Studies relevant to CIMT and TM were sourced from the search identified above, and also from existing systematic reviews.[20,23] Only those trials of CIMT and TM that met the requirements of this review (i.e. RFTP intervention with suitable comparison) were included.

Inclusion criteria

Types of study

Randomised and quasi-randomised trials (such as those allocating by date or alternation) were included in the review. Only the first period of cross-over trials was included.

One arm of the trial had to include RFTP, compared against usual practice (including 'no treatment') or an attention-control group. For trials of TM or CIMT, comparison groups using alternative forms of training were included.

Examples of attention-control treatment are comparable time spent receiving therapy on a different limb or participating in an activity with no

potential motor benefits. Usual-practice comparison groups were accepted when the intervention received by the control group was considered a normal or usual component of stroke rehabilitation practices, including neurophysiological or orthopaedic approaches. Early after stroke it was assumed that usual practice would mean that patients would receive some therapy.

Types of participant

Adults (presumed 18 years and older) who had suffered a stroke were included. Stroke was defined according to the World Health Organization (WHO) definition 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".[49] Trials starting at any time after an acute stroke and in any setting were included.

Types of intervention

Trials were required to include an intervention where an active motor sequence was performed repetitively within a single training session, where the practice aimed towards a clear functional goal. Functional goals could involve complex whole tasks, or pretask movements for a whole limb or limb segment such as grasp, grip or movement in a trajectory to facilitate an ADL. To be included, trials of repetitive activity were required to involve complex multijoint movement with functional measurement of outcome, rather than the exercise of a single joint or muscle group orientated to motor-performance outcomes.

Any intensity and duration of task training schedule was included. However, trials were included only if the duration or number of repetitions within a session of practice, and the number of sessions delivered, could be identified. Trials clearly using motor relearning as a whole therapy approach were included if the amount of task-specific training received could be identified.

Trials using person-delivered, mechanical or robotic movement assistance were included if the purpose of the assistance was to facilitate a task-related repetition. Trials combining repetitive task practice with constraint of the unaffected limb were also included.

Exclusion criteria

Trials were excluded if they combined RFTP with other interventions such as electrical stimulation virtual environments, biofeedback, bilateral movement, or mental rehearsal. Trials were also excluded if the intervention used mechanical means simply to increase endurance through the intensity of practice without monitoring or adjustment according to the quality of movement, such as the use of slot machines.

Trial authors were contacted for clarification of the nature of the intervention if it was unclear whether the trial met the definition.

Types of outcome measure

Primary outcomes

The primary outcomes chosen were global and limb-specific functional measures. Owing to the large range of measures used across trials, selection of outcome measures was done by the review authors to maximise quantitative pooling. If more than one measure was available in an outcome category, measures of functional motor ability used in the primary trials were prioritised as follows in the different categories. Items marked with an asterisk are measures where a low score equals a positive outcome. In all other measures, a high score indicates a good outcome.

Upper limb function/reach

- Arm function: Action Research Arm Test (ARAT), Motor Assessment Scale (MAS) – upper limb component, Frenchay Arm Test, Wolf Motor Function Test (WMFT), Functional Test of the Hemiparetic Upper Extremity (FTHUE), Box and Block Test (BBT), Test Evaluant des Membres Supérieurs des Personnes Agées (TEMPA), University of Maryland Arm Questionnaire for Stroke, Motor Activity Log (MAL).
- Hand function: MAS hand, Jebsen Test of Hand Function*, Peg Test*, Purdue Pegboard.
- Sitting balance/reach: Reaching Performance Scale, Functional Reach.

Lower limb function/balance

- Lower limb function: walking distance, walking speed, functional ambulation, sit-to-stand*, measures of lower limb function, e.g. Rivermead Mobility Index, Sodring Motor Evaluation Scale (SMES), Step Test.
- Standing balance/reach: Berg Balance Scale.

Overall functional ability

MAS, Rivermead Motor Assessment (RMA) Scale.

Secondary outcomes

ADL

Barthel Index (BI), Functional Independence Measure (FIM), Modified Rankin Scale, Global Dependency Scale.

Adverse outcome

Pain, injury, falls.

Timing of outcome assessment

Primary outcome timing was at the end of the intervention period. Where the end of the intervention period was not clearly defined, outcome measures at 3 months post-stroke were chosen as primary. Data are presented for follow-up less than 6 months post-stroke, and between 6 months and 1 year post-stroke.

Data extraction and assessment of study validity

Selection of studies

One reviewer (BF) performed the searches. From the initial references, 4443 obviously irrelevant items were excluded on title and abstract by one reviewer (BF) and checked by a second reviewer (JM). All reviewers (BF, JM, ML and LT) undertook screening on the same titles and abstracts until an acceptable level of inter-rater reliability was achieved (kappa = 0.63). From that point, two reviewers (from BF, JM, ML and LT) independently screened references.

In total, 447 full papers considered potentially relevant were retrieved, including 71 items in languages other than English. For non-English-language papers, decisions about exclusion were made on English abstract or machine translation of the abstract via WorldLingo or Translation Booth, if adequate. Where machine translation was inadequate, or where inclusion was unclear from English abstracts, the methods sections of full papers were commercially translated by native speakers. Seventeen methods sections of papers and three full non-English-language papers that were screened as potentially relevant were also commercially translated. Two reviewers independently screened all full papers and methods section translations for non-English studies. Altogether, 121 papers were progressed to more detailed filtering by two reviewers (from ML, LT, BF and JM).

Data extraction and management

All reviewers (BF, JM, ML and LT) undertook data extraction and critical appraisal on eight studies. Using unweighted multiple kappa, inter-rater reliability of judgement of seven criteria for quality assessment was median kappa = 0.67 (range 0.48–0.85). Disagreements were reviewed and instructions for critical appraisal gradings revised. From that point, two reviewers independently conducted data extraction and review of the methodological quality of the eligible trials. Disagreements were resolved by discussion and referral to a third reviewer. Data were recorded on a standardised checklist, incorporating details of randomisation method, study population, intervention methods and delivery, reason for losses to follow-up, and post-therapy and follow-up outcome measures. In addition, information relating to treatment monitoring, acceptability and adherence was extracted where available.

Assessment of methodological quality

Items were evaluated as adequate, inadequate or unclear, and quality assessment was undertaken using the following criteria:

- ***selection bias***
  - random allocation
  - allocation concealment
  - baseline comparability of groups
- ***performance bias***
  - equal treatment of groups
- ***attrition bias***
  - description of withdrawals, dropouts and those lost to follow-up
  - intention-to-treat analysis
  - percentage loss to follow-up
- ***detection bias***
  - blinding of outcome assessors.

Analyses

The primary comparison to be undertaken was to estimate the overall effect of RFTP. Secondary comparisons were designed to determine whether treatment effects differed for type of intervention (RTT, CIMT or TM), or the timing or amount of intervention.

Measures of treatment effect

For continuous outcomes using similar measurement scales, the weighted mean difference (WMD) with 95% confidence interval (CI) was used. Where similar outcomes were measured using different outcome scales, results were combined using standardised mean difference (SMD) with 95% confidence interval. Outcomes measured using both dichotomous and continuous measurement units were analysed using the generic inverse variance method. For continuous outcomes, means of post-therapy scores and their

respective standard deviations were extracted. Changes from baseline outcome data were extracted if available across all trials.

Unit of analysis issues

Studies with multiple treatment groups

Two RTT trials[50–52] compared upper versus lower limb training, so are included as four intervention–control pairs. In the subgroup analyses, these intervention–control pairs are not included as separate trials, as it was considered that the impacts of the interventions on upper and lower limb function in the same person would not be independent. Results for primary outcome of the lower limb training groups were selected, as studies were showing that treatment effects were greater for lower limbs. This strategy may have the effect of inflating effect sizes, but the effect should not bias the tests of subgroup effects. One RTT trial[53] compared upper and lower limb training groups against the same control group. To avoid the control group being included twice, and to use a limb-specific rather than a global or an ADL measure, the lower limb training versus splint control comparison was selected for the subgroup analyses.

Dealing with missing data

If data were not in a form suitable for quantitative pooling, trial authors were contacted for additional information. Attempts were made to obtain post-therapy scores from trial authors who had reported median and interquartile ranges (IQRs).

Assessment of heterogeneity

The degree of heterogeneity for each outcome was assessed by the I^2 statistic. If less than or equal to 50%, any heterogeneity was deemed insubstantial and a fixed-effects meta-analysis was used. If the I^2 statistic was greater than 50%, the individual trial characteristics were explored to identify potential sources of heterogeneity. Meta-analysis was then performed using both fixed- and random-effects modelling to assess sensitivity to the choice of modelling approach and reported accordingly.

Clinical and methodological diversity was addressed by incorporation of subgroup analyses for type of participant (time from stroke), intervention (type and amount of intervention) and study design (allocation concealment, comparison group, equivalence of treatment, loss to follow-up and trial size).

To test for subgroup effects data were stratified by subgroup and the *Q*-statistic was partitioned from the unstratified analysis into 'within subgroups' and 'between subgroups'. A χ^2 test of the resulting between-subgroups *Q*-statistic was performed, using a 10% significance level.[54]

Assessment of reporting biases

Assessment of the potential for reporting bias was checked by performing a subgroup analysis based on the trial size (number of participants) and producing a funnel plot of the standard error (of effect estimate) against effect estimate.

Subgroup analysis and investigation of heterogeneity

Planned subgroup analyses for upper and lower limb functional outcomes were undertaken as follows.

- Type of intervention: trials were classified as RTT, CIMT or TM.
- Dosage of task practice: this was calculated by multiplying the number of weeks by the number of sessions per week by the session duration in hours. Trials were divided into those providing up to and including 20 hours' training and those providing more than 20 hours' training in total. The division at 20 hours was based on the median value for dosage of task practice from all included trials, and the average length of stay in the National Sentinel Stroke Audit[55] after the first 7 days of acute care, presuming the provision of 1 hour of training per day in the inpatient rehabilitation period.
- Time since stroke: mean time since stroke at recruitment was used to classify trials as within 0–6 months post-stroke or more than 6 months post-stroke. The division at 6 months was based on the interpretation of this as the main period of active rehabilitation. Because a number of trials recruited very early post-stroke, a post hoc analysis grouping was included for trials recruiting within 14 days of stroke.

It had been intended to consider whether effect sizes were related to whether training was based on pre-functional or functional activities or pre-intervention level of disability. In the event, most pre-functional trials were excluded because they contained passive or active-assisted movement, and levels of disability proved too difficult to classify because of mixed groups of participants and unsuitable measures and data for this purpose. Therefore, these planned subgroup analyses are not presented.

The selection of outcome measure for subgroup analysis was complicated by the fact that few trials

used similar outcome measures. Subgroup analyses were performed separately for upper and lower limb interventions. Outcomes for subgroup analyses were limited to measures of walking for lower limbs and arm function for upper limbs. If more than one measure was available, lower limb outcomes were prioritised in the following order: (1) walking speed, (2) walking distance and (3) functional ambulation/walking scales; and upper limb outcomes were prioritised as follows: (1) ARAT, (2) MAS – upper extremity (MAS-UE), (3) WMFT and (4) BBT. Outcome selection was based on evidence for correlation and similar responsiveness to change for walking distance, speed and functional ambulation.[56] For measures of arm function, there is evidence for correlation and similar responsiveness to change for the MAS-UE and ARAT,[57,58] and for correlation between ARAT and BBT.[59] There is less evidence for correlation between WMFT and other tests, but ARAT, BBT and WMFT all correlate well with the Fugl–Meyer measure of arm impairment.[59,60]

Four trials[61–64] were omitted from the subgroup analyses because data were unsuitable for pooling. Of the remaining 27 trials, 26 presented means and standard deviations, so SMD could be used as the effect measure. One trial[65] was excluded from the subgroup analyses because it used a dichotomous main outcome. This trial was excluded rather than using generic inverse variance, because SMD is easier for clinicians to interpret.

Planned subgroup analyses were also carried out for allocation concealment (adequate or inadequate/unclear). In addition, post hoc subgroup analyses were included to consider the impact of different comparison groups (attention-control, usual care), equivalence of therapy time (equivalent time, additional time) and trial size (under 25 participants, 25 participants and over), based on the median value. Planned subgroup analyses for intervention delivery (therapist versus self-administered, group versus individual) and intervention setting (home versus community) were not undertaken, because of insufficient numbers of trials.

Chapter 3
Description of studies

For the RTT search, 1366 records were identified from the Cochrane Stroke Trials Registry and 18,241 records from the main database searches, totalling 19,607. A further 772 records were added from unpublished trial databases, conference proceedings, and hand and citation searching, totalling 20,379. After removal of duplicates, 14,978 records progressed to filtering.

Figure 1 illustrates that, of the 447 papers retrieved, 360 studies were excluded as irrelevant when full-text details were seen. Thirty-four potentially relevant CIMT and TM studies were identified from existing systematic reviews, totalling 121 potentially relevant studies. Forty-four studies were excluded after more detailed filtering, leaving 77 studies identified as potentially appropriate for inclusion. Of these, eight are ongoing studies, of which one was identified from the Cochrane Stroke Trials Registry, four from handsearching, two from secondary referencing, and one from author contact. Thirty-eight studies are still awaiting assessment, because available information is insufficient to be able to make a decision. Seven of

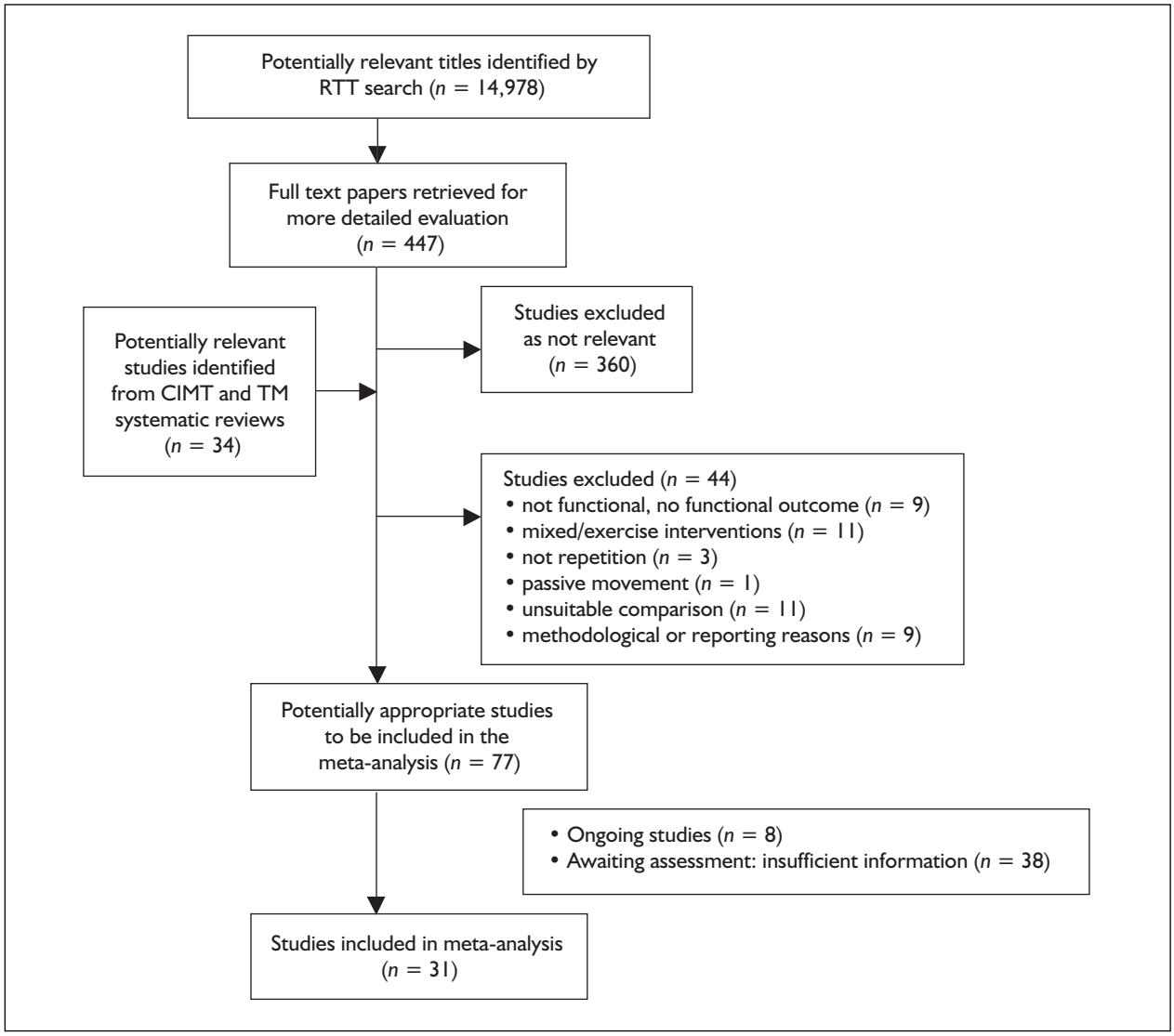

FIGURE 1 *Flowchart of included and excluded studies*

these were identified from the Cochrane Stroke Trials Registry, 20 from handsearching, three from database searching, five from secondary references and three from author contact.

Unpublished data were sourced from the trial authors for 11 RTT trials[50,51,53,65–72] and two CIMT trials.[73,74]

All of the included studies for RTT were identified from the Cochrane Stroke Trials Registry. For CIMT and TM, all of the included studies were identified from existing systematic reviews, except for one recent CIMT trial identified from the Cochrane Stroke Trials Registry.[75]

Description of studies

Thirty-one studies were included in total, including 34 intervention–control pairs and data from 1078 participants relevant to this review. A description of included studies is presented separately for each of the three forms of RFTP, namely RTT, CIMT and TM. A summary of the characteristics of the included studies is given in Appendices 1–3.

Included studies

RTT

Fourteen trials were identified, comprising 17 intervention–control pairs, which met the inclusion criteria. Three trials included two relevant intervention–control pairs: Kwakkel and colleagues[53] refer to a trial with two intervention–control pairs: a lower limb training group versus splint control, and an upper limb training group versus splint control. Blennerhassett and Dite[50] also include two intervention–control pairs: an upper limb training group versus lower limb attention-control, and a lower limb training group versus an upper limb training attention-control. Two papers report on two intervention–control pairs of the same trial: Salbach and colleagues[51] refer to a lower limb training group versus upper limb training attention-control, and Higgins and colleagues[52] refer to an upper limb training group versus lower limb training attention-control.

In one trial[71] there were three arms, consisting of a functional task practice group, a strength training group and a usual-care group. Only the data for the intervention–control pair of functional task practice versus control are included here.

Design

The 14 trials considered comprised 13 randomised controlled trials (RCTs)[50,51,53,65–68,70–72,76–78] and one quasi-randomised trial.[69] Four of the trials were identified as pilot RCTs[67,71,76,77] and three of the trials were multicentre.[51,53,77] Three of the trials were stratified for randomisation: one for baseline level of walking deficit,[51] one for gender and side of stroke,[68] and one for severity of deficit.[71]

Sample size

Four trials had 25 participants or fewer,[66,67,69,76] six trials had between 25 and 49 participants,[50,65,71,72,77,78] and five trials had 50 participants or more.[51,53,68,70,71]

Setting

Of the 14 trials, three were carried out in Canada,[51,65,67] three in Australia,[50,66,78] three in the UK,[69,70,77] one in Taiwan,[72] one in the USA,[71] one in The Netherlands[53] and one in France.[76]

CIMT

Eleven trials met the inclusion criteria. In four trials[61,62,79,80] there were three arms consisting of a modified CIMT group, a traditional rehabilitation group and a no-treatment control group. In two of these trials the traditional rehabilitation group also received RTT, with the only difference between groups being constraint.[79,80] In these trials, therefore, the no-treatment group was included as the comparison group. In the remaining two trials the data for the modified CIMT and traditional rehabilitation groups were included.[61,62]

Design

All 11 trials were identified as RCTs, of which two were identified as pilot[81,82] and two as preliminary,[61,83] and one trial was labelled a 'feasibility and efficacy' study.[80] All trials were single centre.

Sample size

Ten trials had 25 participants or fewer.[61,62,73,74,79–84] One trial had 50 participants or more.[64]

Setting

Nine trials were carried out in the USA,[61,62,73,74,80–84] one in Saudi Arabia[79] and one in Thailand.[64]

TM

Six trials were identified which met the eligibility criteria. One trial with three arms consisted of two TM interventions, speed-dependent TM and limited progressive TM, compared with

conventional gait training.[85] The limited progressive TM group was used in this review, as speed-dependent TM was judged to comprise two mechanisms of action.

Design

One study was a cross-over trial,[63] of which only the first phase was used. The remaining five studies were RCTs. Of these five trials, one was identified as a pilot controlled trial.[86] All of the trials were single centre. Three of the trials were stratified for randomisation, one for walking speed,[87] one for deficit severity and age,[88] and one for initial time to walk 10 m without assistance.[85]

Sample size

Two trials had 25 participants or fewer,[63,86] one trial had between 26 and 49 participants,[87] and three trials had 50 participants or more.[85,88,89]

Setting

Of the six trials, two were carried out in the USA,[86,88] three in Germany;[63,85,89] and one in Australia.[87]

Participants

RTT

The 14 trials included 680 participants, of which 659 were included in the 17 intervention–control pairs relevant to this review. All of the trials included both genders, with three trials having more than 60% male participants.[51,65,66] In two trials, the participants had a mean age of less than 60[50,69] and in five trials the mean age was over 70 years.[51,68,70,77,78]

Six trials included only participants after a first stroke[53,67,68,71,72,76] and two trials included participants with either first or recurrent stroke.[50,51] In the remaining trials, it was unclear whether inclusion was limited to first stroke only.

Mean time since stroke

Three trials recruited within 14 days of stroke.[53,68,70] A further four trials recruited within the first month post-stroke,[65,71,76,77] one trial recruited within 3 months of stroke,[50] two trials recruited within 6 months of stroke,[69,78] two trials recruited within 12 months of stroke[51,72] and two trials recruited participants in the chronic phase of stroke.[66,67]

CIMT

The 11 trials included 203 participants, and data from 190 participants were relevant to this review. Thirteen participants were not included from studies where there was more than one comparison group.[61,62,79,80] All of the studies included both genders, with six studies having more than 60% male participants.[61,62,64,74,82,84] In four trials, participants had a mean age of less than 60 years;[62,64,79,80] no trials had a mean age over 70 years.

Three trials included only subjects after a first stroke.[64,74,83] In the remaining trials, it was unclear whether inclusion was limited to first stroke only.

Mean time since stroke

Three trials recruited within 19 days of stroke,[81,82,84] three trials recruited between 1 and 6 months post-stroke,[61,79,80] and one trial recruited between 3 and 9 months post-stroke.[83] The remaining trials recruited 12 months or more post-stroke.[62,64,73,74]

TM

The six studies included 254 participants, of which data from 229 participants were relevant to this review. Five of the studies included both genders, as participants in one study were all male.[86] Five studies had more than 60% male participants.[63,85–87,89] Two trials had a mean age less than 60;[85,86] no trials had a mean age more than 70 years.

Three trials included only subjects after a first stroke,[63,87,89] one trial included subjects with either first or recurrent stroke,[85] and in the remaining two trials[86,88] it was unclear whether inclusion was limited to first stroke only.

Mean time since stroke

One trial recruited within the first month of stroke,[86] one trial recruited within 3 months post-stroke,[89] one trial recruited within 6 months post-stroke[85] and three trials recruited in the chronic phase of stroke recovery.[63,87,88]

Interventions

RTT

Two trials used whole therapy motor approaches,[68,70] and four trials trained single tasks, all related to balance, reach or sit-to-stand.[65,66,76,77] The remaining trials consisted of mixed functional task training. Of these, three used a circuit-training approach.[50,51,67] While all of the remaining trials included some functional task practice, this was sometimes mixed with other components, including strengthening exercise and

TM,[53] upper limb exercise,[69] lower limb exercise[78] and shaping training.[72]

Of the 17 intervention–control pairs relevant to this review, four included lower limb or mobility training,[50,51,53,67] one trained sit-to-stand movements,[65] two trained balance in sitting and standing,[76,77] one trained functional reach in sitting,[66] and one trained standing balance and mobility.[78] Six intervention–control pairs were upper limb training.[50,52,53,69,71,72] Two intervention–control pairs used whole therapy approaches, training global function.[68,70]

Setting

Four trials were carried out solely in an inpatient setting,[50,65,76,77] four trials included both inpatient and outpatient care,[53,68,70,71] four trials were carried out in outpatient or community settings[51,66,67,72] and two trials were in the home environment.[69,78]

In three trials, the intervention was additional to usual care, of which two were during inpatient rehabilitation[71,77] and one was after discharge from inpatient therapy, but additional to outpatient therapy.[69]

Amount of task practice

The number of hours of training varied considerably across the interventions. Three trials provided less than 10 hours' training in total,[66,70,77] seven trials provided between 10 and 21 hours' training,[50,51,65,67,68,71,76] two trials provided more than 40 hours' training[53,72] and two trials prescribed more than 40 hours' home-exercise therapy.[69,78]

Duration of training

The length of time over which training was spread varied from 2 to 4 weeks for seven trials.[50,66,67,71,72,76,77] For two trials, the length of time was estimated as 3 weeks of hospital inpatient therapy, with therapy for some patients in an outpatient setting if required.[68,70] The intervention in four trials was over 6–8 weeks[51,65,69,78] and in one trial the intervention was over 20 weeks.[53]

Intervention delivery

All of the interventions were delivered by trained physiotherapists or occupational therapists, except for the self-monitored home-exercise programmes,[69,78] where trained staff input was restricted to prescription and programme review, one trial where trained physiotherapy assistants provided balance training[77] and one trial where registered practical nurses delivered sit-to-stand training.[65] Three of the interventions were delivered in a group setting of between four and seven participants per group.[50,65,67]

Of those programmes delivered in a circuit-class format, trial authors reported between 70 and 80% compliance.[50,51,67] For the self-administered programmes in a home setting, trial authors reported 68–75% self-monitored adherence to the prescribed exercise programme.[69,78]

CIMT

Trials were divided into those evaluating CIMT[64,73,74,83,84] and those evaluating modified CIMT (mCIMT).[61,62,79–82] CIMT interventions included wearing a padded mitten and/or sling to reduce use of the unaffected arm, together with a programme for improving task performance of the affected limb using techniques such as 'shaping' (progressively increasing the difficulty of a task in small steps and providing frequent feedback and positive encouragement) and repetitive task practice. Typically, therapy sessions lasted for 6 hours with participants attending 5 days per week. mCIMT comprised similar interventions, but therapy time was reduced to typically 1 hour per day with participants attending 3 days per week.

Setting

Two trials were carried out solely in an inpatient setting,[81,82] and one trial included both inpatient and outpatient care.[84] Seven trials were conducted in outpatient clinic settings,[61,62,64,73,74,79,80] and the final study[83] did not specify a setting, but given that participants were 3–9 months post-stroke it is likely to be an outpatient clinic setting.

Amount of task practice

The number of hours of training varied across trials, with those evaluating CIMT typically providing a larger number of hours, with a minimum of 42 hours[84] and a maximum of 75 hours.[74] Modified CIMT trials typically provided 30 hours' training;[61,62,79,80] with the exceptions of one trial where 15 hours' training was provided,[82] and another providing 20 hours' training.[81]

Duration of training

All CIMT trials spread training over 2 weeks, with the exception of one trial[84] where training spanned 2.5 weeks. Trials evaluating mCIMT spread training over a longer period, typically 10 weeks,[61,62,79,80,82] with the exception of one trial[81] where training lasted for 2 weeks.

Intervention delivery

Interventions in eight trials were delivered by trained physiotherapists and/or occupational

therapists,[61,62,79–84] with one trial also including delivery by 'therapy assistants'.[84] In three trials it is unclear who delivered the intervention.[64,73,74]

In the majority of trials, it is not clear whether interventions were delivered on a one-to-one or group basis. Exceptions are one trial where treatment was on a one-to-one basis,[83] and one trial where participants were treated in groups of three to four.[64]

TM

Two studies evaluated unsupported TM,[87,88] and four studies evaluated bodyweight-supported treadmill training.[63,85,86,89] One trial supported bodyweight to a maximum of 15%,[89] one trial only allowed bodyweight support in the first three training sessions,[85] and one trial progressively decreased bodyweight support as participants acquired greater self-support.[86]

Two trials practised walking training with either a defined training heart rate[89] or a target heart rate of 60–70%.[88] The other trials did not specify a defined heart rate.

Five trials increased the belt speed of the treadmill during the intervention. One trial identifies the use of a treadmill with a variable belt speed, but does not specify how this was used.[63]

Setting

Four trials were carried out in an inpatient setting[63,85,86,89] and two trials in an outpatient setting.[87,88] The four trials in the inpatient setting were in addition to usual care.

Amount of task practice

Only one trial provided more than 20 hours' task practice.[88]

Duration of training

The length of time over which training was spread varied from 2 to 4 weeks for four studies.[63,85–87] For one study the length of time was 6 weeks[89] and for one study it was 6 months.[88]

Intervention delivery

All of the interventions were delivered by trained physiotherapists or occupational therapists.

Comparison interventions

RTT

Ten intervention–control pairs compared the intervention against an attention-control: two intervention–control pairs used a recreation or cognitive therapy control group,[65,66] two intervention–control pairs from the same trial used a splint control[53] and six (four from two trials) used a comparison training programme for the upper or lower limb.[50,51,67,78]

Seven intervention–control pairs compared the intervention against usual care. Of these, three were during inpatient rehabilitation and provided equivalent hours of therapy,[68,70,76] and one provided additional hours of therapy.[71] The other three intervention–control pairs were after discharge from inpatient rehabilitation, and additional to any outpatient treatment.[69,72,78] It is unclear whether the duration of therapy for the intervention–control pair was equivalent for one of these trials.[72]

CIMT

Three studies compared the intervention against an attention-control. One trial used a bimanual neurodevelopmental therapy control group,[64] one trial used procedures designed to focus attention on the affected limb without providing training in active movement,[73] and one trial used a control designed to be less intense and designed to improve task performance with the unaffected side.[74]

Three trials compared the intervention against usual care only.[81,82,84] Control groups received an equal frequency of therapy time in two trials,[81,84] and in one trial control participants received half the amount of therapy time compared with intervention participants.[82]

A further three trials had two comparison groups, one receiving usual care and one receiving no treatment.[61,62,80] Usual-care participants in all three trials received an equal amount of therapy to the intervention group; the no-treatment group received no interventions during the same period. Another trial also had two comparison groups, one receiving no treatment, the other an attention-control group that received the intervention without the restraint component.[79]

The trial by Alberts and colleagues[83] compared the intervention to no treatment, with participants randomised to the latter receiving the intervention 1 year later.

TM

One trial compared the intervention against an attention-control consisting of a home-exercise programme to lengthen and strengthen

muscles.[87] Two trials compared against an alternative intervention.[88,89] One of these interventions was individual physiotherapy concentrated on walking rehabilitation,[89] and one was based on common components of conventional therapy which would not normally have been received as participants were late post-stroke.[88] Three trials compared the intervention against usual care.[63,85,86] These trials were during inpatient rehabilitation and provided equivalent hours of therapy.

Primary outcomes

The 31 included trials used a wide range of different outcome measures, measurement statistics and time intervals for follow-up. Measures selected post-intervention are detailed below.

Upper limb functional outcome measures

Arm

- RTT: ARAT,[53] WMFT,[72] MAS – arm,[50,68,70] BBT,[52] FTHUE[71] and Southern Motor Group Assessment – upper limb activity.[69]
- CIMT: Action Research Arm Test[61,62,64,79,80,82] and WMFT.[61,73,74,79–81,83]

Hand function

- RTT: Nine Hole Peg Test (9HPT),[52] Ten Hole Peg Test (10HPT),[69] MAS – hand.[50,68,70]
- CIMT: Grooved Pegboard Test,[84] a key-turning task,[83] and hand grip and pinch strength.[64]

Sitting balance/reach

- RTT: reaching distance,[66] Sitting Equilibrium Index,[76] MAS – balanced sitting,[68,70] and lateral reach – time to return to quiet sitting.[77]

Lower limb functional outcome measures

Walking distance

- RTT: Six Minute Walk Test (6MWT).[50,51,67]
- TM: 6MWT[87–89] and Five Minute Walk Test.[86] Measures of walking distance over 5 minutes were converted to distance over 6 minutes, on the assumption that participants could maintain effort equivalently over such similar periods.

Walking speed

- RTT: Ten Metre Walk Speed (10MWS) with walking aid,[53,66,67] Five Metre Walk Speed (5MWS) at comfortable speed[51] and Six Metre Walk Speed (6MWS).[70]
- TM: 5MWS,[86] 10MWS[85,87,89] and walking speed over 30 feet (9.1 m).[88]

Functional ambulation

- RTT: Functional Ambulation Classification (FAC)[53,76] and MAS – walking.[68,70,78]
- TM: FAC.[85,86]

Sit-to-stand

- RTT: Timed Up and Go (TUG),[50,51,67] MAS – sit-to-stand,[68,70] sit-to-stand time in seconds,[77] and number of people able to stand safely and independently on two occasions.[65]

Lower limb functional measures

- RTT: SMES trunk, balance and gait subscale,[68] Step Test,[50,67] and Rivermead Leg and Trunk.[70]

Standing balance and reach

- RTT: Upright Equilibrium Index,[76] Functional Reach[78] and Berg Balance Scale.[51]
- TM: measures of standing balance using an instrumented balance assessment system[88] which was not used.

Global motor function

- RTT: MAS[68] and RMA score for gross functions.[70]
- CIMT: none
- TM: RMA score for gross functions.[63,88,89]

Secondary outcomes

ADL measures

- RTT: BI[51,53,68,70] and FIM.[76] Two trials used the BI scoring out of 20,[53,70] while the other trials used the scoring out of 100.
- CIMT: The BI.[81]
- TM: none.

Adverse events

- RTT: number of falls.[65]
- CIMT: levels of stiffness and discomfort on the affected side.[73]
- TM: no trials reported quantitative data for adverse events. Narrative reports and reasons for withdrawal are summarised.

Timing of outcome measurement

- RTT: within the 0–6-month period post-stroke: one trial[77] measured outcome at 1 month post-intervention and three trials at 2 months post-intervention.[67,76,78] Within the 6–12-month post-stroke period, one trial measured outcome at 6 months post-intervention,[50] one trial at 9 months post-intervention,[71] one trial at 6 months post-randomisation,[70] and one trial at 1 year post-stroke.[68]

- CIMT: one trial measured outcome 3–4 months post-stroke[84] and one trial measured outcome 6 months post-intervention.[74]
- TM: two trials measured outcome at 3 months post-intervention.[87,89]

Excluded studies

There is a large number of excluded studies (n = 44), described in Appendix 4. Because of the difficulties in determining whether trial interventions included task-specific functional repetition, the authors have attempted to be as transparent as possible about the basis on which trials were excluded. The reasons for exclusion were:

- not functional, or no functional outcome: nine studies
- mixed interventions, or interpreted as focusing predominantly on exercise: 11 studies
- not repetition, or unable to determine amount of practice: three studies
- passive movement: one study
- comparison group also includes some form of repetitive functional intervention: 11 studies
- methodological or reporting reasons: nine studies.

The excluded studies included three trials that had been either partially or fully translated from Chinese to English. While translation was undertaken by native-speaking health-service workers, there is the possibility that information was misinterpreted or misunderstood.

Ongoing studies

There are eight ongoing studies, where the information available is sufficient to say that the interventions include an element of RFTP. These are detailed in Appendix 5. Three trials involve training for standing, balance or sit-to-stand,[90–92] two trials are of lower limb circuit training[93,94] and one trial is of upper limb task-specific training.[95] One trial uses a motor relearning approach (Langhammer B, Oslo University College, Oslo, Norway: personal communication, November 2006) and one trial is of CIMT.[96] All are with participants in the early stages of stroke recovery, except for the trial by Langhammer.

Studies not assessed at report completion

RTT

Of the 17 studies categorised as unable to be assessed, 12 were ongoing studies identified from trials registers, where the information available was insufficient to be able to exclude them at this stage.[97–108] Two studies are unpublished, and the reviewers are awaiting data.[109,110] One study was published as a conference proceeding, and the reviewers were unable to contact the authors.[111] Two studies are published, and attempts are being made to contact the authors to determine the exact content of the intervention.[112,113]

CIMT

Of the seven studies awaiting assessment, three are ongoing[114,115] (Page S, University of Cincinnati Academic Medical Centre, Ohio, USA: personal communication, February 2007). One recently published study was not in the date range for searching.[75] Two related studies have recently completed and been submitted for publication.[116] The reviewers were unable to contact the authors of one study to assess for eligibility.[117]

TM

Of the 14 studies awaiting assessment, the information available for seven ongoing studies is insufficient to be able to exclude them at this stage.[118–124] Three studies require translation.[125–127] One study is recently completed[128] as a follow-up to an included study,[86] and three studies could not be traced.[129–131]

Quality of included studies

Allocation

RTT

Allocation concealment was adequate in eight trials.[50,51,53,67,70,71,77,78] In five trials, allocation concealment was unclear; of these, three trials stated that random allocation was used, but provided no description of the procedure for its concealment from those recruiting participants;[68,72,76] one trial used coin flipping to randomise participants with no further description of the procedure,[65] and one trial attempted concealment with a procedure involving participants drawing cards out of a box containing ten control group and ten experimental group cards, but the procedure for ensuring that those recruiting participants remained unaware of assignments is not described.[66] One trial was quasi-randomised, allocating participants to intervention or control groups in alternate runs of five.[69]

CIMT

The procedure for allocation concealment was unclear in all trials. Seven trials stated that random allocation was used, but provided no description

of the procedure.[61,62,73,79,80,83,84] Four trials stated use of tables of random numbers to allocate participants to intervention or control groups, with no description of the procedure.[64,74,81,82]

TM

Allocation concealment was adequate in four trials.[86–89] In two trials, allocation concealment was unclear. One trial stated that participants were assigned to groups by block randomisation on the basis of walking speed, but provided no description of the procedure for concealing the allocation, or the block length.[85] One trial stated randomisation, with no description of the procedure.[63]

Blinding of outcome assessors

RTT

Blinding of primary outcome assessment was stated in all but two trials.[69,71] Of the studies that stated observer blinding, three gave no details of how this was done.[68,72,78] Four trials checked whether the outcome assessor had become unblinded,[51,53,67,70] and out of these, three trials reported that some degree of unmasking might have occurred.[51,53,67]

CIMT

Blinding of outcome assessment was attempted in all trials with the exception of one trial,[79] where there was no mention of blinding. In two trials[73,84] action taken at blinding was judged likely to have been effective, for example employing personnel from outside the hospital who were blind to treatment assignment. Eight trials stated that outcome assessment was blinded, but did not describe the procedure.[61,62,64,74,80–83] No trial reported checking for the possibility that unblinding had occurred.

TM

Blinding of primary outcome assessment was stated in two trials.[85,87] Neither trial described checks for unblinding. Two trials attempted blinding, but report that this may not have been successful,[88,89] for example one trial stated that as a result of staffing limitations and institutional safety regulations, treadmill exercise testing was conducted by the same staff who provided training,[88] hence metabolic fitness tests were unblinded. In one trial, physiotherapists not involved in the therapy were responsible for the assessment of the RMA Scale, but disclosure by patients and team-mates could not be fully excluded.[89] One trial did not mention blinding of outcome assessors to participants' treatment status.[86]

Owing to the nature of the interventions, blinding of participants, intervention providers or usual care providers was not assessed, as it is essentially impractical in this type of study.

Follow-up and exclusions

RTT

All trials provided information about numbers of withdrawals and reasons for withdrawal. All trials accounted for all participants at the end of the trial, except for one, which included participants in the analysis only if they completed the treatment programme.[71] Of the 14 trials in total, three trials had 10–20% loss[53,68,78] and two trials had more than 20% loss.[67,70] The remaining nine trials had less than 10% loss to follow-up.

CIMT

Nine trials had no withdrawals.[61,62,64,73,74,79,80,82,83] One trial provided information about numbers of withdrawals and reasons for withdrawal;[84] and one trial[81] states overall numbers of withdrawals, but not by intervention group. All except one trial[81] accounted for all participants at the end of the trial. All trials had no loss to follow-up, except for one trial with 13% loss[81] and one trial with 29%.[84]

TM

Five trials provided information about numbers of withdrawals and reasons for withdrawal, and accounted for all participants at the end of the trial. Withdrawals and follow-up were unclear in one trial.[63] Two trials had less than 10% loss to follow-up post-treatment,[87,89] two trials had 11–20% loss to follow-up post-treatment[85,86] and one trial had more than 20% loss to follow-up post-treatment.[88]

Other potential sources of bias

To detect systematic differences in care provided to participants in comparison groups other than the intervention under investigation, trials were assessed to determine whether groups were treated equally during the intervention and during usual care.

RTT

During the intervention, groups were treated equally in all trials, with the following exceptions: in one trial[70] there was no significant difference in the amount of treatment; however, the authors state in a supplementary paper that there may have been differences in elements of treatment such as detailed feedback and social conversation;[132] in one trial it is not clear whether groups were treated equally[72] and in two trials participants in the intervention group received

additional hours of therapy.[71,77] During usual care, groups were treated equally in eight trials.[50,53,65–69,77] In four trials no information is provided[70–72,76] and in a further two trials[52,78] there was no usual-care group.

CIMT

During the intervention, comparison groups receiving therapy were treated equally in all except two trials. In one trial,[73] participants in the intervention group spent 7 hours at the rehabilitation centre each weekday for 2 weeks; the comparison group received only four 10-minute periods encouraging them to focus on performing new activities with the affected upper extremity at home and two sessions of 'physical therapy', plus a range of exercises to carry out at home. (As it was unknown how long control group participants practised, equivalence of therapy time was assumed for subgroup analyses.) In another trial,[74] participants in the intervention arm of the trial similarly received longer periods of therapy (6 hours per day over 8 weekdays and 4 hours per day over 2 weekend days) than the comparison group (3 hours per day over 8 weekdays and 2 weekend days of rest). Groups were treated equally in all trials with a usual-care comparison.

TM

During the intervention, other than the intervention provided, groups were treated equally in all except one trial,[87] where the control group was given a home-exercise programme to carry out for the same number of sessions as in the intervention group. However, this programme was not prescribed in sufficient number or intensity to provide a training effect and instead aimed to provide a credible sham programme. Groups were treated equally in all trials with a usual-care comparison.

Chapter 4

Results of the review

Primary outcomes

Results are presented separately for upper and lower limb outcomes and global function, concluding with an overall treatment effect for all forms of RFTP on functional outcome. All results are post-therapy, except for Langhammer and Stanghelle,[68] which are 3 months post-stroke, and Van Vliet and colleagues,[70] which are 3 months post-baseline.

Upper limb function: post-therapy

Results are presented for arm function, hand function, and sitting balance and reach.

Arm function

Eighteen trials recruiting 634 participants measured arm function, with data suitable for pooling available for 76% (n = 485) (*Figure 2*). There was some heterogeneity of treatment effects

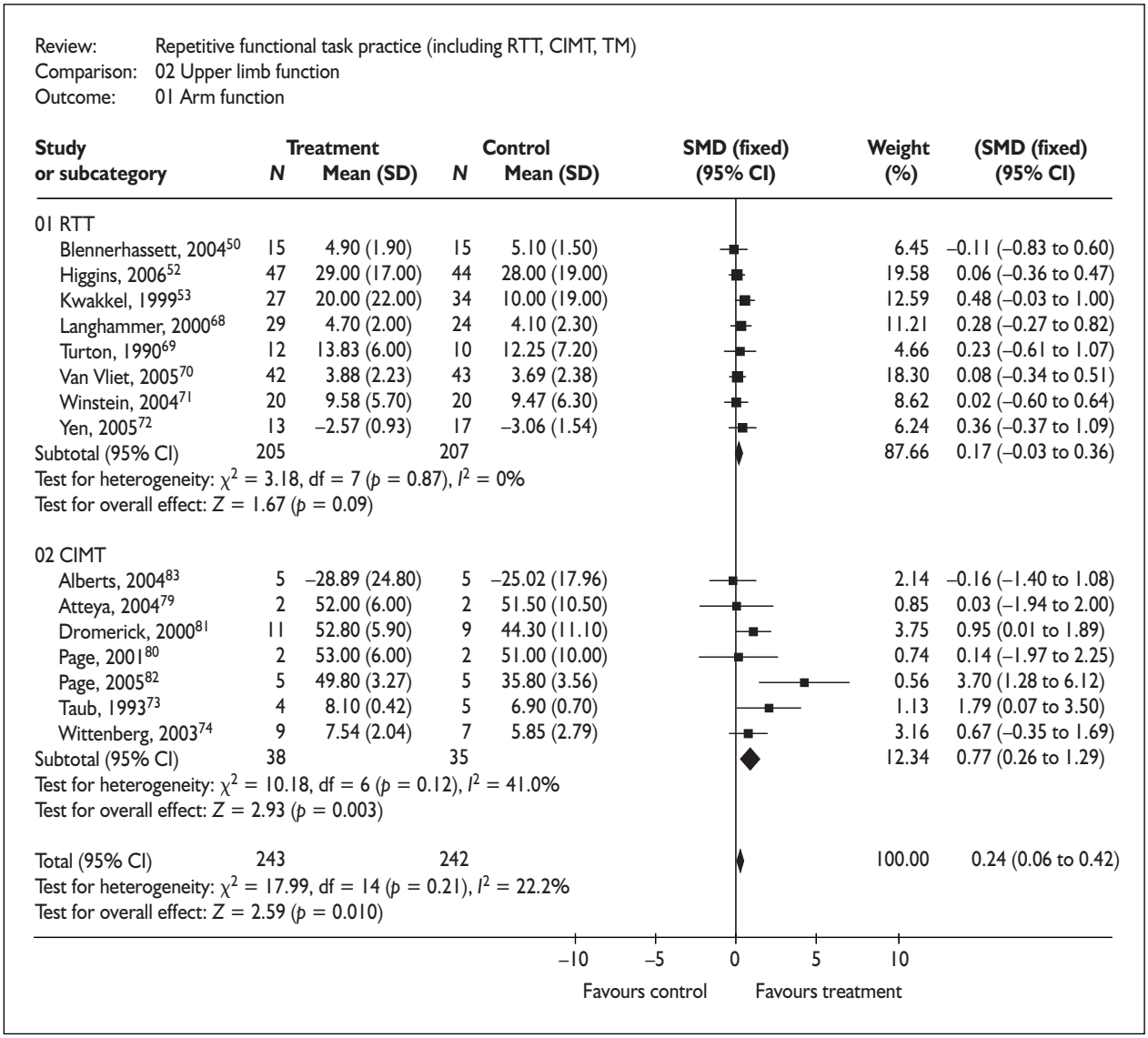

FIGURE 2 *Arm function*

(I^2 = 22.2%), although not sufficient to merit the use of a random-effects approach.

Eight RTT trials recruited 467 participants,[50,52,53,68–72] with data available for 88% (n = 412) of participants. Ten CIMT trials recruiting 167 participants measured arm function.[61,62,64,73,74,79–83] In three of the CIMT trials with 91 participants in total, data were unsuitable for pooling.[61,62,64] Page and colleagues (2002)[61] included outcome data for nine participants, and provided means with no standard deviations (ARAT: CIMT group mean change +11.5, traditional therapy group mean change +1.4). Page and colleagues (2004)[62] included data for 13 participants, and also provided means with no standard deviations (ARAT: CIMT group mean change +11.4, traditional therapy group mean change +7.1). Suputtitada and colleagues[64] reported median and ranges for 69 participants (ARAT: CIMT group n = 33, median 55, range 30–57, control group n = 36, median 47.5, range 15–54). Of the remaining seven CIMT trials with 76 participants, data were available for 96% (n = 73).

The pooled effect for the impact of RFTP on arm function across all trials showed a small effect size, which was statistically significant: (SMD 0.24, 95% CI 0.06 to 0.42).

Hand function

Seven trials recruiting 357 participants measured hand function, with data available for 86% (n = 307) (*Figure 3*). Five RTT trials recruited 324 participants,[50,52,68–70] with data available for 87% (n = 281) of participants. Two CIMT trials[83,84] recruited 33 participants, with data available for 79% (n = 26). The pooled effect for RFTP on hand function across all trials was small, and marginally statistically non-significant (SMD 0.19, 95% CI –0.03, 0.42).

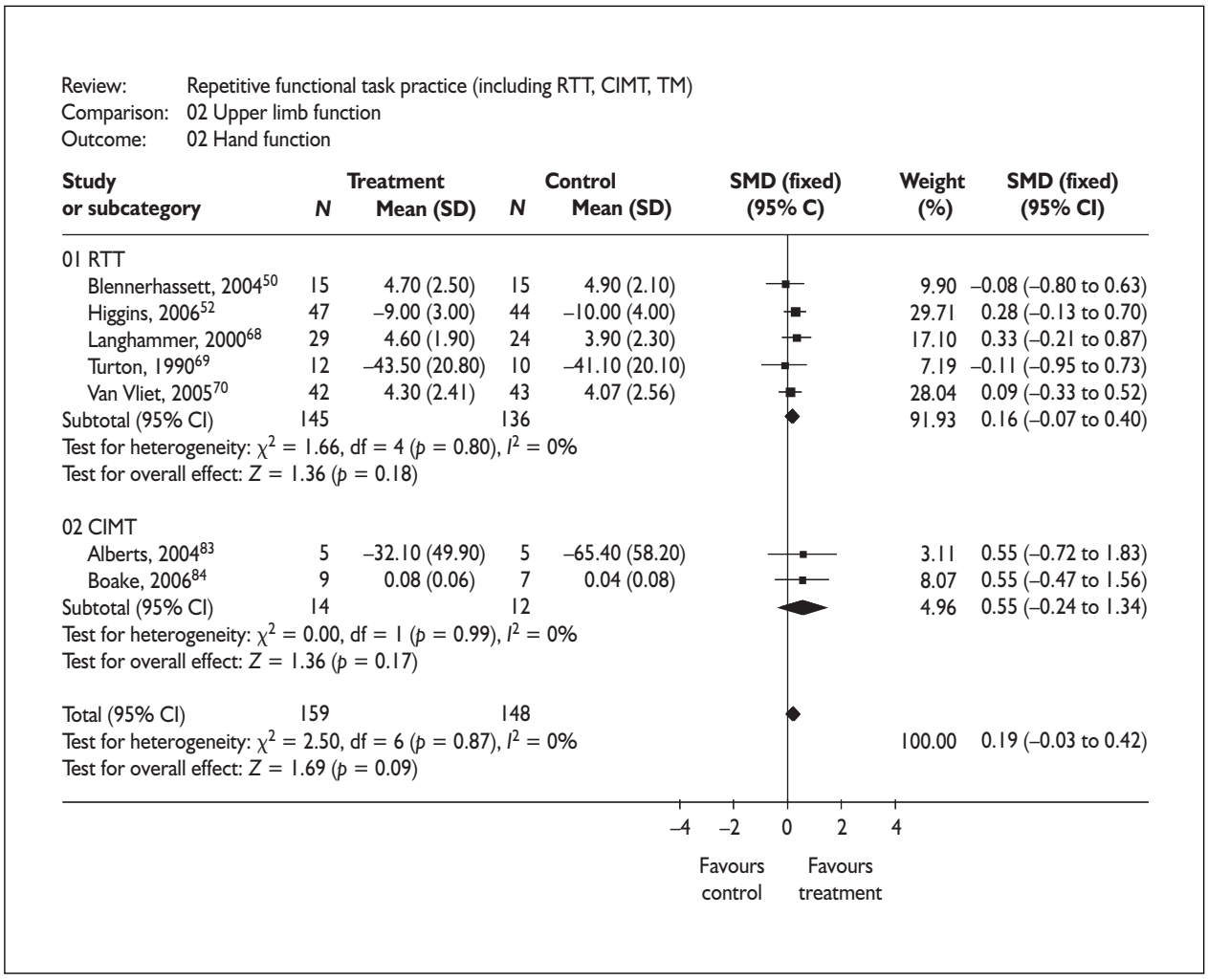

FIGURE 3 *Hand function*

Sitting balance/reach

Five trials (all RTT) recruiting 256 participants measured sitting balance or functional reach (*Figure 4*).[66,68,70,76,77] Data were available for 82% (n = 210). There was some heterogeneity of treatment effects (I^2 = 32%), although not sufficient to merit the use of a random-effects approach.

The impact on sitting balance/reach showed a small effect size that was not statistically significant (SMD 0.23, 95% CI –0.05 to 0.50).

Upper limb function: follow-up

Under 6 months post-therapy

One CIMT trial measuring hand function[84] and two RTT trials measuring sitting balance,[76,77] recruiting 78 participants in total, measured for retention effects between post-therapy and under 6 months post-therapy (*Figure 5*). Data were available for 86% (n = 67) and effects across trials were homogeneous (I^2 = 0%). There was a moderate effect size, which was statistically significant (SMD 0.55, 95% CI 0.06 to 1.04).

Between 6 and 12 months post-therapy

Four trials[50,68,70,71] (all RTT) recruiting 254 participants measured arm function for retention effects between 6 and 12 months post-therapy (*Figure 5*). Data were available for 76% (n = 195). Effects across trials were homogeneous (I^2 = 0%). Results showed no effect of treatment (SMD –0.02, 95% CI –0.31 to 0.26).

Subgroup analysis: upper limb function

Subgroup analyses for upper limb interventions are based on trials providing measures of arm function. Trials that only provide measures of hand function[84] or sitting balance/reach[66,76,77] are therefore excluded. Subgroup analyses are presented for type, amount and timing of intervention, and to consider the impact of

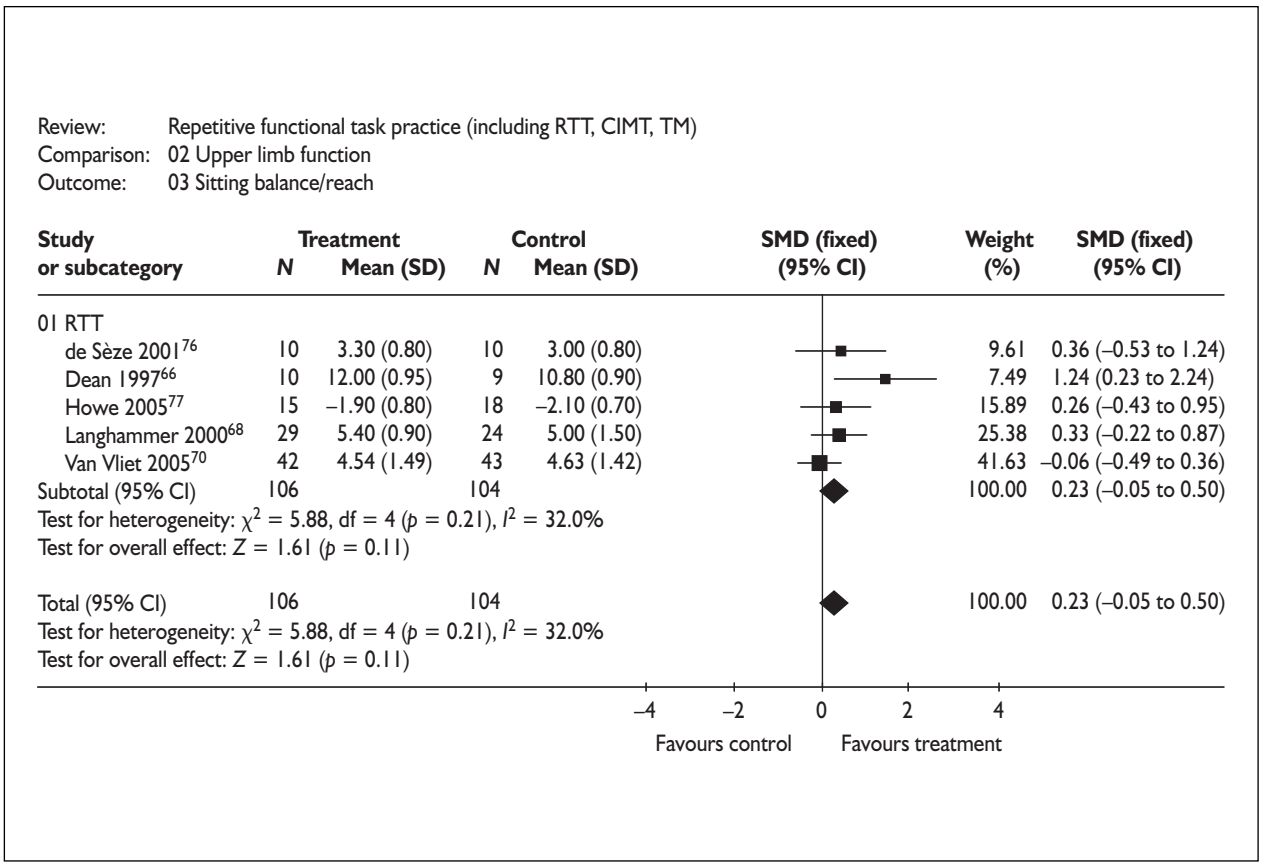

FIGURE 4 *Sitting balance/reach*

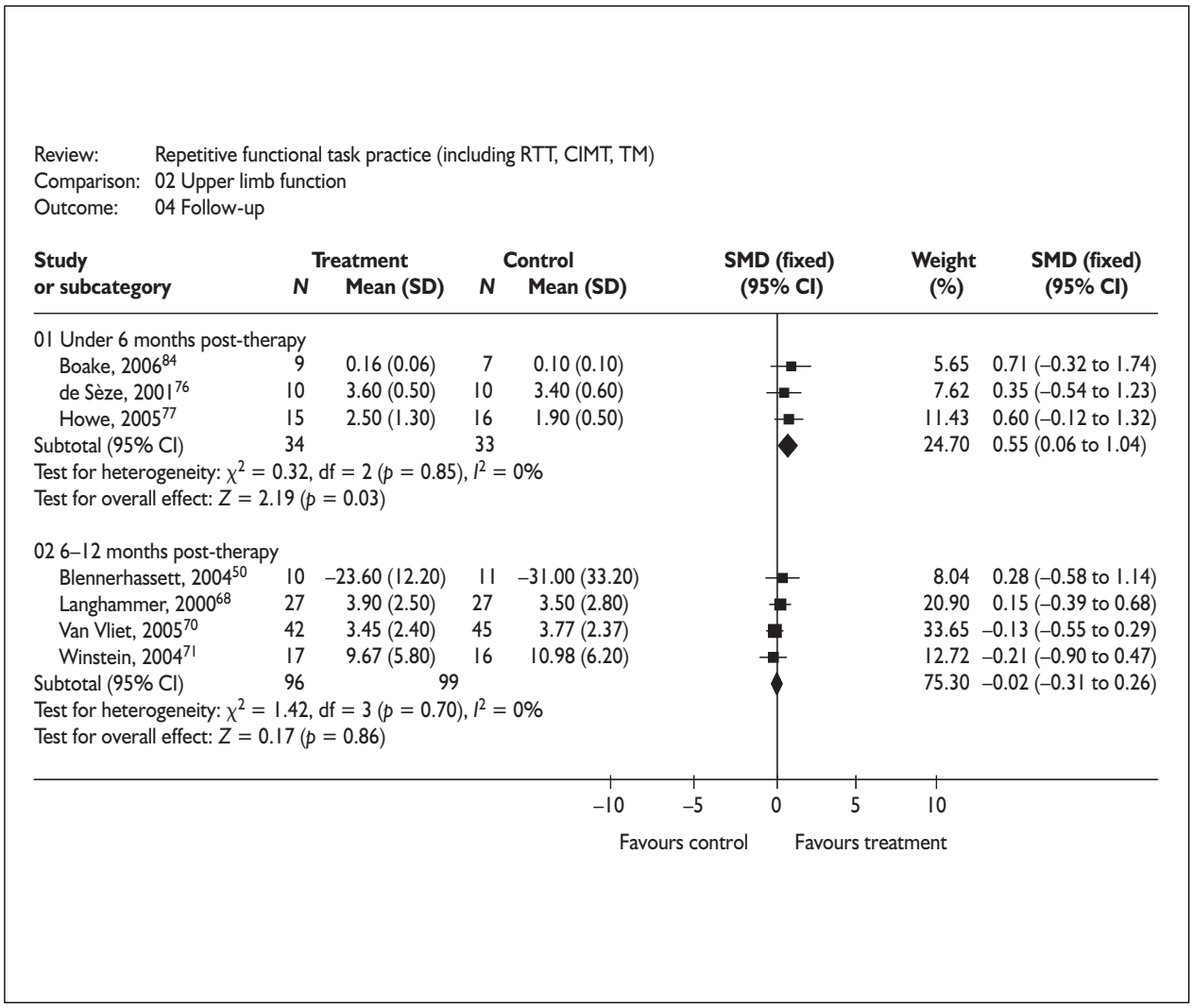

FIGURE 5 *Arm function: follow-up at 0–6 months and more than 6 months post-therapy*

specific trial features on the results. The classification of trials for each subgroup analysis is given in Appendix 6.

Type of intervention

Subgroups compared the treatment effects for eight RTT trials recruiting 467 participants, and seven CIMT trials recruiting 76 participants (*Figure 6*). The impact of RTT on upper limb function post-treatment just failed to reach statistical significance (SMD 0.17, 95% CI –0.03 to 0.36). The impact of CIMT on arm function showed some heterogeneity (I^2 = 41%), but not sufficient to necessitate the use of a random-effects approach. There was a large and statistically significant effect size (SMD 0.77, 95% CI 0.26 to 1.29). The difference between effect sizes for CIMT and RTT was statistically significant (p = 0.03).

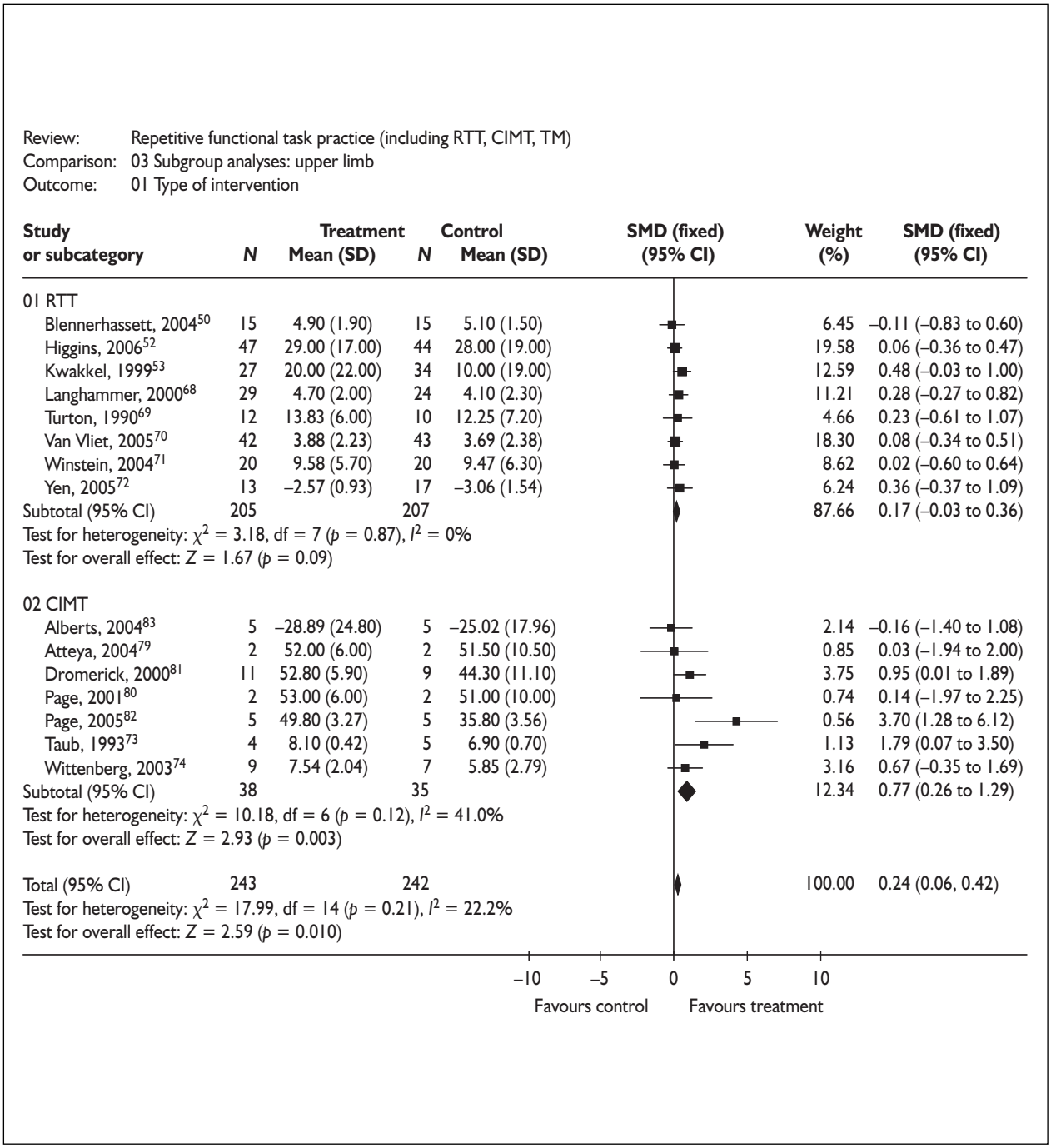

FIGURE 6 *Subgroup analysis: type of intervention – upper limb trials*

Dosage of task practice

Seven trials (five RTT, two CIMT) with 399 participants provided up to 20 hours' task practice. Eight trials (three RTT, five CIMT) with 163 participants provided more than 20 hours' task practice (*Figure 7*). There was substantial heterogeneity ($I^2 = 50.8\%$) in the trials providing up to 20 hours' task practice, Using a random-effects model to combine the effects from individual trials, while the estimated effect was greater for the subgroup with more than 20 hours of task practice, the difference between subgroups failed to reach statistical significance ($p = 0.18$).

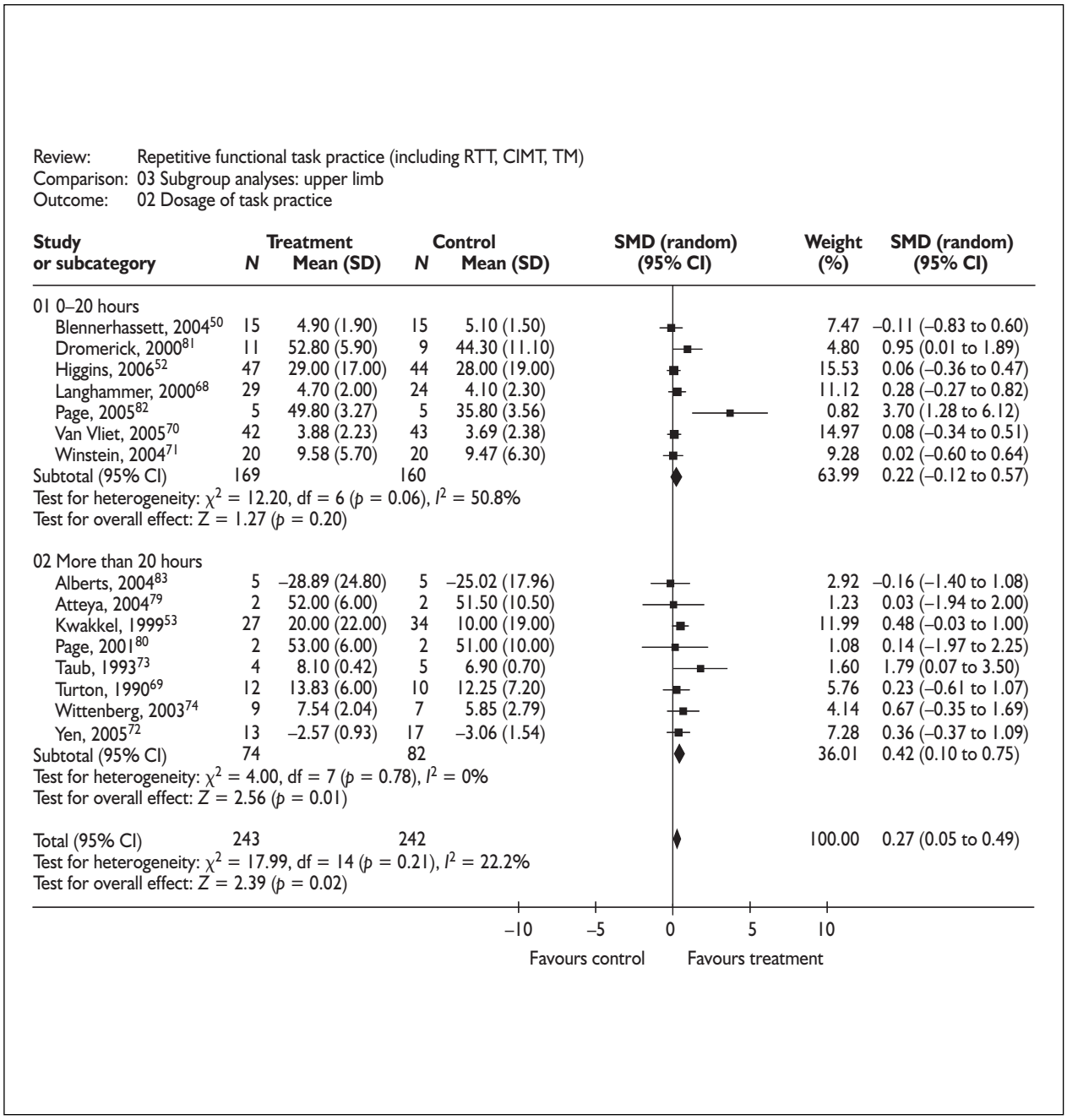

FIGURE 7 *Subgroup analysis: dosage of task practice – upper limb trials*

Time since stroke

Nine trials (four RTT, five CIMT) with 364 participants measured arm function in participants up to 6 months post-stroke. Six trials (four RTT, two CIMT) with 189 participants included participants more than 6 months post-stroke (*Figure 8*). There was some heterogeneity in trials 0–6 months post-stroke (I^2 = 34.8%), but not sufficient to warrant using a random-effects model. The difference between subgroups did not reach statistical significance (p = 0.65).

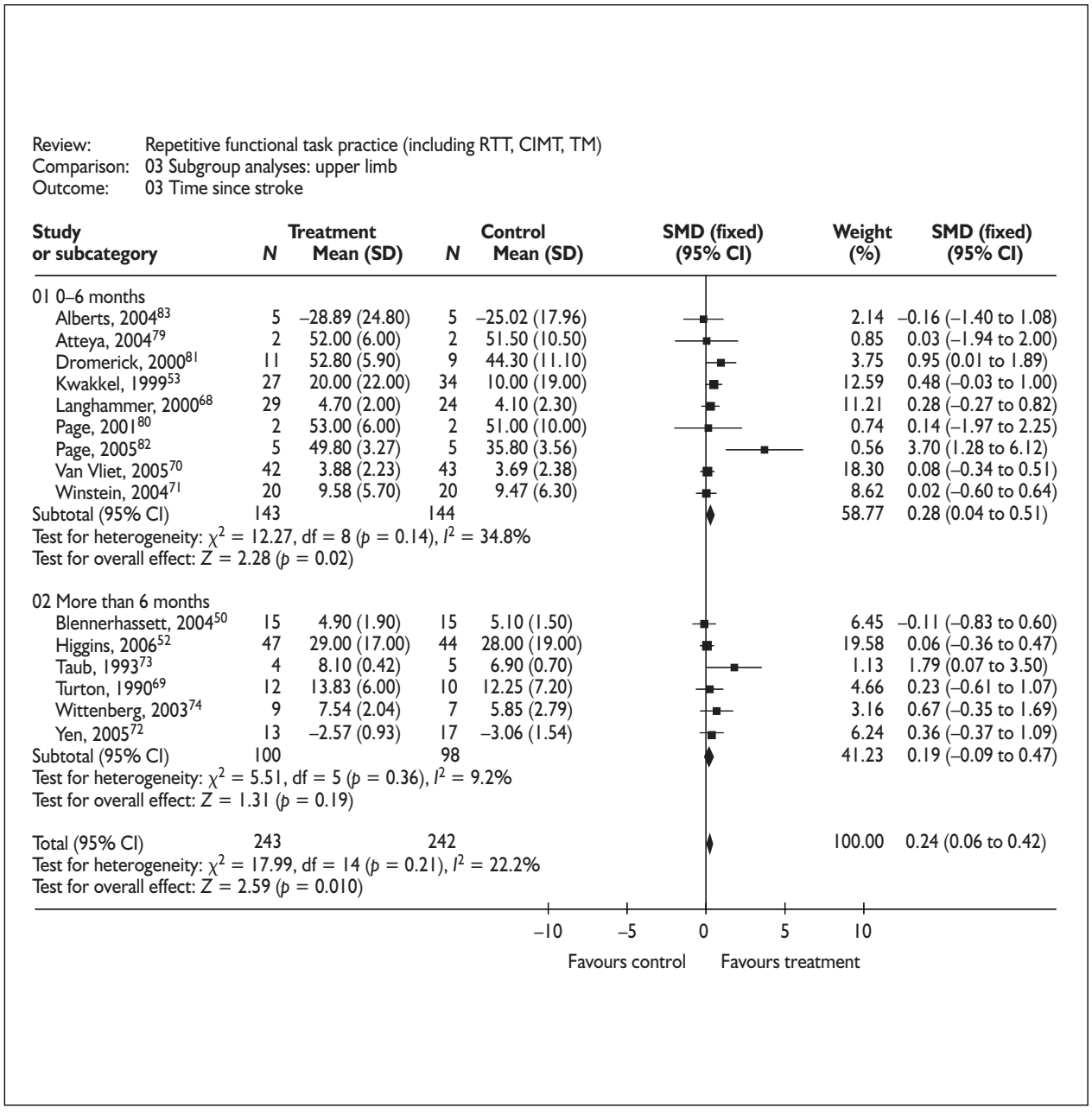

FIGURE 8 *Subgroup analysis: time since stroke – upper limb trials*

Allocation concealment

Trials were grouped according to whether allocation concealment was judged to be adequate (five RTT trials) or inadequate/unclear (ten trials: three RTT, seven CIMT) (*Figure 9*). There was some heterogeneity observed in the 'inadequate/unclear' subgroup (I^2 = 27.3%). The difference between subgroups was statistically significant (p = 0.08), indicating that the effect of RFTP was greater for trials where allocation concealment was either inadequate or unclear.

Review: Repetitive functional task practice (including RTT, CIMT, TM)
Comparison: 03 Subgroup analyses: upper limb
Outcome: 04 Allocation concealment

Study or subcategory	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	SMD (fixed) (95% CI)	Weight (%)	SMD (fixed) (95% CI)
01 Adequate							
Blennerhassett, 2004[50]	15	4.90 (1.90)	15	5.10 (1.50)		6.45	–0.11 (–0.83 to 0.60)
Higgins, 2006[52]	47	29.00 (17.00)	44	28.00 (19.00)		19.58	0.06 (–0.36 to 0.47)
Kwakkel, 1999[53]	27	20.00 (22.00)	34	10.00 (19.00)		12.59	0.48 (–0.03 to 1.00)
Van Vliet, 2005[70]	42	3.88 (2.23)	43	3.69 (2.38)		18.30	0.08 (–0.34 to 0.51)
Winstein, 2004[71]	20	9.58 (5.70)	20	9.47 (6.30)		8.62	0.02 (–0.60 to 0.64)
Subtotal (95% CI)	151		156			65.55	0.12 (–0.10 to 0.35)
Test for heterogeneity: χ^2 = 2.58, df = 4 (p = 0.63), I^2 = 0%							
Test for overall effect: Z = 1.08 (p = 0.28)							
02 Inadequate/unclear							
Alberts, 2004[83]	5	–28.89 (24.80)	5	–25.02 (17.96)		2.14	–0.16 (–1.40 to 1.08)
Atteya, 2004[79]	2	52.00 (6.00)	2	51.50 (10.50)		0.85	0.03 (–1.94 to 2.00)
Dromerick, 2000[81]	11	52.80 (5.90)	9	44.30 (11.10)		3.75	0.95 (0.01 to 1.89)
Langhammer, 2000[68]	29	4.70 (2.00)	24	4.10 (2.30)		11.21	0.28 (–0.27 to 0.82)
Page, 2001[80]	2	53.00 (6.00)	2	51.00 (10.00)		0.74	0.14 (–1.97 to 2.25)
Page, 2005[82]	5	49.80 (3.27)	5	35.80 (3.56)		0.56	3.70 (1.28 to 6.12)
Taub, 1993[73]	4	8.10 (0.42)	5	6.90 (0.70)		1.13	1.79 (0.07 to 3.50)
Turton, 1990[69]	12	13.83 (6.00)	10	12.25 (7.20)		4.66	0.23 (–0.61 to 1.07)
Wittenberg, 2003[74]	9	7.54 (2.04)	7	5.85 (2.79)		3.16	0.67 (–0.35 to 1.69)
Yen, 2005[72]	13	–2.57 (0.93)	17	–3.06 (1.54)		6.24	0.36 (–0.37 to 1.09)
Subtotal (95% CI)	92		86			34.45	0.46 (0.15 to 0.77)
Test for heterogeneity: χ^2 = 12.37, df = 9 (p = 0.19), I^2 = 27.3%							
Test for overall effect: Z = 2.93 (p = 0.003)							
Total (95% CI)	243		242			100.00	0.24 (0.06 to 0.42)
Test for heterogeneity: χ^2 = 17.99, df = 14 (p = 0.21), I^2 = 22.2%							
Test for overall effect: Z = 2.59 (p = 0.010)							

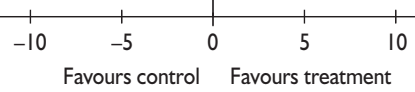

FIGURE 9 *Subgroup analysis: allocation concealment – upper limb trials*

Post hoc analysis: type of comparison group

Seven trials (five RTT, two CIMT) were classified as usual care or alternative treatment, and eight trials (three RTT, five CIMT) were classified as attention-control or no treatment (*Figure 10*), with some heterogeneity observed in trials with usual care/alternative treatment controls (I^2 =46.1%). There was no statistically significant difference between subgroups (p = 0.84).

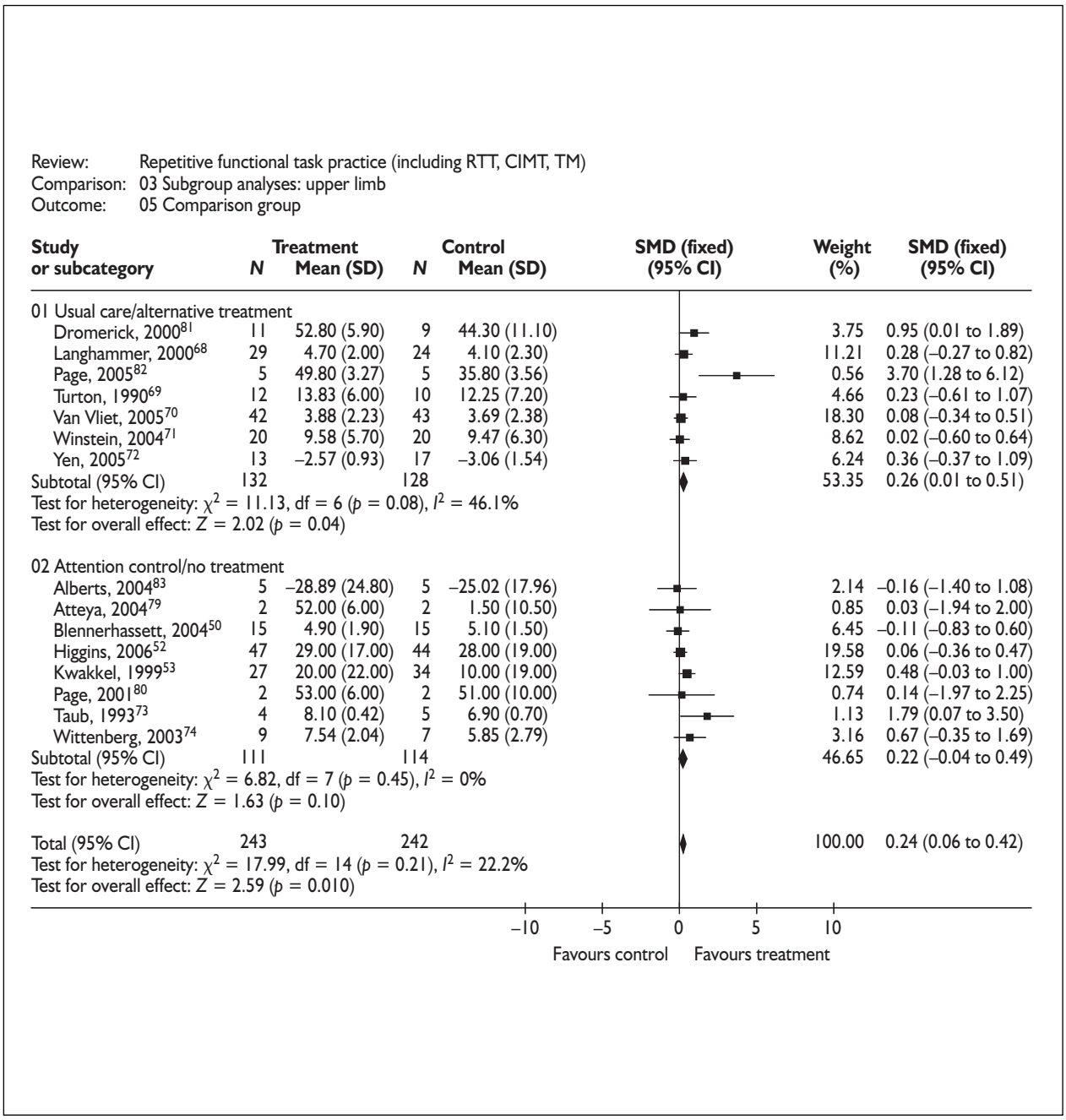

FIGURE 10 *Subgroup analysis: type of comparison group – upper limb trials*

Post hoc analysis: equivalence of therapy time

One subgroup comprised seven trials (two RTT, five CIMT) which gave, additional therapy time to the experimental group, and the other contained eight trials (six RTT, two CIMT) where therapy time for experimental and control groups was equivalent (*Figure 11*). There was some heterogeneity of treatment effects in each subgroup, but not sufficient to merit the use of a random-effects meta-analysis. There was no significant difference between the two subgroups ($p = 0.92$).

Post hoc analysis: trial size

The median number of participants in the trials was 23. A post hoc analysis was therefore undertaken for trials with under 25 participants versus those with 25 or more participants (*Figure 12*). Some heterogeneity was observed in trials with under 25 participants ($I^2 = 38.2\%$), but not enough to warrant the use of a random-effects model. The difference between effect sizes in the small trial sub-group (<25 participants) and the larger trial sub-group (≥25 participants) was statistically significant ($p = 0.06$). As the effect in the small trial subgroup (SMD 0.62, 95% CI 0.18 to 1.07) is significantly larger than in the larger trial subgroup (SMD 0.16, 95% CI –0.04 to 0.36), this may indicate some degree of reporting bias in upper limb trials. This is supported by the funnel plot in *Figure 13*, which has some apparent asymmetry indicating a potential lack of reporting of small negative trials with large standard errors.

Review: Repetitive functional task practice (including RTT, CIMT, TM)
Comparison: 03 Subgroup analyses: upper limb
Outcome: 06 Equivalence of therapy time

Study or subcategory	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	SMD (fixed) (95% CI)	Weight (%)	SMD (fixed) (95% CI)
01 Additional therapy time							
Alberts, 2004[83]	5	–28.89 (24.80)	5	–25.02 (17.96)		2.14	–0.16 (–1.40 to 1.08)
Atteya, 2004[79]	2	52.00 (6.00)	2	51.50 (10.50)		0.85	0.03 (–1.94 to 2.00)
Page, 2001[80]	2	53.00 (6.00)	2	51.00 (10.00)		0.74	0.14 (–1.97 to 2.25)
Page, 2005[82]	5	49.80 (3.27)	5	35.80 (3.56)		0.56	3.70 (1.28 to 6.12)
Turton, 1990[69]	12	13.83 (6.00)	10	12.25 (7.20)		4.66	0.23 (–0.61 to 1.07)
Winstein, 2004[71]	20	9.58 (5.70)	20	9.47 (6.30)		8.62	0.02 (–0.60 to 0.64)
Wittenberg, 2003[74]	9	7.54 (2.04)	7	5.85 (2.79)		3.16	0.67 (–0.35 to 1.69)
Subtotal (95% CI)	55		51			20.76	0.25 (–0.15 to 0.65)
Test for heterogeneity: $\chi^2 = 9.44$, df = 6 ($p = 0.15$), $I^2 = 36.5\%$							
Test for overall effect: $Z = 1.23$ ($p = 0.22$)							
02 Equivalent therapy time							
Blennerhassett, 2004[50]	15	4.90 (1.90)	15	5.10 (1.50)		6.45	–0.11 (–0.83 to 0.60)
Dromerick, 2000[81]	11	52.80 (5.90)	9	44.30 (11.10)		3.75	0.95 (0.01 to 1.89)
Higgins, 2006[52]	47	29.00 (17.00)	44	28.00 (19.00)		19.58	0.06 (–0.36 to 0.47)
Kwakkel, 1999[53]	27	20.00 (22.00)	34	10.00 (19.00)		12.59	0.48 (–0.03 to 1.00)
Langhammer, 2000[68]	29	4.70 (2.00)	24	4.10 (2.30)		11.21	0.28 (–0.27 to 0.82)
Taub, 1993[73]	4	8.10 (0.42)	5	6.90 (0.70)		1.13	1.79 (0.07 to 3.50)
Van Vliet, 2005[70]	42	3.88 (2.23)	43	3.69 (2.38)		18.30	0.08 (–0.34 to 0.51)
Yen, 2005[72]	13	–2.57 (0.93)	17	–3.06 (1.54)		6.24	0.36 (–0.37 to 1.09)
Subtotal (95% CI)	188		191			79.24	0.24 (0.03 to 0.44)
Test for heterogeneity: $\chi^2 = 8.54$, df = 7 ($p = 0.29$), $I^2 = 18.0\%$							
Test for overall effect: $Z = 2.28$ ($p = 0.02$)							
Total (95% CI)	243		242			100.00	0.24 (0.06 to 0.42)
Test for heterogeneity: $\chi^2 = 17.99$, df = 14 ($p = 0.21$), $I^2 = 22.2\%$							
Test for overall effect: $Z = 2.59$ ($p = 0.010$)							

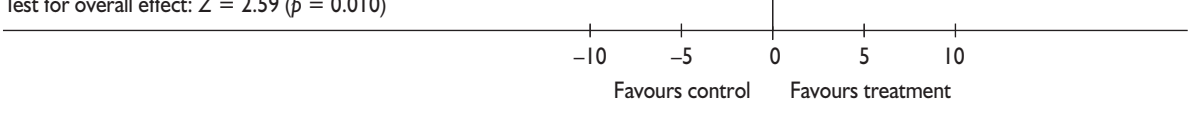

FIGURE 11 *Subgroup analysis: equivalence of therapy time – upper limb trials*

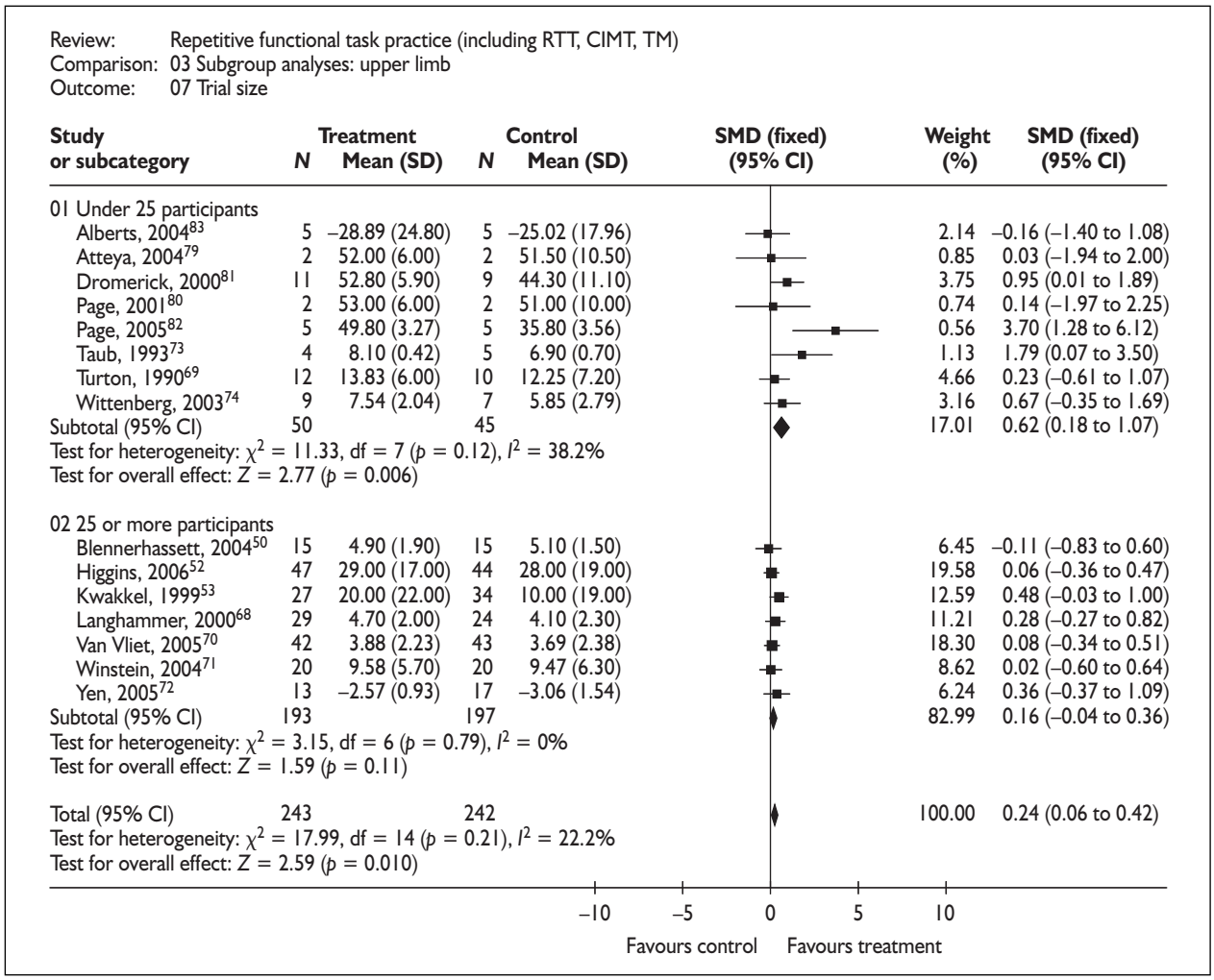

FIGURE 12 *Subgroup analysis: trial size – upper limb trials*

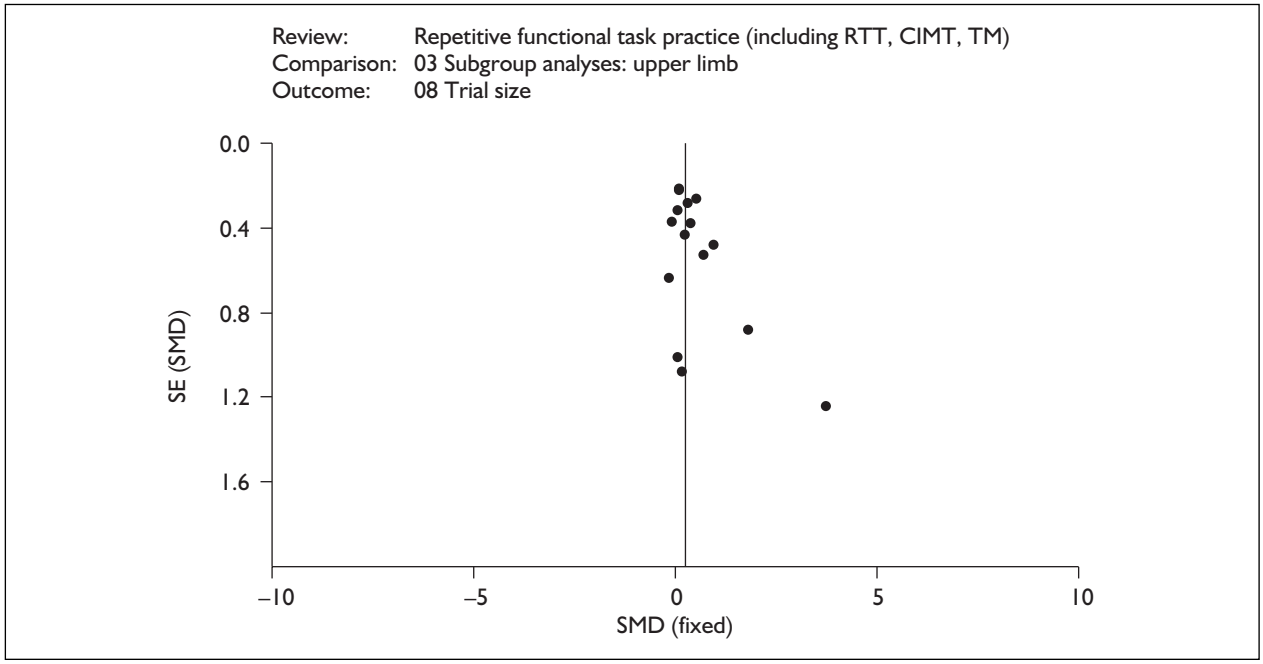

FIGURE 13 *Funnel plot of precision versus effect size – upper limb trials*

Lower limb function: post-therapy

Results are presented for walking distance, walking speed, functional ambulation, sit-to-stand, lower limb functional measures and standing balance/reach. All results are post-therapy, except for Langhammer and Stanghelle,[68] which is 3 months post-stroke, and Van Vliet and colleagues,[70] which is 3 months post-baseline.

Walking distance

Seven trials included a measure of walking distance (*Figure 14*). All results are change from baseline scores except for Macko and colleagues,[88] and are expressed as metres walked in 6 minutes. The degree of heterogeneity (I^2 = 49.1%) in the effect sizes of the seven trials was very close to the study criterion for 'substantial' heterogeneity, so a random-effects model was used. Three RTT trials[50,51,67] recruiting 133 participants measured walking distance, with outcome data available for 98% (n = 130) of participants. Four TM trials[86–89] recruiting 155 participants measured walking distance, with outcome data available for 96% (n = 149).

For RFTP overall, pooled results showed a statistically significant difference (WMD 50.05 m, 95% CI 29.65 to 70.44 m). Owing to the lack of homogeneity of standard deviations, resulting in a substantial impact on the weighting of several trials, results were reanalysed using the SMD and a random-effects model. The result showed a large effect size, which remained highly statistically significant (SMD 0.98, 95% CI 0.58 to 1.39, excluding Macko and colleagues,[88] which did not provide 'change-from-baseline' data). To improve comparability with effect sizes for other outcomes and for use in the economic analysis, the SMD based on the post-treatment data from the seven trials was also computed (SMD 0.45, 95% CI 0.20 to 0.70; figure not shown). As expected, the SMD based on the post-treatment data is considerably smaller than that based on the change-from-baseline data, primarily owing to its poorer sensitivity to change.

Walking speed

Ten trials included a measure of walking speed (*Figure 15*). Results were converted into metres per

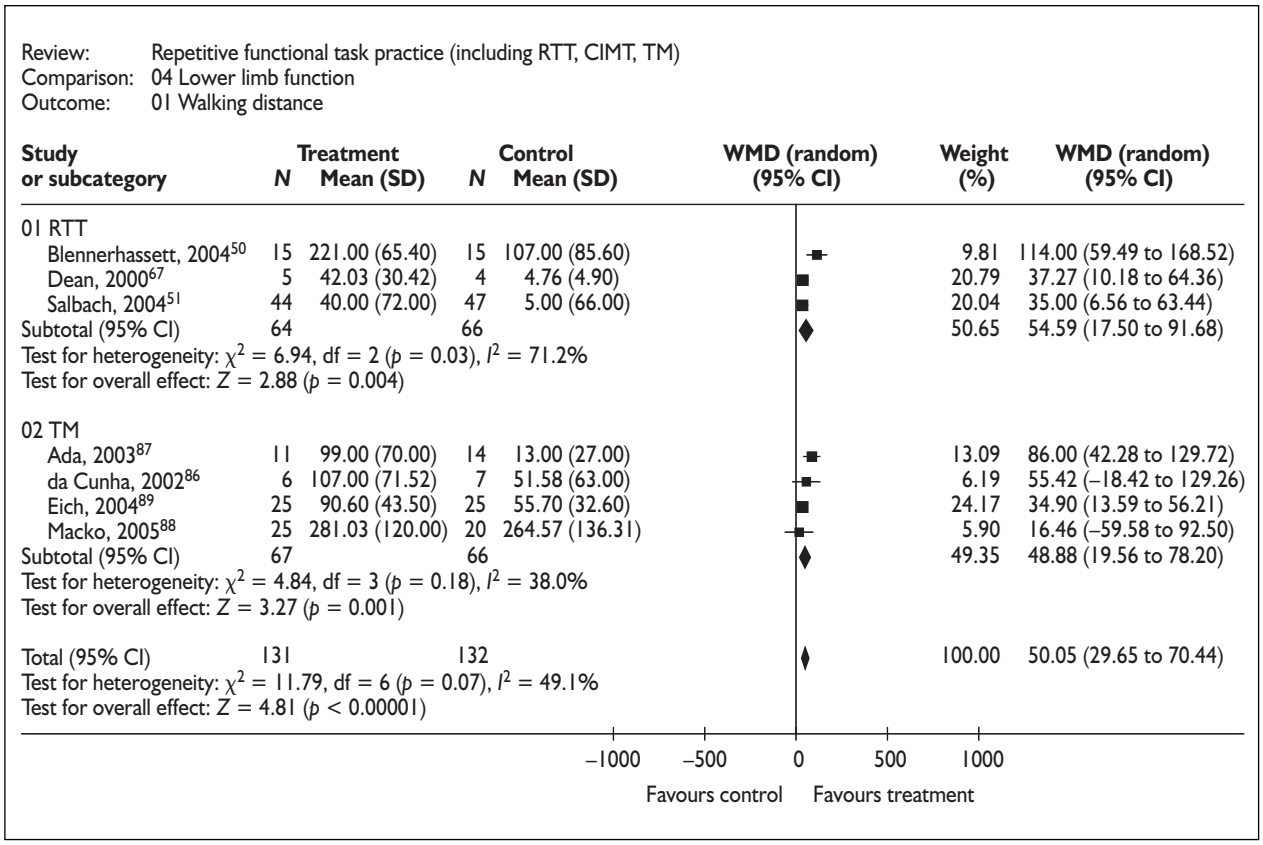

FIGURE 14 *Walking distance*

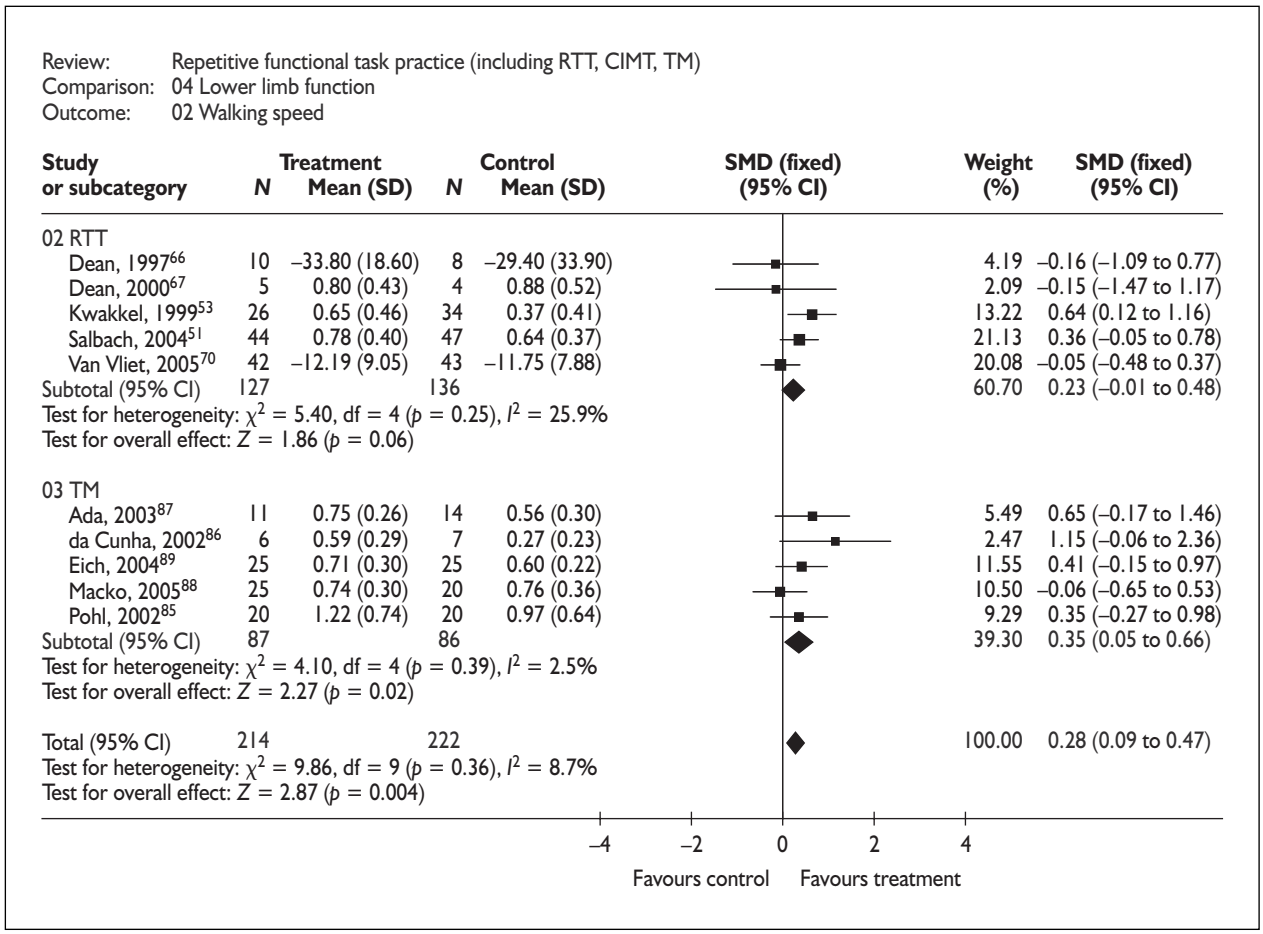

FIGURE 15 *Walking speed*

second, with the exception of Dean and Shepherd[66] and Van Vliet and colleagues,[70] who presented statistics for the number of seconds to walk 10 m and 6 m, respectively. There was some heterogeneity of treatment effects ($I^2 = 8.7\%$), although not sufficient to merit the use of a random-effects approach. Five RTT trials recruited 311 participants,[51,53,66,67,70] with outcome data available for 85% ($n = 263$) of participants. Six TM trials recruited 229 participants.[63,85–89] One TM trial with 30 participants provided data unsuitable for pooling, with data for mean distance walked but no standard deviations.[63] Of the five remaining trials with 199 participants, outcome data were available for 87% ($n = 173$) of participants.

Overall, pooled results for the impact of RFTP on walking speed showed a small effect size, which was statistically significant (SMD 0.28, 95% CI 0.09 to 0.47). A subgroup analysis was undertaken for walking speed measured over short (5 or 6 m) or medium (10 m) distances, with no significant difference found ($p = 0.57$).

Functional ambulation

For RFTP overall, seven trials recruiting 368 participants measured functional ambulation, with outcome data available for 79% ($n = 291$) (*Figure 16*). Effects across trials were homogeneous ($I^2 = 0\%$). Five RTT trials[53,68,70,76,78] recruited 295 participants, with outcome data available for 81% ($n = 238$). Two TM trials[85,86] recruited 59 participants, with outcome data available for 89% ($n = 53$).

Pooling the results from seven trials showed RFTP to have a statistically significant but small effect on functional ambulation measures (SMD 0.28, 95% CI 0.05 to 0.51), with no significant difference in effects between RTT and TM ($p = 0.66$).

Sit-to-stand

Seven trials (all RTT) recruiting 397 participants included a measure of sit-to-stand,[50,51,65,67,68,70,77] with outcome data available for 87% ($n = 346$) (*Figure 17*).

Effects across trials were homogeneous ($I^2 = 0\%$), showing a small to moderate effect size, which was

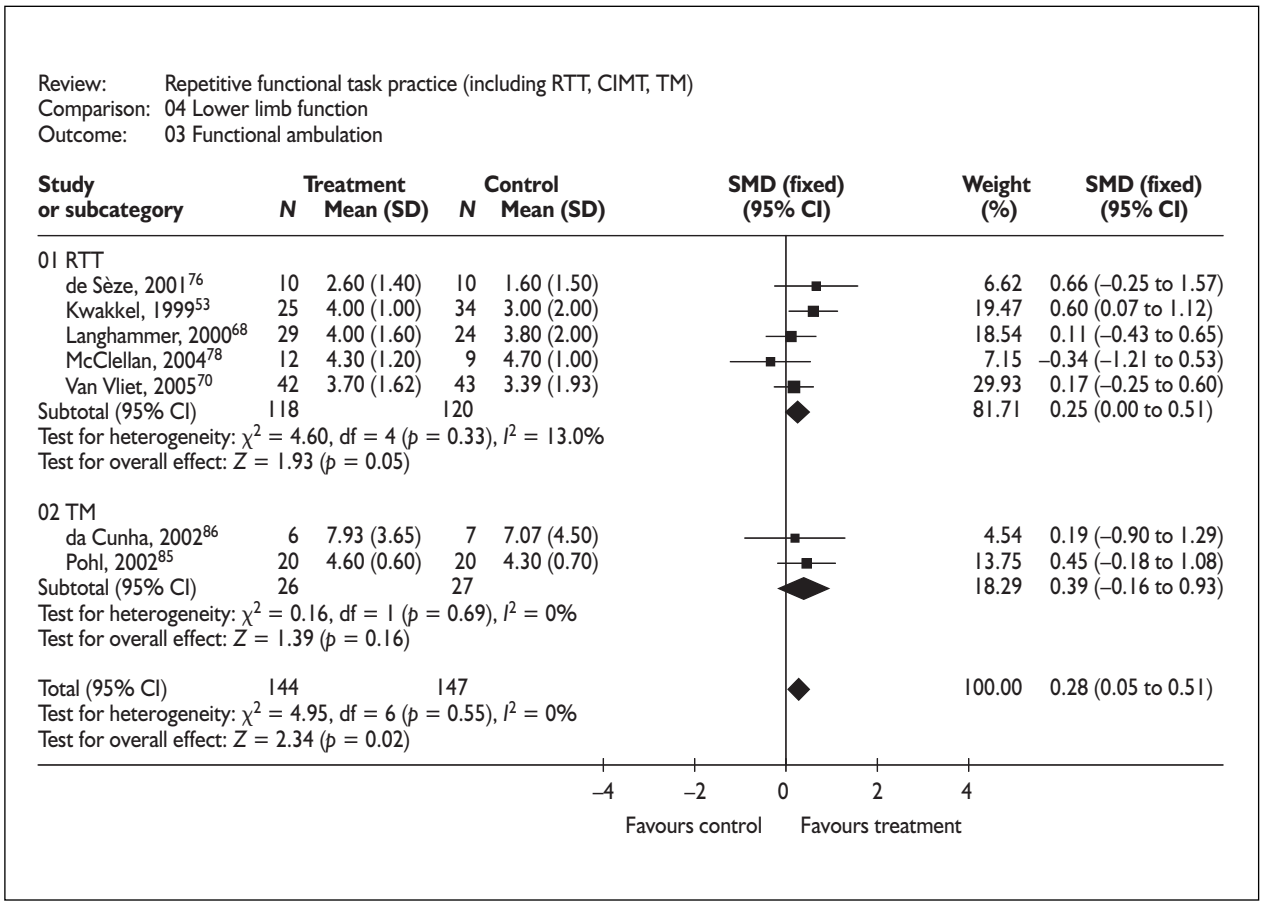

FIGURE 16 *Functional ambulation*

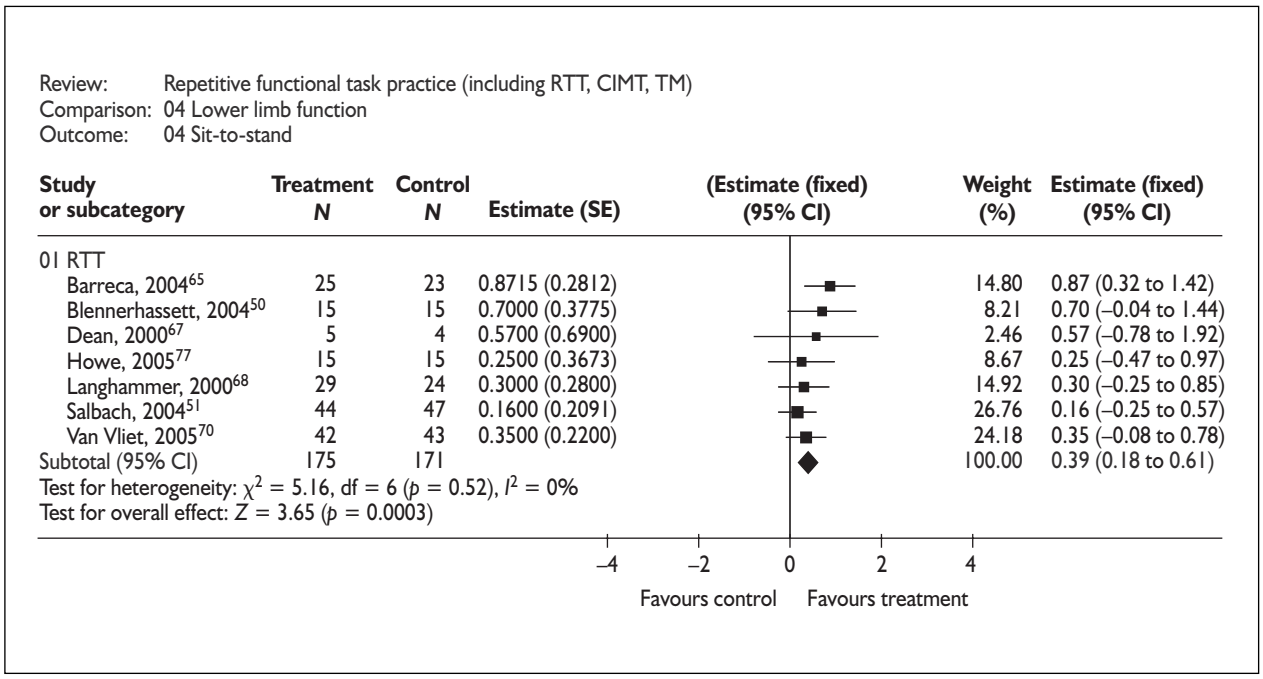

FIGURE 17 *Sit-to-stand*

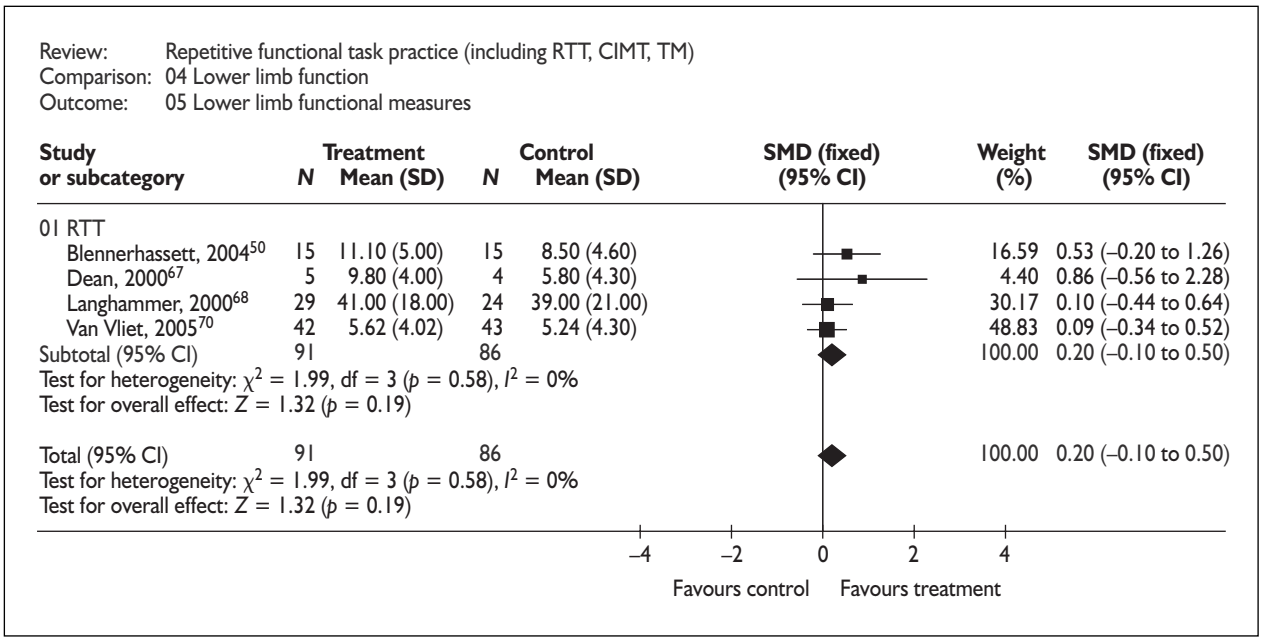

FIGURE 18 *Lower limb functional measures*

statistically significant (standardised effect size 0.39, 95% CI 0.18 to 0.61).

Lower limb functional measures

Four trials (all RTT) recruiting 223 participants included a measure of lower limb function,[50,67,68,70] with outcome data available for 79% (n = 177) (*Figure 18*). Effects across trials were homogeneous (I^2 = 0%).

Results overall showed a small effect size, which was not statistically significant (SMD 0.20, 95% CI –0.10 to 0.50).

Standing balance and reach

Three trials (all RTT) recruiting 137 participants measured standing balance or functional reach,[51,76,78] with outcome data available for 96% (n = 132) (*Figure 19*).

Effects across trials were homogeneous (I^2 = 0%), showing a small effect size, which was not statistically significant (SMD 0.29, 95% CI –0.06 to 0.63).

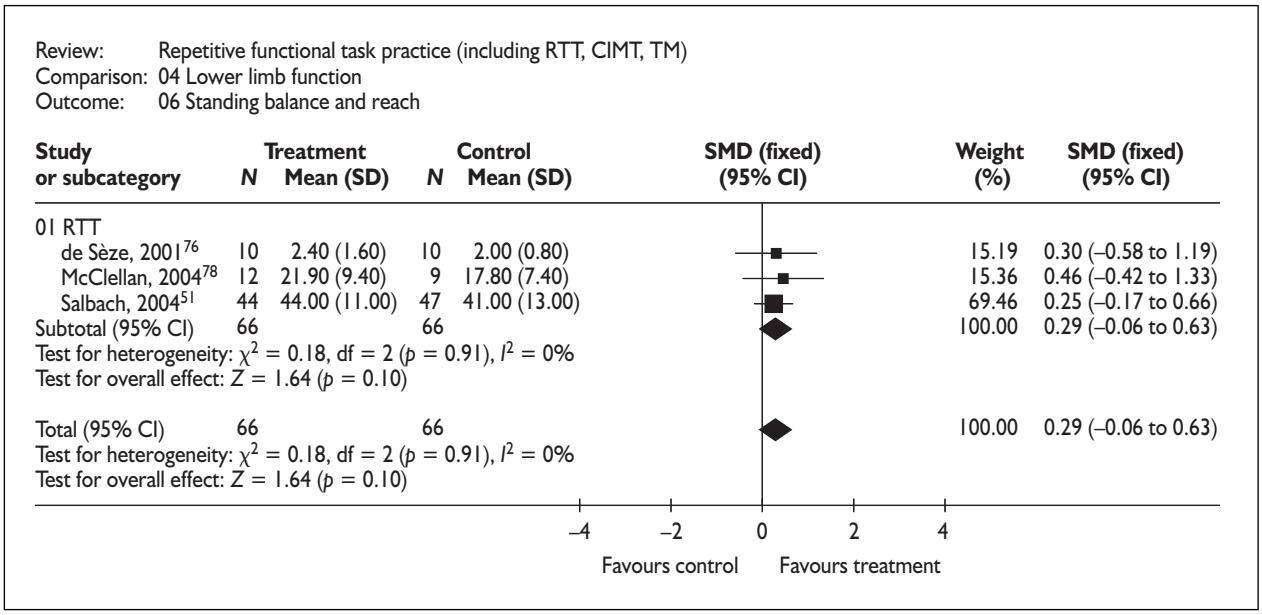

FIGURE 19 *Standing balance/reach*

Lower limb: follow-up

Under 6 months post-therapy

Six trials (four RTT[67,76–78] and two TM[87,89]) recruiting 174 participants measured some aspect of lower limb function for retention effects between post-therapy and under 6 months post-therapy (*Figure 20*). Outcome data were available for 90% (n = 155). Effects across trials were homogeneous (I^2 = 0%). Results showed a small to moderate effect size which was statistically significant (SMD 0.37, 95% CI 0.05 to 0.69).

Between 6 and 12 months post-therapy

Three RTT trials recruiting 211 participants measured some aspect of lower limb function for retention effects of RTT interventions between 6 and 12 months post-therapy (*Figure 20*).[50,68,70] Outcome data were available for 80% (n = 170). There was some degree of heterogeneity of treatment effects (I^2 = 49.1%), although not sufficient to merit the use of a random-effects approach (and the small effect size precludes the need to perform a sensitivity analysis on the choice of analytic approach). Results showed no treatment effect (SMD –0.01, 95% CI –0.32 to 0.29).

Subgroup analyses: lower limb function

Subgroup analyses for lower limb interventions are based on trials providing measures of walking function (walking distance, walking speed or functional ambulation rating). Trials that only provide measures of standing balance/reach[76] or sit-to-stand[65,77] are therefore excluded. Subgroup analyses are presented for type, amount and timing of intervention, and to consider the impact of adequacy of allocation concealment

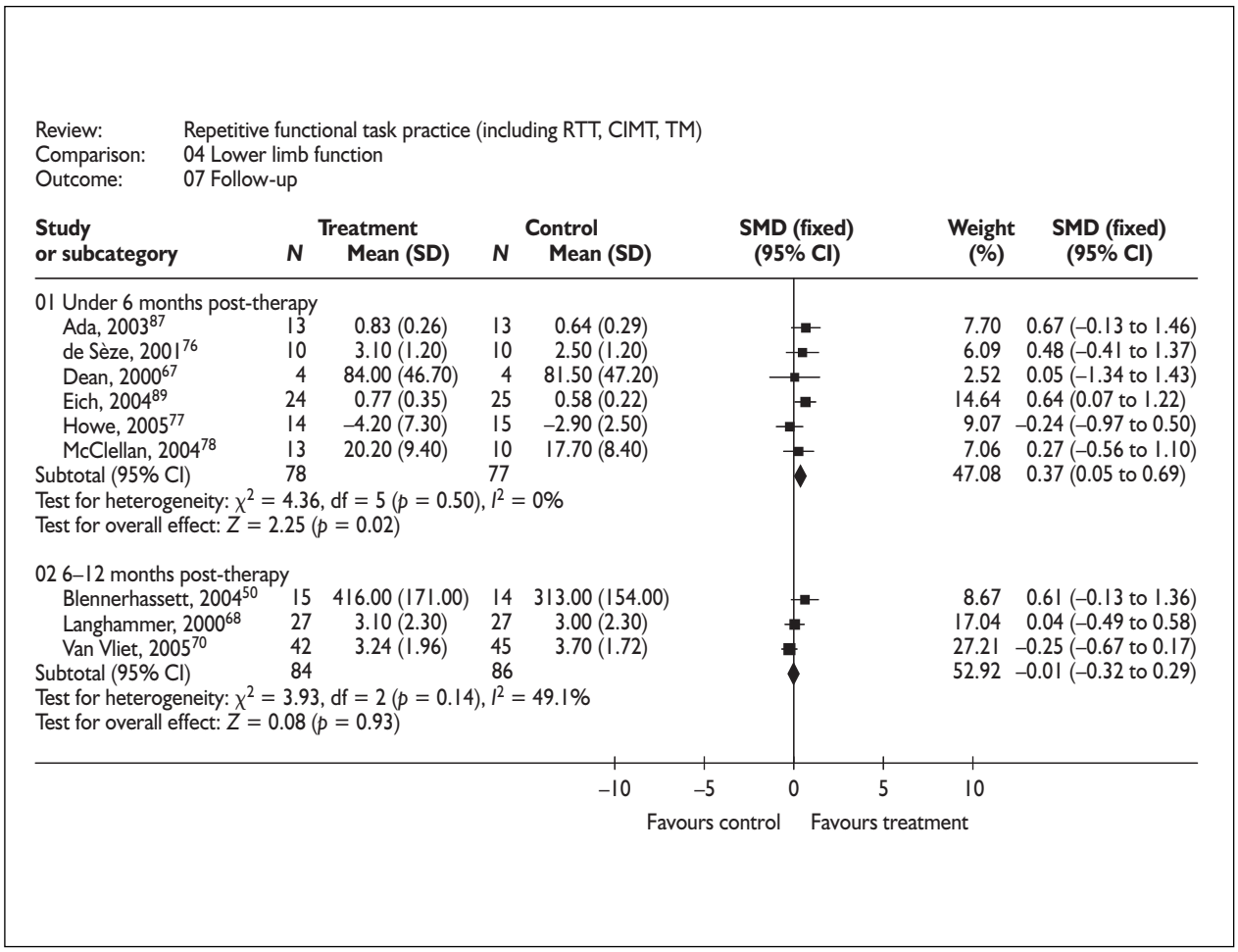

FIGURE 20 *Lower limb follow-up at 0–6 months and more than 6 months post-therapy*

and type of comparison group. There were insufficient trials providing additional therapy time or trials of fewer than 25 participants to undertake subgroup analyses. The classification of trials for each subgroup analysis is given in Appendix 6.

Type of intervention

Twelve trials (seven RTT, five TM) included a measure of walking ability (*Figure 21*). There was some heterogeneity of treatment effects within each subgroup, but not sufficient to merit the use of random-effects analysis.

There was no statistically significant difference between RTT and TM interventions ($p = 0.62$).

Dosage of task practice

Nine trials (five RTT, four TM) provided up to 20 hours' training time and three trials (two RTT, one TM) provided more than 20 hours' training time (*Figure 22*). There was substantial heterogeneity in the more than 20 hours' practice subgroup ($I^2 = 59.4\%$), so a random-effects model was used. There was no statistically significant difference between subgroups ($p = 0.65$).

Time since stroke

Six trials (three RTT, three TM) recruited 0–6 months post-stroke and six trials (four RTT, two TM) recruited more than 6 months post-stroke (*Figure 23*). There was some heterogeneity of treatment effects in both subgroups, but not

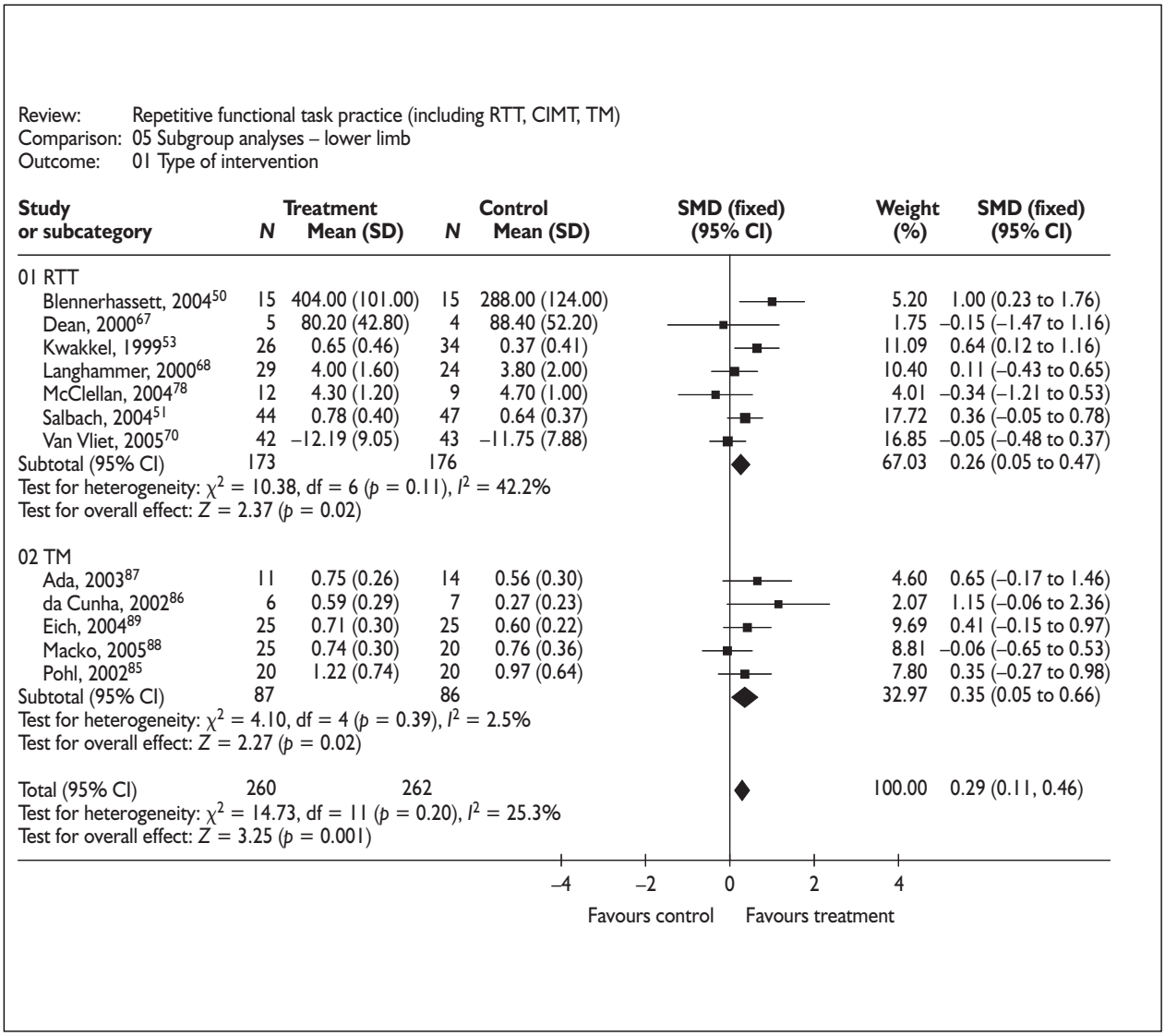

FIGURE 21 *Subgroup analysis: type of intervention – lower limb trials*

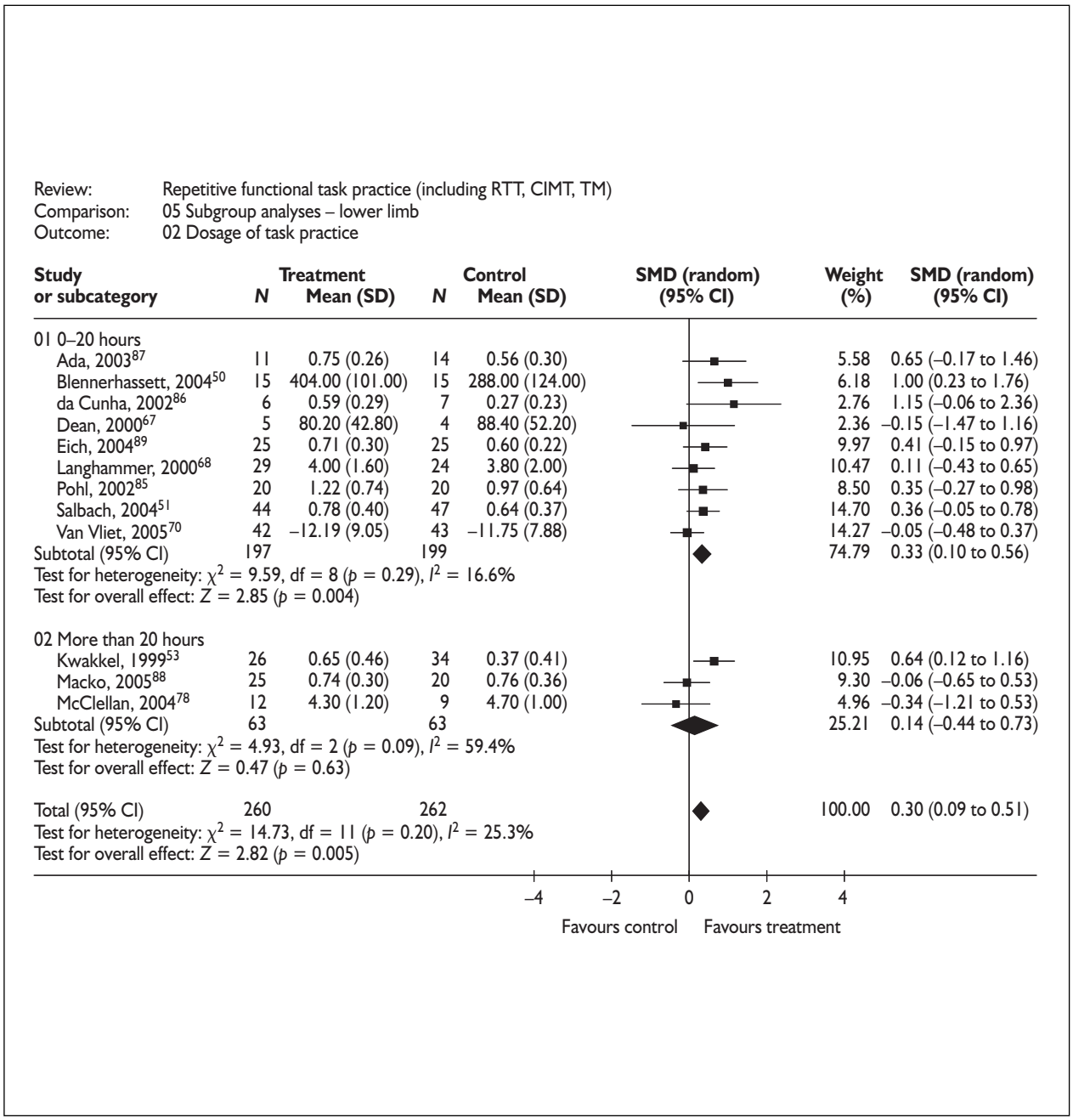

FIGURE 22 *Subgroup analysis: dosage of task practice – lower limb trials*

sufficient to merit a random-effects analysis. There was no significant difference between subgroups (p = 1.0).

Allocation concealment

Trials were grouped according to whether allocation concealment was judged adequate (eight trials: six RTT, two TM) or inadequate/unclear (four trials: one RTT, three TM) (*Figure 24*). There was heterogeneity within each subgroup, but insufficient to warrant using a random-effects meta-analysis. There was no statistically significant difference between subgroups (p = 0.51).

Post hoc analysis: type of comparison group

Six trials (two RTT, four TM) were classified as usual care or alternative treatment, and six trials (five RTT, one TM) as attention-control or no treatment (*Figure 25*). There was some

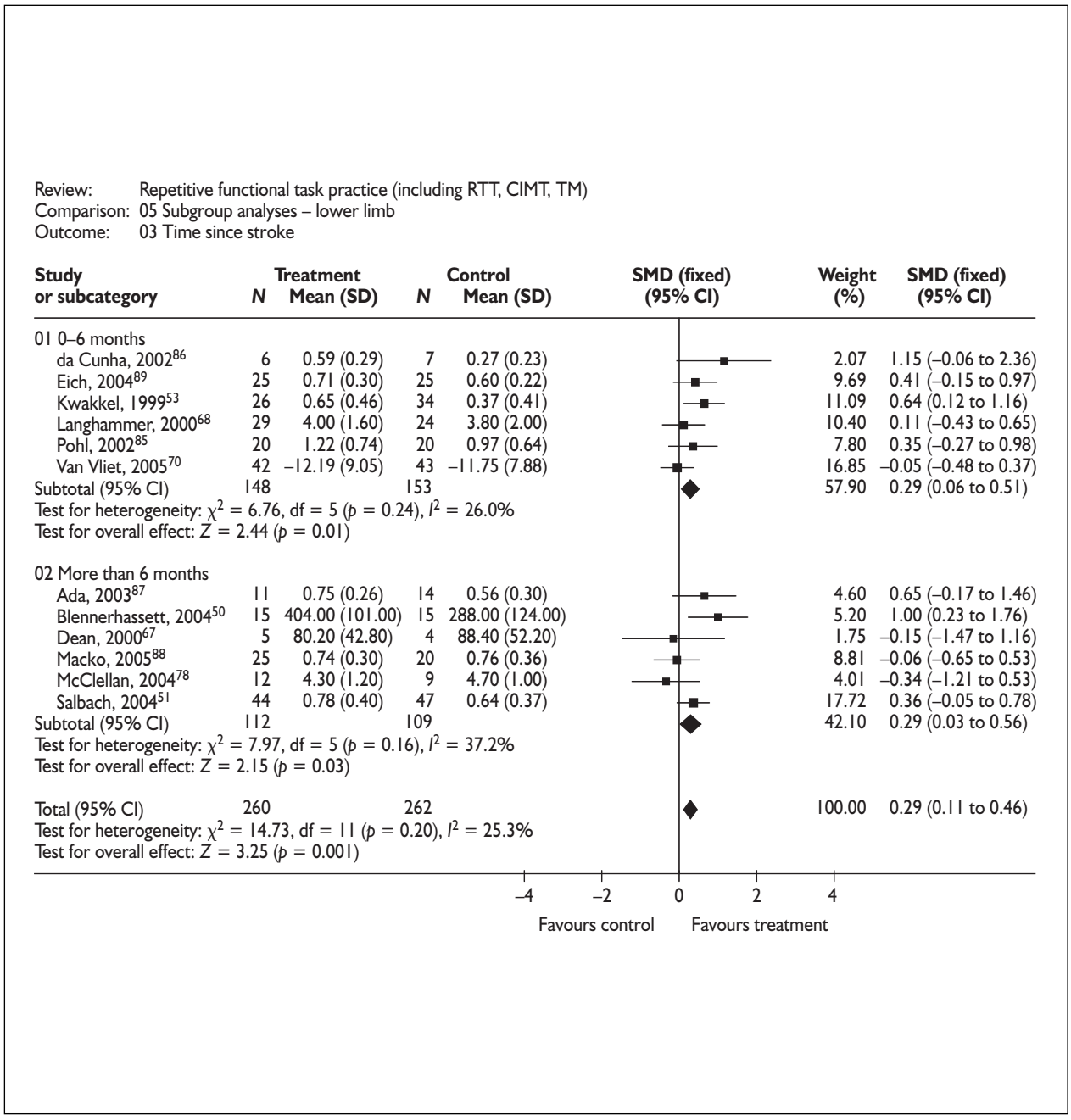

FIGURE 23 *Subgroup analysis: time since stroke – lower limb trials*

heterogeneity within each subgroup, but insufficient to warrant the use of a random-effects meta-analysis. The difference between subgroups was marginally non-significant ($p = 0.10$), with the estimated effect somewhat larger for the attention-control/no treatment subgroup.

Trial size

No trials of lower limb interventions had fewer than 25 participants, so subgroup analysis was not undertaken. The funnel plot in *Figure 26* does not suggest reporting bias.

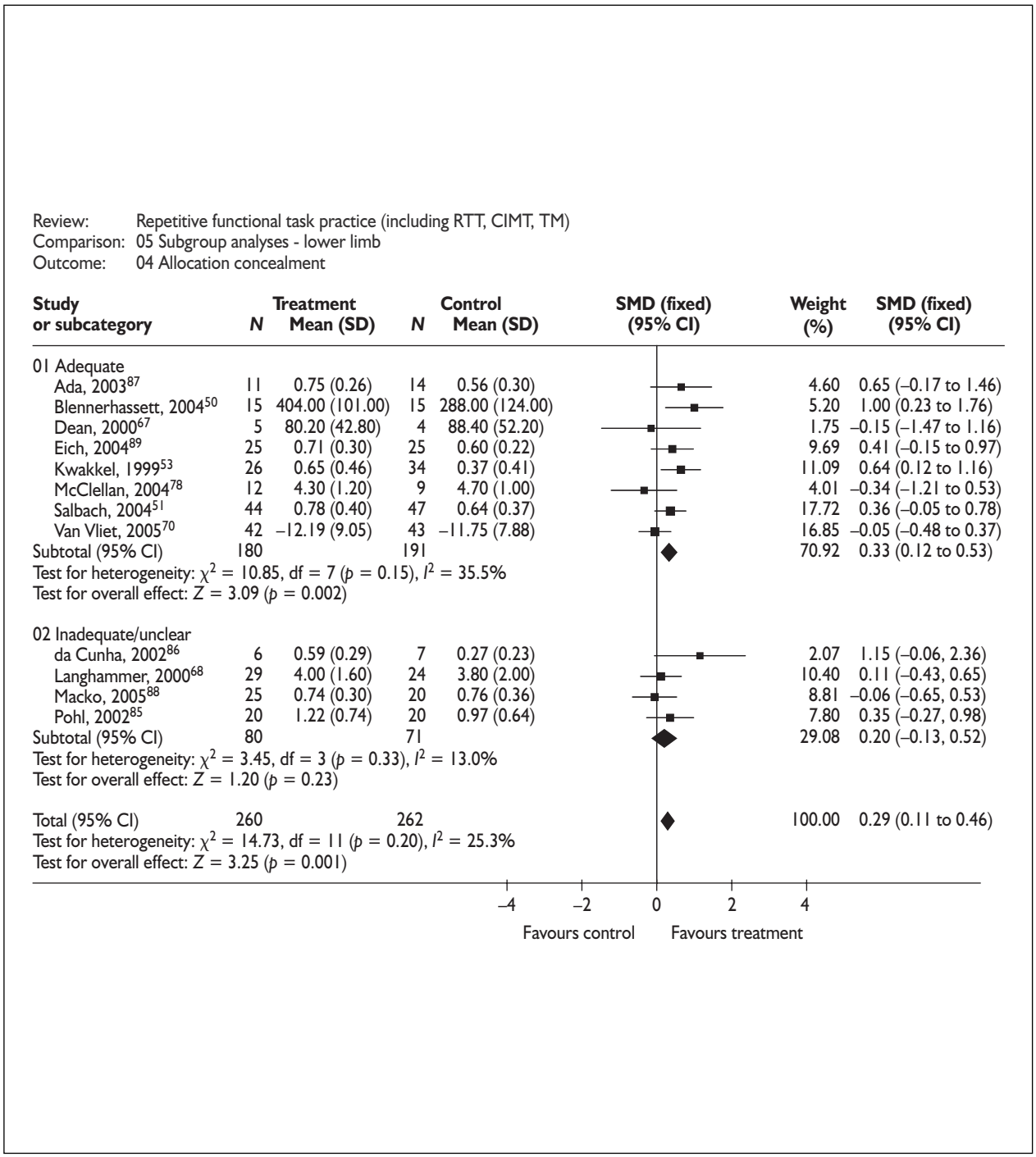

FIGURE 24 *Subgroup analysis: allocation concealment – lower limb trials*

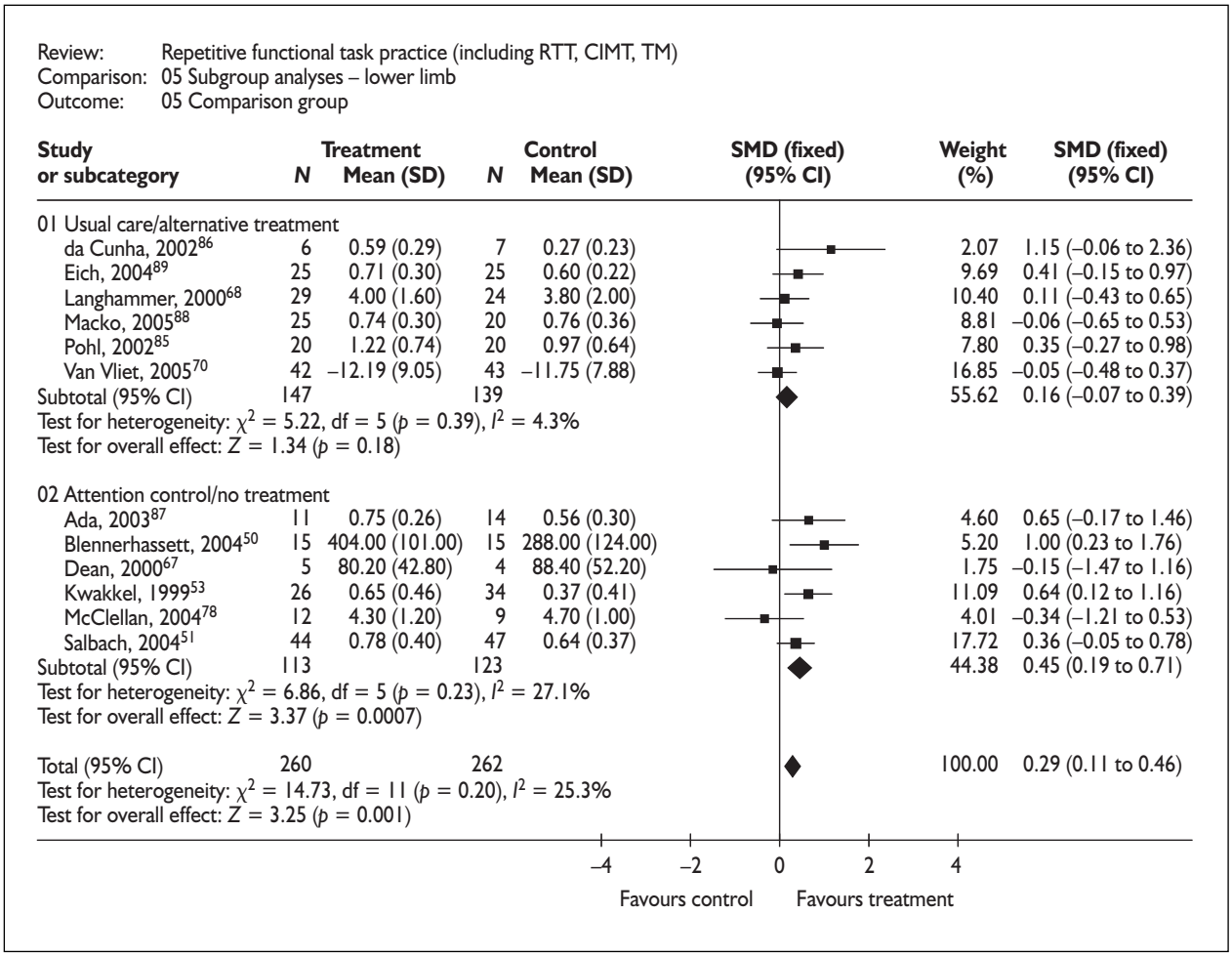

FIGURE 25 *Subgroup analysis: type of comparison group – lower limb trials*

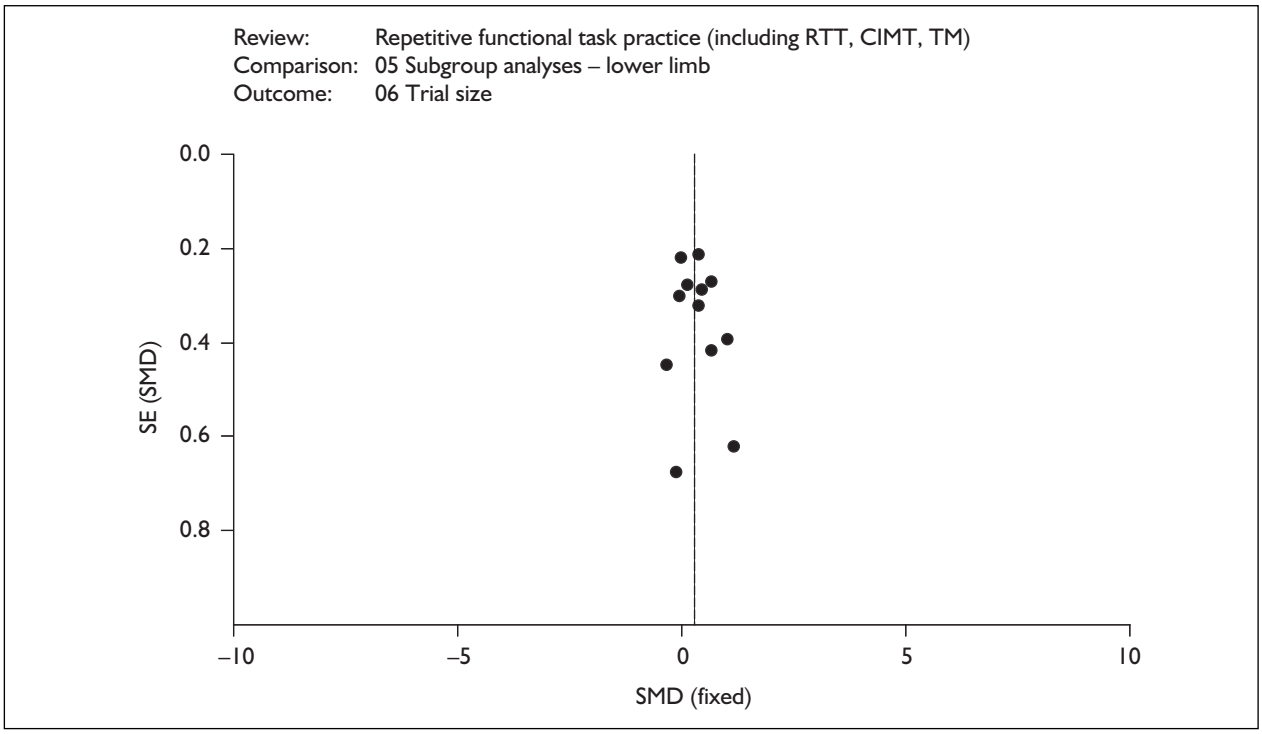

FIGURE 26 *Funnel plot of precision versus effect size – lower limb trials*

Global motor function

Two RTT trials[68,70] recruiting 181 participants measured global motor function (*Figure 27*). Outcome data were available for 76% (n = 138). Three TM trials[63,88,89] recruiting 105 participants measured global motor function. Data were not suitable for pooling from two trials.[63,89] Standard deviations were not given for one trial.[63] One trial[89] showed no significant difference in RMA score for gross functions, but provided median and IQR scores only: experimental group median 11 (IQR 11–11), control group median 11 (IQR 10–11).

The trials with outcome data suitable for pooling showed a small to moderate effect size which was statistically significant (SMD 0.38, 95% CI 0.09 to 0.68).

Overall summary analysis

The primary analysis requires an overall estimate of the effect of RFTP on functional outcome (*Figure 28*). To gain an overall measure of RFTP as a preliminary basis for the economic analysis, a summary plot was constructed, with subcategories for the different intervention types. Some RTT trials included both upper and lower limb intervention–control pairs. To avoid their being included twice, the lower limb intervention–control group was chosen, as it is known that lower limb treatment effects are more likely. By privileging lower limb outcomes, this would have the effect of providing a slightly inflated overall effect size.

Twenty-six intervention–control pairs with 876 participants provided data suitable for pooling, with outcome data available for 88% (n = 775). *Figure 28* shows that the overall treatment effect of RFTP (with selection of lower limb functional outcomes in studies with multiple intervention–control pairs, or in studies with both upper and lower limb intervention) was small to moderate and statistically significant (SMD 0.34, 95% CI 0.19 to 0.48).

If selection is based on upper limb functional outcomes from trials with multiple intervention–control pairs, or in studies with both upper and lower limb intervention, the results are small and statistically significant (SMD 0.26, 95% CI 0.12 to 0.41), indicating that the findings are not particularly sensitive to the choice of lower limb rather than upper limb outcomes.

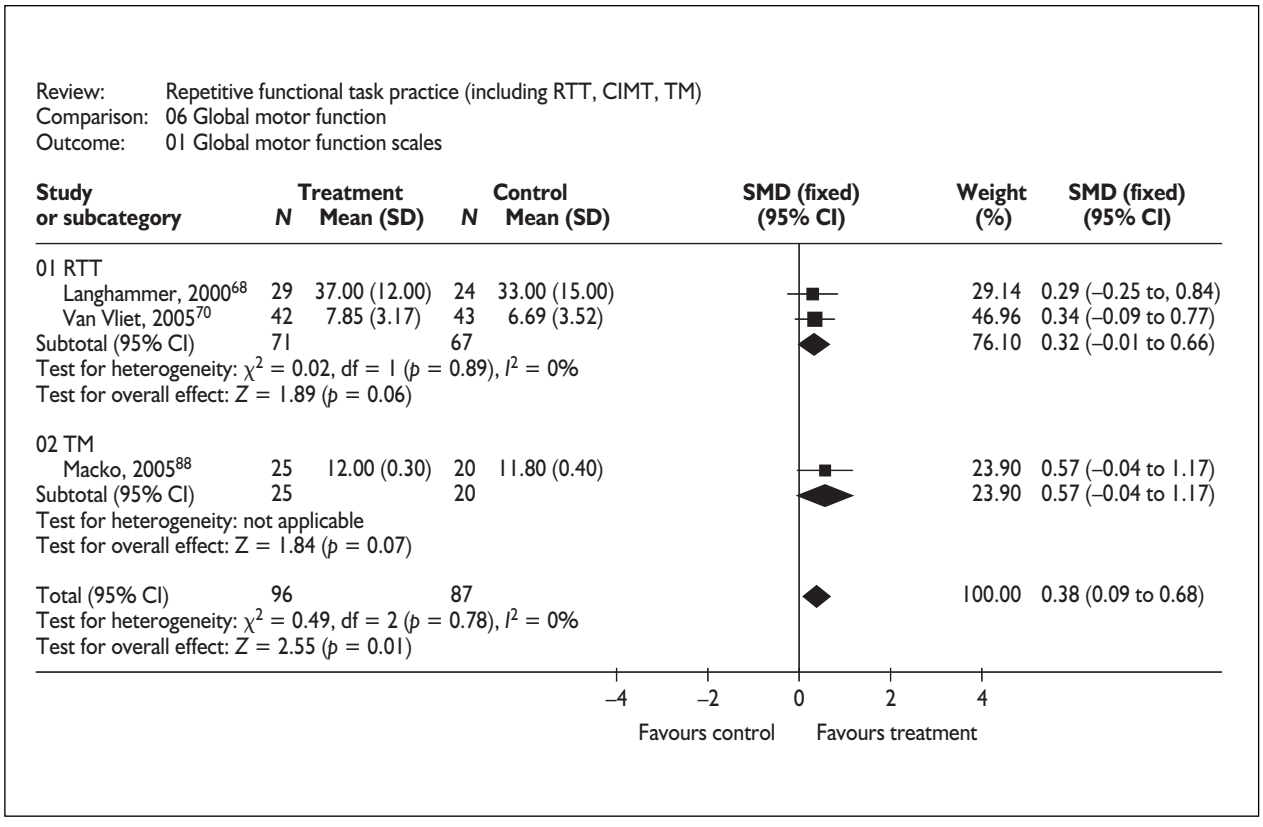

FIGURE 27 *Global motor function*

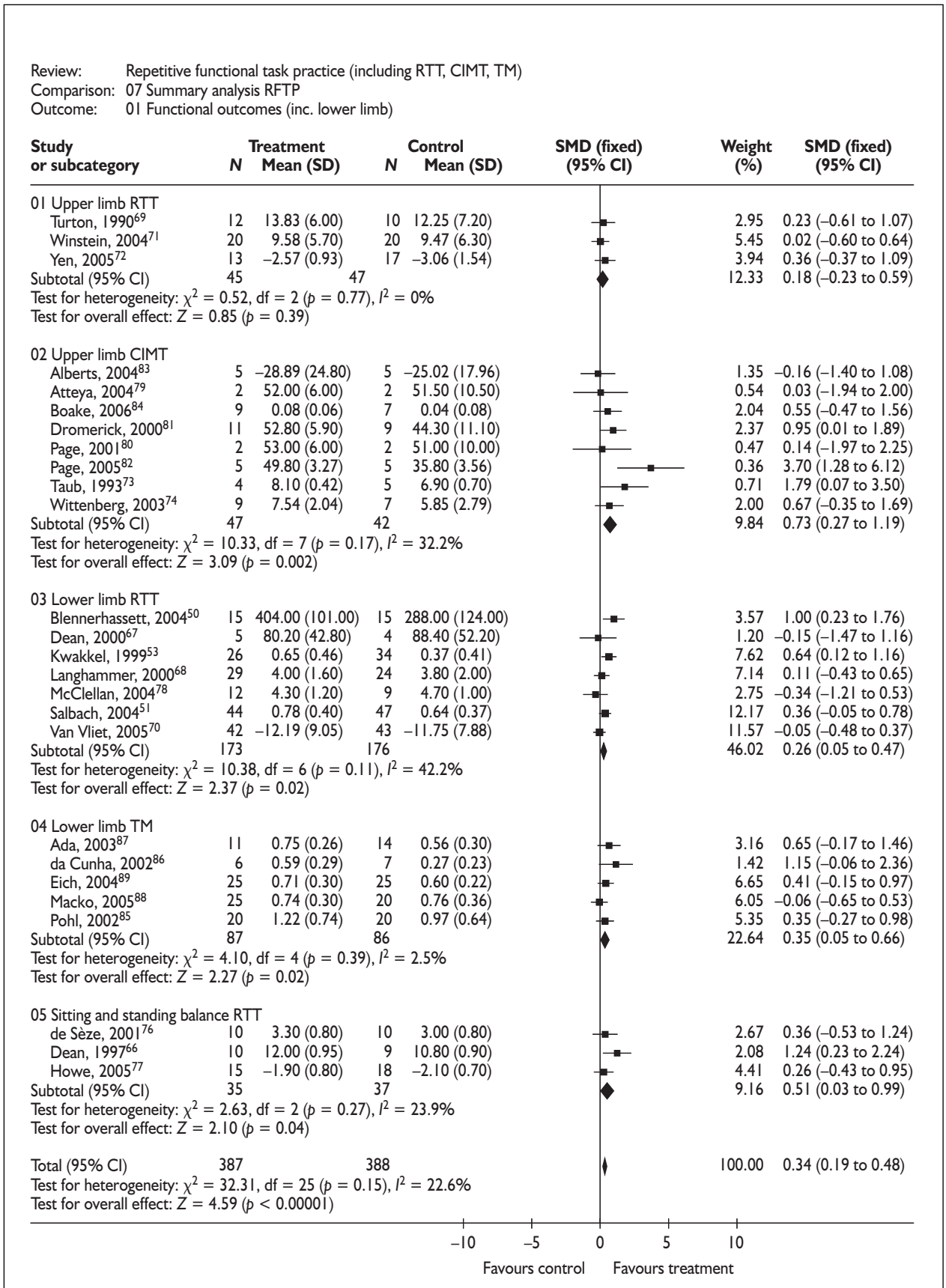

FIGURE 28 *Overall impact of all forms of RFTP on functional outcome*

Secondary outcomes

ADL function

Five RTT trials with seven intervention–control pairs[51,53,68,70,76] and recruiting a total of 399 people used a measure of ADL, with data available for 81% (n = 325) (*Figure 29*). One CIMT trial[81] recruiting 23 participants used a measure of ADL, with data available for 87% (n = 20). No TM trials included ADL data. For RFTP overall, six trials recruiting 422 participants included a measure of ADL, with outcome data available for 82% (n = 345).

Results showed a small statistically significant effect size (SMD 0.30, 95% CI 0.09 to 0.52).

Adverse effects

One RTT trial of sit-to-stand training[65] presented data for the number of falls: intervention group 3/25 (12%) versus control group 4/23 (17.4%), (odds ratio 0.65, 95% CI 0.13 to 3.27). No other trials presented data for adverse events, but two trials narratively reported no adverse effects.[76,78] In one trial,[51] intervention-related reasons for withdrawal that could be interpreted as adverse events included one person out of 47 in a mobility-training group who experienced the onset of groin pain. Four participants also fell during the mobility intervention, but did not suffer injury and continued to participate in the group. Two falls also occurred during evaluation. No other trials reported intervention-related reasons for withdrawal.

Eight CIMT trials did not mention adverse events,[61,62,64,74,79,80,82,83] although four of these trials stated that participants were highly satisfied with the protocol.[61,79,80,82] A further two trials stated there were no adverse events,[81,84] with one trial author commenting further that there was no

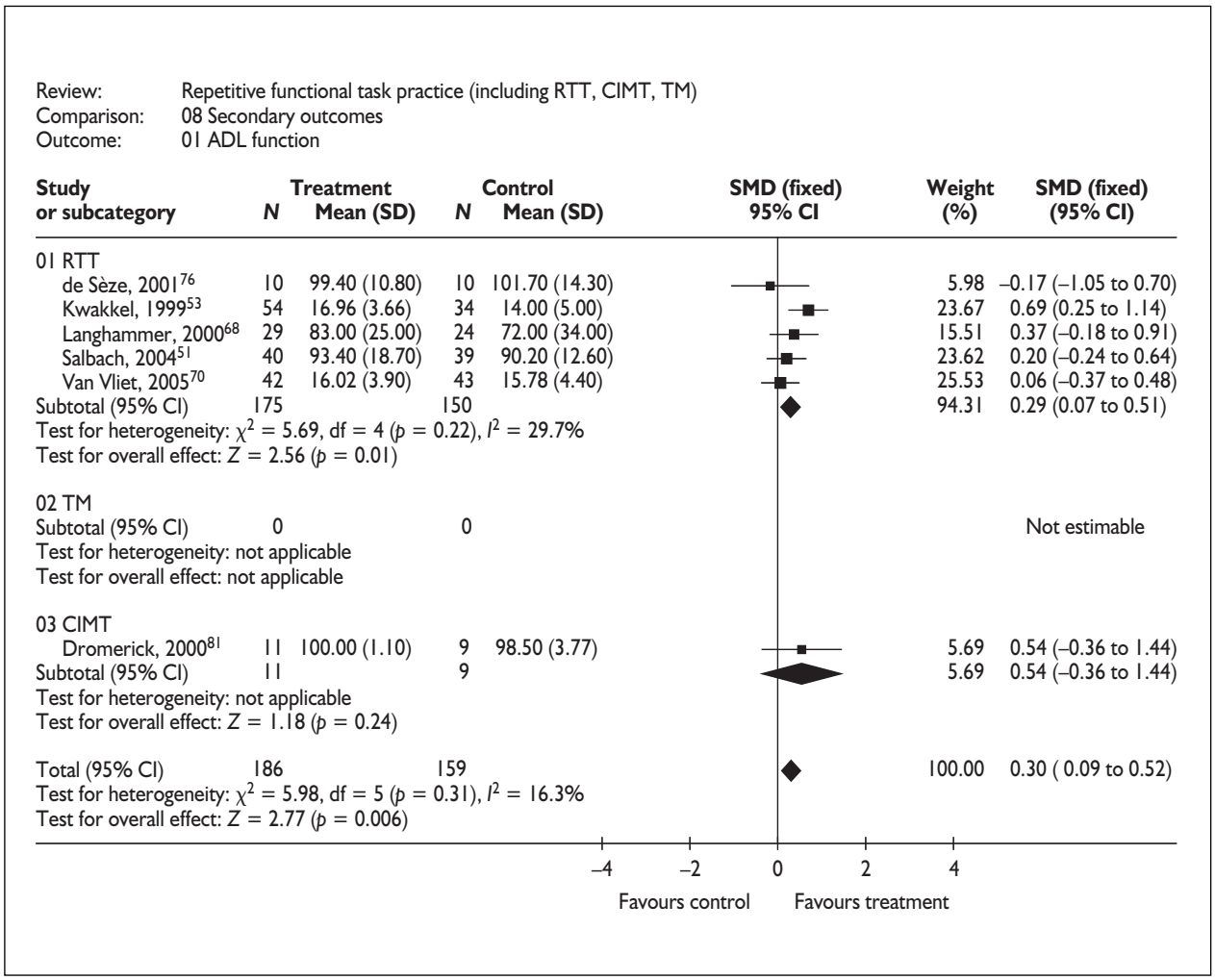

FIGURE 29 *ADL function*

evidence of excess disability associated with CIMT.[81] In one trial, the first three participants to receive restraint reported stiffness and discomfort on the involved side half-way through the 2-week treatment period.[73] These effects were associated with overuse of the affected limb and led to modification of the intervention protocol for the fourth participant, with motor demands increasing more slowly. The fourth participant reported no muscle soreness. There were no intervention-related reasons for withdrawal in any CIMT or mCIMT trial. Of the six TM trials, three reported that there were no adverse events.[85,87,89] There are no reports of adverse events in three trials.[63,86,88] None of the trials reported intervention-related reasons for withdrawal that could be interpreted as adverse events.

Sensitivity analysis

A sensitivity analysis was undertaken to evaluate the effect on upper limb outcomes of including cross-over and quasi-randomised trials,[63,69] finding no substantive difference between including (SMD 0.24, 95% CI 0.06 to 0.42) and not including (SMD 0.24, 95% CI 0.05 to 0.43) these trials. A sensitivity analysis was also undertaken on lower limb trials to evaluate the effect of excluding studies with more than 20% loss to follow-up (only one upper limb trial had loss to follow-up of greater than 20%). The effect of RFTP was significantly greater ($p = 0.02$) for trials with loss to follow-up of 20% or less (SMD 0.42, 95% CI 0.22 to 0.63) than for trials with more than 20% loss to follow-up (SMD –0.06, 95% CI –0.39 to 0.27).

Chapter 5
Economic analysis

Background

The systematic review identified studies that will potentially alter patient outcomes by using RTT. There were three forms of therapy that had RTT as a major component: RTT, CIMT, and TM. The therapies will subsequently be referred to as RFTP. The economic modelling reported below was designed to determine whether RFTP is cost-effective.

Study question

From the perspective of the NHS, is RFTP for stroke (in addition to usual care) cost-effective over 3 years as judged by the incremental cost per quality-adjusted life-year (QALY) gained?

Perspective

The analyses performed took the perspective of the NHS and Personal Social Services (PSS). The cost of stroke tends to be higher in the acute stage owing to the inpatient cost. Once a patient is discharged from hospital, some of the costs will be borne by the NHS through provision of therapy and aids, and some will be borne by PSS through provision of support services. RFTP would take place after the acute stage of treatment and hence will have no effect on these costs; therefore they are not considered in this analysis.

Current treatment

At present, the amount of physical therapy input to post-stroke patients varies widely. In hospital, most patients receive physiotherapy and occupational therapy. Once their care is transferred into the community, the provision of therapies is much less structured. This means that it is difficult to define a standard package of physical therapy after stroke. For this analysis usual care was based on observations of a cohort of patients treated in the NHS over time with the amount of physical therapy varying between patients. For the cost analysis the alternative treatments compared here are usual care and usual care plus RFTP.

Methods

Form of evaluation

A cost–utility approach was adopted, assessing gains in QALYs. The authors believe this to be the most meaningful outcome measure on which to base the economic evaluation. The nature of RFTP means that it will not directly prevent death, excluding a cost-effectiveness analysis of life-years gained. An alternative would be to express the effects of RFTP in terms of a change in units of some measure of function; however, the authors believe that this would be generally less meaningful than identifying a cost per QALY gained. The modelling is based over a 3-year period.

Choice of RFTP intervention

The economic analysis is based around the three forms of therapy described in the systematic review: RTT, CIMT and TM.

Measures of benefit

The health outcome summary measure is the number of QALYs gained. A health outcome was needed that could be used across the three forms of therapy described.

The patient data set

The patient data set used for the modelling is a longitudinal data set that contains follow-up data for a cohort of 539 stroke patients, consecutively identified over a 6-month period in 1996, on stroke registers in two hospitals.[134] Data were collected on admission, at discharge, and at 3 and 6 months, and subsequently 1, 2, and 3 years post-stroke. The data collected in hospital included admission and discharge dates, basic demographics, stroke characteristics and scan results. At each follow-up time patient status (alive or dead) was identified, and data were collected regarding residence, function, social service input, therapy input and aids provided. These patients received usual stroke care and their 3-year data were used as the baseline from which to judge the potential impact of RFTP. The baseline characteristics of these patients can be seen in Appendix 7. The characteristics of the data set compare favourably with the characteristics of the patients in the included studies.

Assumptions about health outcomes

The Barthel Activities of Daily Living Index (BI)[135] at 3 years post-stroke was used to define outcome groups, which represented a range of disability

levels, and such that there were similar numbers in each group. The choice of the BI was based on its widespread usage as a global outcome in stroke research and because it had been mapped onto the EuroQol-5 Dimensions (EQ-5D).[136] The BI is a ten-item scale ranging from 0 (dependent on others for ADLs) to 20 (independent of others for ADLs); the items measured include mobility, transfers, grooming and feeding. The number of patients in each Barthel category was 28 (BI ⩽ 10); 34 (BI = 11–14); 33 (BI = 15–17), 25 (BI = 18 or 19) and 30 (BI = 20).

Efficacy of RFTP

A range of different outcome measures was used in the systematic review. For each outcome the effectiveness of RFTP was expressed as the SMD with associated 95% CI. The exception to this was for walking distance, which was expressed as WMD. However, for the economic analysis, the SMD will be used. In the economic analysis the focus was on those outcomes that showed a significant benefit of RFTP and where there were at least 250 patients in the analysis of efficacy, because the estimates based on such a sample size would be more robust. However, walking speed was not included in the economic analysis because it was felt that walking distance was the more meaningful of these two outcomes. To determine the potential impact of RFTP, it was necessary to estimate how a change in the SMD would equate to a change on the BI. It was estimated that a change in the SMD of 0.2 was equivalent to a change in 1 point on the BI. This was based on the following assumption: SMD = (treatment mean – control mean)/SD; a 'typical SD' for the BI in a rehabilitation stroke population might be 5 units; therefore, an SMD of 0.2 would be 1 Barthel unit.

Patient values preferences

A study was identified that examined the association between the BI and the EQ-5D.[136] Although this study was based in The Netherlands, the characteristics of the patients included in the study are similar to the characteristics of those in the present patient data set (at 6 months). The study[136] suggested that 1 point on the BI was equivalent to 0.05 of a QALY.

Cost

The cost estimates reflect 2005/06 prices. Direct costs have been used, valued from an NHS public-sector perspective. The majority of the costs were obtained from national figures.[137] The exception to this was the cost for aids, which were obtained from an NHS loan store. The assumptions made about the costs for the RFTP studies are detailed below.

Assumptions about costing

Patient data set

The analysis focused on the costs that were likely to be influenced by RFTP, which included the cost of services, therapy and aids post-discharge. Costs were estimated from the following inputs: home care, meals on wheels, chiropody, physiotherapy, occupational therapy, day centre, day hospital, wheelchair, walking frame, walking stick, toilet seat raiser, chair raiser, bed raiser, toilet frame, trolley and shopping trolley. The costs that were not included were GP attendance, readmission to hospital, clinic attendance or medication. Also excluded were hospital costs for the index stroke and subsequent hotel costs for residence in institutions. Although RFTP is likely to promote independence in everyday activities, it is unlikely that it would prevent admission to institutions. Moreover, there was some concern that high hotel costs of institutions, or even readmissions to hospital, would unduly influence the model and the authors wished to adopt a conservative approach to the estimates of cost-effectiveness.

RFTP studies

The RFTP studies included in the review exhibited some diversity in when and where they were performed; some were more than 10 years old and many were not based in the UK. To estimate the costs of such studies, an assumption was made that they could be performed in a similar manner in the UK. In addition, although the studies reported on how much therapy was provided, there were no data on the impact of the training on subsequent resource use. Therefore, it was assumed that the RFTP training did not result in additional costs owing to readmission or clinic attendance, caused by patients' conditions worsening.

Because of the diverse nature of studies and the data reported therein, a somewhat pragmatic approach to costing methodology was taken. It was assumed that for all studies the therapy staff cost was £40 per hour and that as well as the cost of providing the therapy there would be an additional 20 hours of staff training per study. The lack of CIMT data from the UK meant that an estimate of the cost of CIMT equipment had to be made, of £100 per patient. The TM studies used a cost of £25,000 for the equipment plus an additional £1500 for installation. Within the RTT studies there were miscellaneous costs for which the following cost estimates were made: Bon Saint Côme trunk control and retraining device £1000, videotaped instructions and telephone contacts £500, and instruction booklets £600. In one study[67] a Kinetron machine was used in one

workstation out of ten. The original cost of this machine was approximately £32,000. Because this device is no longer manufactured and it contributed only a small part to the RTT input, a cost of £1000 was attributed to this device. For all equipment the one-off cost of purchase was used and no assumptions were made about the lifetime of the equipment or how often it was used.

For each trial an average cost per patient was calculated based on staff time, equipment used and number of patients randomised into the trial. Subsequently, an average cost per therapy (i.e. RTT, CIMT and TM) was calculated based on the average cost for each trial and the number of trials that contributed to that therapy modality. From this calculation the estimated average cost per patient for the individual therapies was £651 for RTT, £1773 for CIMT and £1870 for TM. Further estimates were then made of the average cost per patient for combinations of therapy. To make the calculation for combinations of therapy, an average cost for all trials in the relevant therapy modalities was estimated. This resulted in an average cost per patient of £1126 for RTT and CIMT combined, and £999 for RTT and TM combined. The overall average cost per person of RFTP (i.e. RTT, CIMT and TM combined) for the base model was estimated to be £1265.

Where outcome measures reflected all forms of therapy (overall effect), the cost of the intervention was taken from the overall average cost of RFTP. Where outcome measures reflected therapy focusing on the upper limb (arm function and ADL), the cost of the intervention was taken from the average cost of RTT and CIMT. Where outcome measures reflected therapy focusing on the lower limb (walking distance, functional ambulation and sit-to-stand), the cost of the intervention was taken from the average cost of RTT and TM.

The model

Groups were identified, based on the BI at 3 years as described above. For each group the 3-year cost was estimated: the baseline cost in this analysis. It was then assumed that for an SMD of 0.2, there would be a 1-point increase per patient on the BI, that the BI scores were evenly distributed within the groups and that the effect would be maintained over 3 years. Using this assumption, the number of patients in each of the Barthel groups was re-estimated. A new (3-year) cost was then calculated based on the new numbers in each of the groups. The difference between the baseline cost and the new cost was considered to represent the impact of RFTP on cost. An average cost per patient, reflecting the potential cost saving of RFTP, was subsequently calculated, as £47,523/150 = £316.82 (Appendix 8).

Adjustment for timing of costs and benefits

For the base model the cost–utility of RFTP over 3 years was assessed, and costs and effects were discounted at an annual rate of 3.5%.

Allowances for uncertainty

Several sensitivity analyses were performed to explore the impact of varying certain parameters on the base model:

- RFTP efficacy
- association between the SMD and the BI
- association between the BI and the EQ-5D
- cost of therapy
- discount rates.

The relationship between the cost of RFTP per patient and the cost per QALY was also explored.

Results

From the systematic review, the overall effect size for RFTP was SMD 0.34 (95% CI 0.19 to 0.48). The following outcomes were based on studies where the combined sample size was more than 250 patients, and revealed a significant effect of RFTP.

- arm function: SMD 0.24 (95% CI 0.06 to 0.42)
- ADL: SMD 0.30 (95% CI 0.09 to 0.52)
- walking distance: SMD 0.45 (95% CI 0.20 to 0.70)
- functional ambulation: SMD 0.28 (95% CI 0.05 to 0.51)
- sit-to-stand: SMD 0.39 (95% CI 0.18 to 0.61).

The effect sizes for the five outcomes are based on RTT plus one of either CIMT or TM. For arm function there was heterogeneity of effect between RTT, which was non significant (SMD 0.17, 95% CI –0.03 to 0.36) and CIMT, which was significant (SMD 0.77, 95% CI 0.26 to 1.29). However, the estimates of cost-effectiveness will use the combined effect size.

Cost-effectiveness at 3 years

In the base-case analysis using the overall effect size, the incremental cost-effectiveness ratio

(ICER) of RFTP was £10,870. Considering the efficacy and cost data for the outcome of arm function, the cost per QALY gained was £15,185 and when focusing on the efficacy and cost data for ADLs the cost per QALY gained was £11,009. Based on efficacy and cost data for walking distance the cost per QALY gained was £4187, and for functional ambulation and sit-to-stand the cost per QALY gained was £10,187 and £5708, respectively. An intervention with an ICER of less than £20,000 is considered cost-effective[138] (although interventions with an ICER of up to £30,000 may be considered cost-effective). Therefore, for all outcomes listed, the base analysis suggests that RFTP is cost-effective. Moreover, for walking distance and sit-to-stand, when the ICER was calculated using the lower limit of effectiveness from the 95% CI, both of the ICER values were less than £20,000 (Appendix 9; Analysis 1).

Varying the association between the SMD and the BI

If a unit change of the SMD was related to a smaller change on the BI, the cost per QALY gained increases for all outcome measures. In the base case the ratio of SMD to BI is 1:5. Even if this ratio is changed to 1:4, the ICER remains below £20,000 per QALY gained for all outcomes except for arm function (£20,405). Sit-to-stand remains cost-effective at a ratio of 1:3 and walking distance remains cost-effective at a ratio of 1:2 (Appendix 9; Analysis 2).

Varying the association between the BI and the EQ-5D

If a unit change on the BI is associated with a smaller change in the EQ-5D the ICER increases for all outcome measures. If a change in 1 point on the BI is equivalent to only 0.04 of a QALY, all outcomes continue to suggest that RFTP is cost effective (Appendix 9; Analysis 3).

Varying therapy cost

RFTP remains cost-effective on all outcomes except for arm function if the cost of therapy per hour is increased to £60. However, RFTP is marginally cost-effective for arm function if the cost of therapy rises to £50 per hour (Appendix 9; Analysis 4).

Varying discount rate (cost)

If the discount rate for costs is reduced from 3.5% to 0% then the ICER is reduced to £10,228 for the overall outcome and, for example, £3545 for walking distance and £14,543 for arm function. If the discount rate for cost is increased from 3.5% to 6%, RFTP is cost-effective on all outcomes (Appendix 9; Analysis 5).

Varying discount rate (outcome)

If outcome is not discounted then the ICER is reduced to £9191 for the overall outcome and, for example, £3186 for walking distance and £13,068 for arm function. Even if the discount rate is increased to 6%, RFTP is cost-effective on all outcomes (Appendix 9; Analysis 6).

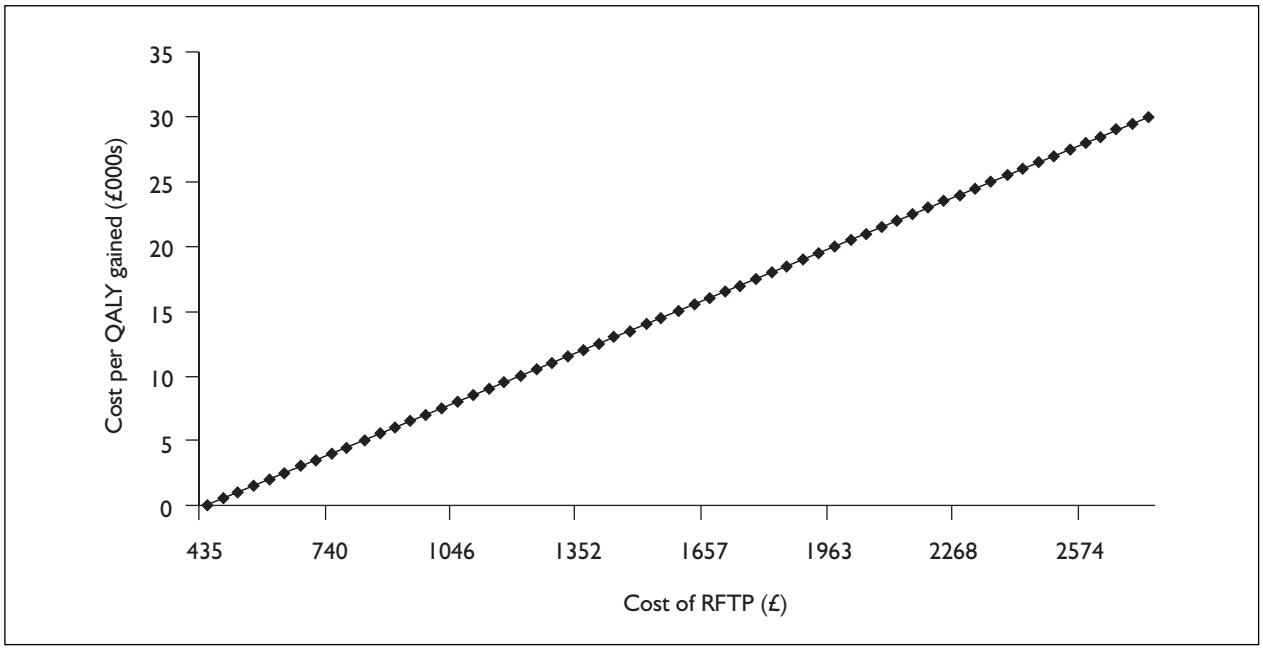

FIGURE 30 *Impact of varying the cost of RFTP on the cost per QALY gained*

Association between cost of RFTP and cost per QALY gained

The base costs were used to calculate how a change in the cost of RFTP per patient affects the ICER per QALY gained. At an ICER of £20,000 per QALY gained the average cost of RFTP per patient is £1963, which approximates to 49 hours' contact per patient, excluding equipment costs (*Figure 30*).

Chapter 6
Discussion

Summary of main results

Upper limb function/sitting balance

In total, 19 RFTP trials with 634 participants measured arm or hand function. Eight were RTT trials with 467 participants. Of these, two trials were whole therapy approaches,[68,70] two trials were circuit-training approaches,[50,52] three trials were functional task practice mixed in with other forms of upper limb exercise,[53,69,71] and one trial was the intensive practice component of constraint-induced movement therapy, without the constraint.[72] All of these interventions were delivered by a therapist, except for one trial, which consisted of self-initiated practice in the home environment, using a booklet of exercises, after instruction by a therapist.[69] Of the upper limb training trials, all but two[52,72] were carried out 0–6 months post-stroke. Five trials had a total training time of 20 hours or less,[50,52,68,70,71] and three trials provided more than 20 hours' total training time.[53,69,72] In two of the trials training time was additional.[69,71] All eight trials with eight intervention–control pairs relevant to this review provided data suitable for pooling.

Eleven of the 19 trials measuring arm or hand function were CIMT trials with 190 participants. Of these, five trials were of constraint-induced therapy,[64,73,74,83,84] and six trials were of modified constraint-induced therapy.[61,62,79–81,139] All of the interventions were delivered by a therapist, in one-to-one therapy. Three trials recruited within 14 days post-stroke,[81,82,84] four trials recruited between 15 days and 6 months post-stroke,[61,79,80,83] and four trials recruited after more than 6 months post-stroke.[64,73,74,139] All but two trials[81,82] had a total training time of over 20 hours, with the majority providing between 30 and 60 hours' training. In four trials, training time was additional to the amount of training time provided to the comparison group,[74,79,80,82] while in one trial it was unclear whether training time between experimental and comparison groups was equivalent.[73] Eight CIMT trials including 151 participants in eight intervention–control pairs relevant to this review provided data suitable for pooling. Pooled results show evidence of a small effect (SMD 0.24, 95% CI 0.06 to 0.42).

Seven RFTP trials with 357 participants measured hand function. There was no statistically significant pooled effect (SMD 0.19, 95% CI –0.03 to 0.42).

Five trials (all RTT) with 256 participants measured sitting balance/reach from sitting.[66,68,70,76,77] Of these, two trials were whole therapy approaches,[68,70] while the other three trials specifically trained sitting balance or reach from sitting. All of the interventions were carried out in the 0–6-month post-stroke period and were delivered by a therapist in a hospital setting, except for one trial where the intervention was carried out at home, with people more than 6 months post-stroke.[66] All of the interventions were 20 hours' training or less. There was no evidence for impact on sitting balance/reach (SMD 0.23, 95% CI –0.05 to 0.50).

Results at follow-up for all upper limb trials to 6 months post-therapy were moderate and statistically significant (SMD 0.55, 95% CI 0.06 to 1.04). Evidence for a retention effect at more than 6 months post-therapy was unclear (SMD –0.02 to 95% CI –0.31 to 0.26), as it was noted that the trials with 6–12-month follow-up also showed little or no effect post-treatment.

Treatment effects for upper limb interventions were not modified by amount/dosage of task practice or time since stroke, but were modified by type of intervention, with RTT showing a small effect size just failing to reach significance (SMD 0.17, 95% CI –0.03 to 0.36), and CIMT showing a large, statistically significant effect (SMD 0.77, 95% CI 0.26 to 1.29). However, tests for the effect of quality of allocation concealment and trial size were also significant, with all of the CIMT trials in both the inadequate/unclear allocation concealment subgroup and the small trials subgroup. This suggests that the results for CIMT trials could be influenced by quality issues and reporting bias.

Lower limb function/standing balance

Seventeen RFTP trials with 747 participants measured some aspect of lower limb function or standing balance/reach. Eleven were RTT trials with 531 participants. Of these, one trial

specifically trained sit-to-stand movements,[65] three trials trained balance,[66,76,77] two trials were whole therapy approaches,[68,70] three trials were circuit-training approaches,[50,51,67] and two trials were lower limb task practice mixed in with other forms of mobility exercise.[53,78] All interventions were delivered by a therapist in a hospital or community setting, except for one trial, which was a home mobility programme, where the participant followed videotaped exercise with therapist telephone contact and follow-up.[78] Three of the interventions were carried out more than 6 months post-stroke.[51,67,78] Two trials included more than 20 hours' total practice time.[53,78] All 11 trials had data suitable for pooling. Six of the 17 trials were TM trials with 229 participants. Of these, two trials were of unsupported TM[87,88] and four trials were of bodyweight supported TM.[63,85,86,89] All interventions were delivered by a therapist in a hospital setting. Two interventions were carried out more than 6 months post-stroke.[87,88] Only one of the trials included more than 20 hours' training time.[88] Five trials with 199 participants provided data suitable for pooling.

Results show large statistically significant effects for walking distance (WMD 50.05 m, 95% CI 29.65 to 70.44 m; SMD 0.98, 95% CI 0.58 to 1.39). In effect, participants in the experimental groups could walk on average 50 m further in 6 minutes than the control groups. However, there was some heterogeneity of treatment effects for walking distance. There were also small statistically significant effects for walking speed (SMD 0.28, 95% CI 0.09 to 0.47) and functional ambulation (SMD 0.28, 95% CI 0.05 to 0.51). Trials of RTT showed a small to moderate effect on sit-to-stand (standardised effect size 0.39, 95% CI 0.18 to 0.61), but no evidence of effect on lower limb function measures (SMD 0.20, 95% CI –0.10 to 0.50) or standing balance/reach (SMD 0.29, 95% CI, –0.06 to 0.63).

Retention effects on lower limbs were small to moderate and statistically significant up to 6 months post-therapy (SMD 0.37, 95% CI 0.05 to 0.69), but there was no evidence of an effect at later than 6 months (SMD –0.01, 95% CI –0.32 to 0.29). This difference in retention effects was borderline statistically significant ($p = 0.09$). However, few trials had long follow-up and those that did tended to show little or no effect post-treatment. Findings are also quite heterogeneous, which suggests that they are inconclusive.

Treatment effects were not modified by amount of task practice, time since stroke or type of intervention. Tests for the effect of quality of allocation concealment were not statistically significant. However, trials with high (>20%) loss to follow-up showed a significantly lower effect of RFTP than did trials with lower (≤20%) loss. This is an indication that any bias due to very high dropout is not in favour of RTT, although it would be important in future trials to try to characterise dropouts and attempt to determine their effect on the effectiveness of RFTP. There was some indication that treatment effects might be modified by type of comparison group ($p = 0.10$), with usual care or alternative treatment comparisons showing a smaller treatment effect than attention-control or no-treatment comparisons. This suggests that type of comparison group should be taken into consideration in future analyses.

Global motor function

Two RTT trials[68,70] and one TM trial with data suitable for pooling[88] recruiting 242 participants in total measured global motor function. Data were available for 76% ($n = 183$). There was a pooled small to moderate, statistically significant effect (SMD 0.38, 95% CI 0.09 to 0.68).

ADL function

Five RTT trials and one CIMT trial recruiting a total of 422 participants used an ADL measure. Outcome data were available for 83% ($n = 345$). Overall results indicated a small effect size that was statistically significant (SMD 0.30, 95% CI 0.09 to 0.52).

Adverse events

Ten out of the 31 trials included some report of adverse events. Of these, seven reported no adverse events. One RTT trial reported a number of falls occurring during the intervention or evaluation, none of which was serious,[51] and one CIMT trial reported that three participants had some discomfort in the unaffected limb, attributed to overuse during the constraint period.[73] The protocol was subsequently modified. The only trial formally to measure adverse events did not show any significant difference in fall rates between the intervention and control groups.[65]

Overall completeness and applicability of evidence

The included trials were clinically diverse in terms of timing and focus, and there are gaps in the evidence base, particularly for people more than 6 months post-stroke. Of the five trials that

evaluated more than 20 hours' therapy for upper limbs in this participant group, only three had usable data.[72–74] Only one trial evaluated 20 hours or less of upper limb therapy in people at least 6 months post-stroke.[52]

There were only three trials that evaluated up to 20 hours of lower limb therapy in people more than 6 months post-stroke,[51,67,87] and two trials evaluating more than 20 hours of lower limb therapy in this group.[78,88]

There have been more trials undertaken with people in the 0–6-month post-stroke period, but here there are also gaps in the evidence base. Of the seven trials evaluating upper limb therapy of more than 20 hours' duration, one had data unsuitable for pooling. Of the remaining six, one was quasi-experimental, and three had ten participants or fewer. While 11 trials have evaluated 20 hours or less of lower limb therapy, only one trial has evaluated more than 20 hours of lower limb therapy in the 0–6-month post-stroke period.

Although it was not possible to classify studies into more disabled or less disabled participant subgroups, the tables of included studies (Appendixes 1–3) illustrate the wide range of disability levels of the participants in the included trials. However, many of the trials had inclusion criteria specifying either minimum, or minimum and maximum levels of ability, motivation to participate and ability to understand instruction. The general evidence provided by the review therefore appears to be widely applicable, perhaps with the exception of very severely disabled people with little postural control or voluntary movement, those with very mild deficits and those with severe communication difficulties who were excluded by trialists. The exception to the above may be in CIMT studies, which identified criteria for minimum levels of finger and wrist extension. Treatment effects for CIMT may only be applicable to a subgroup of participants with a degree of voluntary movement in the hand or arm. There is also the possibility that exclusion criteria for maximum residual ability reduce generalisability. The preliminary phase of a CIMT trial reported that less than 5% of stroke admissions qualified for randomisation.[84]

Trials were excluded where repetition appeared to be primarily for strength or endurance training (e.g. cycling and gait training), or where the type of training appeared divorced from the functional aim (e.g. backward walking training, slot machines and computer games). This may have consequences for the applicability of the evidence. The exclusion of trials of what could be defined as 'prefunctional' types of movement will effectively have excluded a group of people who cannot yet participate in functional movement. The same consequence applies to the exclusion of trials with a large element of passive and active assisted movement.

In terms of generalisability to the UK, only RTT-type interventions have been evaluated in this setting. One trial is a whole therapy approach,[70] one trial evaluates balance training[77] and one quasi-experimental trial evaluated self-delivered exercise in the home environment.[69] RTT has not traditionally been a significant part of therapy after stroke in the UK, which has been dominated by the Bobath approach. This specifically minimises repetitive active movement, and relies on therapist-guided restoration of 'normal movement' patterns, rather than the functional but unnatural ones that could occur as a result of the more pragmatic approach within RFTP. Many studies in this review were from outside the UK, or used therapy approaches that have been less popular, such as motor learning. While clinical experience suggests that modern UK stroke units have a more eclectic therapy approach, it may take longer for the results to change practice within the UK than in countries that already use RFTP routinely.

There are no published trials of either CIMT or TM in a UK setting. While all of the interventions are likely to be transferable in principle, their effectiveness against other forms of care usual in the UK and their acceptability in this healthcare setting have not been tested. In particular, the feasibility and acceptability of CIMT and circuit-training interventions delivered in community settings would need to be evaluated. The intensity of CIMT and the delivery of interventions after the normal rehabilitation period represent additional periods of treatment to those currently provided.

The acceptability and safety of the different forms of RFTP to all types of participants are also unclear. While there were few adverse effects reported overall, the lack of formal reporting in many trials means that this finding is inconclusive. Of the information provided about reasons for dropouts in the trials, the most frequent cause was physical illness, and only a very small proportion of those participating dropped out for physical reasons that might have been related to the intervention. However, there was also a small

number of participants who were lost to follow-up for reasons related to compliance or treatment preference. In the CIMT trials in particular, relatively long periods of constraint and intensive periods of practice with the affected limb have the potential to impact on acceptability, although none of the trials reported problems.

Information about recruitment was not often provided, but of those that did provide information, a trial recruiting in hospital in the early rehabilitation period had relatively low numbers of refusal to participate (e.g. Kwakkel[53] had four out of 101 people who did not give consent), while a trial recruiting in the community after rehabilitation had high numbers of refusal of the intervention (e.g. Salbach[51] had 73% refusal). It may be that some forms of intervention are less acceptable, or that interventions only appeal to a subset of stroke survivors, particularly if travel is involved.

No conclusions could be reached about the impact of numbers of repetitions as a measure of the intensity of practice, as this information was only provided in one or two trials. The amount of task practice is therefore a measure of the duration (i.e. time spent).

By virtue of its focus on functional movement, this review does not consider the evidence for electronic forms of delivery of repetitive movement such as robotics or computer-mediated practice. The authors were also unable to comment on the implications of different sites of treatment, therapist-delivered versus self-delivered interventions or group versus individual delivery, as there were too few trials for comparison. However, the presence of two trials involving self-delivery in the home environment and four trials involving group delivery of task-specific training suggests that these modes of delivery are feasible, and further ongoing trials should provide more information. The studies that collected information showed generally high levels of satisfaction with the programme. Attendance levels at community programmes were also very good, suggesting that training programmes were well received by those who chose to participate.

Quality of evidence

For lower limb trials, Salbach and colleagues[51] estimate that a sample size of 60 would be required to detect a group difference of 28 m in average change in the 6WMT (type I error = 0.05, type II error = 0.10, expected dropout rate of 10%) based on the results of a pilot study[67] which recruited 91 patients. Five of the 17 trials of lower limb interventions had sample sizes above 60 (four RTT, one TM). For upper limb trials, the same research group estimated that a sample size of 60 participants was required to detect a clinically meaningful difference for the BBT.[52] Of the 19 trials of upper limb interventions, five trials had sample sizes greater than 60 (five RTT). No CIMT trial had more than 25 participants.

Two-thirds of RTT trials had adequate allocation concealment and most of the trials stated that blinded independent assessors were used. Therapy time was non-equivalent in two trials. For TM, two out of five trials with data included in the meta-analysis described adequate allocation concealment methods, blinding of outcome assessors was attempted in three trials, and all trials provided equivalent therapy time to experimental and comparison groups. Only four trials (two RTT, one CIMT, one TM) had over 20% dropout. For CIMT, three trials provided data unsuitable for pooling; and all of the CIMT trials had unclear allocation concealment.

The overall quality of the included trials provides a degree of confidence in the pooled results for RTT and TM, although there were only five TM trials with data suitable for pooling from 199 participants. The results for CIMT have to be considered in the light of small size of the trials, together with the confounding effects of the selection of trials with non-equivalent therapy time in the experimental and control groups (i.e. no-treatment control groups). A number of CIMT trials did include comparison groups who received therapy with no constraint, but these were intervention–control pairs that could not be used for this review as the comparison was also repetitive task practice. The use of no-treatment control comparison may lead to a different conclusion from other reviews of CIMT. Three out of eight included CIMT trials compared the intervention against no therapy. This may explain the large effect of the intervention on upper limb function, as the differential between these groups may be larger than would be expected by comparing the intervention against usual care or another intervention, such as bimanual training.

Non-reporting bias also has to be considered. Subgroup analysis for trial size and the funnel plot for upper limb interventions suggested greater effects for smaller trials, suggesting an absence of small, negative trials. This might have led to small or negative effect estimates not being included

and, in particular, an 'unbalancing' due to the four trials with large effects.

Potential limitations in the review process

This review combined the results of trials of RTT with results from trials of enhanced forms of RTT, namely TM and CIMT. Care must therefore be taken regarding attribution of pooled treatment effects solely to the task practice component. For this reason, both separate and pooled results are shown. This study also generally used fixed-effect analyses, which some might criticise owing to the presence of some clinical heterogeneity in the treatments and trials combined. Many of the trials originally reported data in median and interquartile ranges. In addition, many of the outcomes are measured on scales that are short and bounded, where the use of means and standard deviations can be misleading. However, the effect size for RFTP is greatest for walking distance, which is a truly quantitative measure. It is also relatively consistent across other outcomes, including walking speed which is, like walking distance, a continuous measure with essentially no strict upper bound. This would tend to indicate that the use of means and standard deviations for short, bounded, ordinal scales has not substantively affected the conclusions, at least for the lower limb outcomes.

The major focus in this review was impact on task-specific function. In practice, a large number of studies was excluded on the basis that the reviewers did not judge the outcomes to be functional or the intervention to be task specific. Studies were also included where the reviewers' interpretation of the intervention was that repetition of functional movement was a major mechanism of action, even when this was not explicitly stated by the authors (e.g. de Sèze[76]). Whether balance training is truly 'functional' is also a matter of interpretation, but its inclusion was felt to be important so as not unintentionally to exclude RFTP training for people with more severe levels of disability, where the recovery of balance is a prerequisite of functional activity.

As CIMT and TM trials were sourced from existing reviews, trials with alternative or no-treatment comparisons were included. Two TM trials included comparisons against alternative forms of treatment, which is potentially likely to have resulted in lower estimates of effect than comparison against usual care; subgroup analysis for type of comparison group was close to statistical significance, with a lower effect estimate for the usual care/alternative treatment than for the attention-control/no-treatment comparison subgroup. Three CIMT trials included comparison against a no-treatment group, with the potential to result in greater estimates of effect than comparison against usual care. However, analysis of the impact of comparison group provided no evidence of any difference between the effects in the two subgroups.

Agreement or disagreement with previous reviews

All of the studies included in this review have a core component of repeated, task-specific practice, but they are also very diverse. The CIMT and TM components of the review were subsets of existing reviews.[20,23] While combining the results from such a diverse group of studies has potential dangers, the summary finding of a pooled moderate impact on functional ability (SMD 0.34, 95% CI 0.19 to 0.48) supports previous authors who have suggested a focus on the efficacy of task-specific treatments.[14,34]

Whether functional gain can be attributed to task specificity or repeated practice is unclear and any attribution is highly speculative. This review did not find a significant difference in treatment effect dependent on the amount of practice for lower limb interventions. Conversely, the greatest gains for lower limbs were seen in walking distance, while gains for walking speed were of a smaller magnitude, suggesting that an endurance training element contained in repeated motor practice makes some contribution to impact. In addition, this review could not take into account the pretherapy ability levels of the participants, and it may also be that the mechanisms of repetition and task specificity have different roles at different stages of recovery. Repetition is the major mechanism of action of robotics, and a recent review has shown impact at the level of impairment, but not for functional ability.[36]

For upper limb interventions, five out of eight CIMT studies with data suitable for pooling provided more than 20 hours of therapy. Although the overall difference between smaller and larger amounts of task practice was not statistically significant, there was potential evidence of a trend ($p = 0.18$) towards larger effect sizes for more than 20 hours' practice (SMD 0.42, 95% CI 0.10 to 0.75) versus 0–20 hours' practice (SMD 0.22,

95% CI –0.12 to 0.57) for arm function. This finding is consistent with other reviews that have suggested that upper limb recovery may require intensive intervention.[16]

Overall for RFTP, there were small to moderate effects for ADLs and global motor function, and a small effect on functional ambulation classification. Even though the amount of change for these outcomes is modest, the clinical benefits are likely to be meaningful in relation to quality of life.[136]

In those studies that did show a benefit and provided later assessments, improvements at the end of training were not evident at the later stage. It is unclear from this review whether this is related to characteristics of the participants, the intensity of training or the degree of improvement required before detectable change was noted.

Evidence from RFTP interventions does not concur with the suggestion that earlier provision of treatment results in greater functional improvement, as treatment effects were not modified by time since stroke. Improvement in function was possible even in the later stages of recovery.[139] A recent review concluded that it was surprising that CIMT should work in the chronic phase of stroke, but agreed that the trial and laboratory evidence suggested that this was the case. However, they concluded that teaching bimanual activities rather than constraint might create the same outcome.[140]

The authors were unable to come to any conclusions about the previously identified dose–response relationship between amount of therapy and improved outcome,[15] but the results from subgroup analysis suggest this as a priority for further research.

Economic analysis

The base-case analysis suggested that RFTP is cost-effective. This analysis is based on a number of assumptions about therapeutic inputs that had to be made because of the paucity of economic data associated with the individual trials. Furthermore, in calculating cost-effectiveness the authors had to estimate the potential impact of RFTP on pre-existing longitudinal data. To allow for these assumptions their magnitude was varied in sensitivity analysis. The sensitivity analyses tended to find that RFTP was cost-effective overall, and in particular on the outcome measures of walking distance and sit-to-stand.

The existing data set used to estimate the impact of RFTP was appropriate to the study's needs because it reflected the normal course of recovery after stroke in a cohort of patients that had been systematically identified. The disadvantage of using this data set was that the analysis was based around predetermined data, which did not specifically lend itself to assessing the impact of RFTP. However, the existing data did allow reasonable assumptions to be made about how RFTP may have affected outcomes and costs, and meant that the research team did not have to wait for 3 years to collect data on resource use and outcomes in a UK post-stroke population.

One of the costs from the existing data set that could have been included was the cost incurred through residence in institutions. These costs tend to be high and would most likely be important in patients with more severe disability. Not including the cost of residence in institutions means that the costs of these severe states are likely to have been underestimated. Evidence from this review suggested that RFTP reduced disability. Therefore, by excluding the high severe state costs due to institutionalisation, the review is likely to have underestimated the potential savings and consequently the cost-effectiveness of RFTP.

Translation of the potential effect of RFTP on the patients in the data set made an assumption about the relationship between the effect size and the BI. This assumption was based around the size of the standard deviation in rehabilitation trials. The assumption that the standard deviation was about 5 is consistent with published data.[53,68,141–143] Furthermore, in this systematic review the effect of RFTP on ADLs resulted in an SMD of 0.30. This would suggest that the assumption about the relationship between the SMD and the BI was, if anything, a conservative one, therefore, it is likely that the cost-effectiveness of RFTP has been underestimated.

A further assumption was then made about the relationship between the BI and the EQ-5D. This assumption allowed the calculation of ICER per QALY gained. The systematic review showed that none of the studies used the EQ-5D and only one[65] used a measure of quality of life (not including health status) as an outcome. It therefore seemed unreasonable to generate an effect size for quality of life, based on one study. Consequently, this makes it difficult to compare directly the relationship between RFTP and quality of life, and suggests that future RFTP studies should use a quality of life measure as an outcome.

To test the assumptions that were made about the relationships between the effect size, the BI and QALYs, sensitivity analyses were performed. These analyses explored what would happen if the impact of RFTP on outcome was less than in the base model. For the assumptions made, the cost per QALY gained was more sensitive to variations between the effect size and the BI than to variations between the BI and the EQ-5D. Overall, the cost per QALY gained for walking distance did not rise much above £20,000, except for one of the assumptions made in the sensitivity analysis. This means that even when the assumptions are stacked against RFTP, this intervention still demonstrates cost-effectiveness.

The estimation of the cost of providing RFTP in the trials was complicated for a number of reasons. Many of the trials were not conducted in the UK, so it was difficult to cost some items of equipment. The grade of staff performing the training was not often reported; this was further compounded by the trials not being UK based. In addition, because the individual trials had not specifically recorded resource-use data, no information was available about the impact of RFTP on future therapy, support services or provision of mobility aids. Moreover, there were no consistent data about adverse events, which would have the potential to increase costs through patients attending clinics or being admitted to hospital. In one study[87] some patients were transported to hospital at the expense of the researcher; for all other studies post discharge, patients made their own way to clinics. It is likely that this cost was incurred because the intervention was being used in the context of a research study rather than normal clinical practice. Furthermore, if RFTP was introduced as a rehabilitation therapy it is unlikely that it would incur major direct costs for patient transport. For this reason the cost of this transport was not included as a source of cost for RFTP. Given the lack of associated economic data, the costing of RFTP was a fair reflection of the direct costs incurred by this intervention.

The systematic review revealed the complex nature of RFTP in terms of what is being delivered as well as when (after stroke), where and how it is delivered. This provided a challenge for modelling the cost-effectiveness of this intervention. It was therefore decided that rather than develop a complex model, the modelling should be kept simple and transparent. As a result of this decision the reviewers considered how RFTP might influence 3-year costs by looking at the potential impact on the 3-year BI. It is self-evident that to have a 3-year BI a patient must be alive; this meant that the estimate did not take into account the possibility that a patient who had RFTP died within the 3-year period, which may have impacted on the cost. A further analysis was subsequently performed that examined how the impact of RFTP on the 3-month BI would affect cost at 3 years, i.e. this analysis included people alive at 3 months, some of whom had died by 3 years. It was found that the magnitude of the potential cost saving was similar whether the 3-month or 3-year BI scores were used.

To make the modelling feasible a number of other assumptions had to be made. The costing of usual care went from discharge to 3 years post-stroke, which makes the assumption that the cost over 3 years would be the same whenever RFTP was started. Another related assumption was that the effect of RFTP is constant over time. It is acknowledged that these assumptions are rather general. However, given the complex nature of the intervention, described in the previous paragraph, and the lack of economic data about the intervention and its likely impact on cost, the authors believe that these assumptions provided a reasonable estimate.

In summary, the systematic review was able to combine the results from different studies and provide an overall effect size for RFTP. The lack of economic data associated with the existing studies meant that an economic model had to be developed to estimate the potential cost-effectiveness of RFTP. The modelling had the advantage of using effect sizes from a large sample; the disadvantage was that it relied on pre-existing data. This meant that the modelling that was performed relied on a number of assumptions about costs and effectiveness. The assumptions that were made were generally weighted against RFTP. Despite these assumptions, RFTP demonstrated that it was cost-effective.

To combat the issues around measures of costs and effectiveness, future trials need to be sufficiently powered to detect the effectiveness of both functional and economic outcomes. Furthermore, trials need to decide a priori what resources to cost; because the effects of RFTP are likely to extend beyond its impact on direct costs future trials should also consider indirect and possibly intangible costs. Economic analysis would be facilitated further by including quality of life as an outcome measure.

Chapter 7
Conclusions

Implications for practice

The results of this review provide sufficient evidence to validate the general principle that RFTP for lower limbs can result in functional gain, when compared against other forms of usual care or attention-control. While functional gain overall is modest, impact does appear to be of a clinically meaningful magnitude. It is, however, unclear as to whether effects are sustained over 6 months post-therapy.

There is insufficient evidence to make any recommendations for upper limb interventions. Although effects of RFTP on arm function were statistically significant, the variable quality of the evidence and the clinical heterogeneity of the interventions mean that further research is needed before specific recommendations can be made.

Some caution is needed in interpreting the lack of evidence for adverse effects, as few trials specifically monitored these as an outcome. If task-specific training is used in clinical practice, adverse effects should be monitored.

While the overall effectiveness of RFTP is relatively modest, this sort of intervention appears to be cost-effective, primarily because the intervention itself has a relatively small cost.

Recommendations for future research

There is a large number of ongoing trials in this area. The first recommendation is that this review is updated within 2 years. The updated review should also consider any potential interaction effects between type of training, amount of task practice and stroke-related impairments. This review focused initially on the evidence for the efficacy of RFTP versus usual care or attention-control comparisons. Any future review should include comparison of RFTP against alternative forms of therapy, such as strength and stamina training.

Further well-designed, adequately powered trials evaluating the impact of upper limb interventions, and in particular CIMT, are needed. One trial was published shortly after the closing date for this review, and should provide more information on efficacy. Future CIMT trials should also target and measure hand function.

There were insufficient trials included in this review to evaluate the efficacy and cost-effectiveness of different intervention delivery methods for RFTP, such as group training, delivery by assistants or practice in the home environment. Further research should address practical and cost-effective ways of delivering such interventions. In particular, the acceptability of CIMT and of circuit-training-type interventions delivered in community settings would need to be evaluated.

The existence of retention effects up to 6 months post-therapy is a promising finding, and further research should be directed towards evaluating long-term functional gain by routine inclusion of longer follow-up periods of 1 or possibly 2 years. Suitable methods to maintain functional gain should also be investigated.

Future trials need to be designed to take account of the following:

- This study was unable to investigate the impact of training on people with different levels of pre-intervention disability, because of the wide range of baseline measures used. Analyses of this type would be facilitated by the inclusion in trials of baseline data using a common measure such as the BI, which can be related to population norms dependent on time since stroke.
- Monitoring and reporting of adverse effects should be explicitly included.
- When designing future trials of any type of RFTP it is critical that the study is powered to detect not only a clinical effect, but also whether it is cost-effective.
- Future studies need to identify clearly which resources are likely to be affected by RFTP and ensure that they are included in any economic analysis. In addition, studies should include a quality of life measure as one of the outcomes to facilitate economic analysis.
- The benefit of RFTP may not be clear from direct costs alone; therefore, future studies should include indirect costs and give some consideration to the inclusion of intangible costs.

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Contribution of authors

Beverley French (Senior Research Fellow, University of Central Lancashire) led the systematic review, including coordinating the review process, managing searching and main data input and drafting the final report. Michael Leathley (Postdoctoral Research Fellow, University of Central Lancashire) led the cost-effectiveness component of the review, and contributed to data extraction and appraisal for the review. Christopher Sutton (Senior Lecturer, University of Central Lancashire) provided statistical expertise to the review and cost-effectiveness analysis. Joanna McAdam (Research Coordinator, University of Central Lancashire) managed the TM component of the review, was responsible for administration of the review process and contributed to data extraction and appraisal and to drafting the final report. Lois Thomas (Senior Research Fellow, University of Central Lancashire) managed the CIMT component of the review and contributed to data extraction and appraisal, and to drafting the final report. Anne Forster (Reader, Elderly Care, University of Leeds), Peter Langhorne (Professor of Stroke Care, University of Glasgow) and Christopher Price (Clinical Senior Lecturer/Consultant Physician, Northumbria Healthcare NHS Trust) directed the review focus and quality, and undertook critical reading of outputs. Andrew Walker (Senior Lecturer in Health Economics, University of Glasgow) directed the focus and quality of the cost-effectiveness component of the review. Caroline Watkins (Professor of Stroke and Older People's Care, University of Central Lancashire) was lead investigator for the project, responsible for managing the overall review process and quality of outputs.

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Appendix 1

Included studies: repetitive task training

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Barreca, 2004[65]	Single-centre RCT Randomisation by coin flip. During first 4 months, eligible subjects were assigned to a conventional practice group; during second 4 months, eligible subjects were assigned to an extra practice group, with this sequence of block randomisation occurring three times in total	Canada 48 participants: 25 intervention, 23 control Participants recruited from admission to a rehabilitation centre within 1 month of stroke *Inclusion criteria*: Between the ages of 18 and 90, medically stable, postural control stage 3 or greater on the Chedoke McMaster Stroke Assessment (lying to sitting in bed using strong side), but not stage IV (lying to sitting on side of bed, using strong side) *Exclusion criteria*: None stated *Mean age*: 68 years (range 56–78) 65% male *Stroke details*: Not stated whether first or recurrent stroke, 73% ischaemic, 42% right hemiparesis *Time since stroke*: 30 days, range 18–50 days *Preintervention functional ability level*: Lack of postural control	*Sit-to-stand training*: Group class practice in attaining standing from sitting from a variety of different heights and surfaces Training was additional to usual care, which included daily strengthening exercise, repetitive training, functional training, electrical stimulation and other exercise Sessions were 45 minutes, three times a week until competence or discharge (approx. 6 weeks) = 13.5 hours + practice on ward. Each session aimed to involve three practice sets of five sit-to-stand manoeuvres per class. Average total repetitions during training = 450–500. Classes had six or seven participants, supervised by two registered practical nurses, with extra practice delivered by nurses trained on the sit-to-stand protocol in a ward setting using videotapes, written instruction and practice *Comparison group*: Usual care plus recreation therapy	Outcomes recorded at competence or discharge (approx. 6 weeks) *Limb-specific function*: Number of people able to stand independently and safely on two consecutive occasions *Other*: Number of falls, health status satisfaction (with ability to stand) and satisfaction with quality of life (Dartmouth Primary Care Cooperative Chart)	No significant differences in baseline characteristics No loss to follow-up at end of treatment phase Outcome assessors blinded to group allocation No intervention related withdrawals

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Blennerhassett, 2004[50]	Single-centre RCT Randomisation procedure not described. Concealed allocation to groups using independent allocator and sealed opaque envelopes	Australia 30 participants: 15 intervention, 15 control Participants recruited from inpatient admissions to a rehabilitation centre, 2001–2003, with a primary diagnosis of stroke, within 3 months of stroke *Inclusion criteria*: Able to walk 10 m, able to provide informed consent *Exclusion criteria*: Deteriorating medical condition, independent community ambulation *Mean age*: Mobility group 53.9 years (SD 19.8), upper limb group 56.3 years (SD10.5) 56.6% male *Stroke details*: First or recurrent stroke: 73% ischaemic, 47% right hemiparesis *Time since stroke*: Mobility group 36 days (SD 25.1), upper limb group 50 days (SD 49.2) *Preintervention functional ability level*: Able to walk 10 m, 6MWT 182 m (SD 85)	*Mobility intervention*: Lower limb circuit training: functional tasks such as sit-to-stand, step-ups, obstacle course walking, plus stretching and strengthening exercise, and some endurance training on stationary bikes/treadmills *Upper extremity intervention*: Functional tasks to improve reach and grasp, hand–eye coordination activities, and stretching and strengthening exercises Both groups were during inpatient rehabilitation and additional to usual care of 1 hour of physiotherapy, 5 days a week, based on Movement Science Approach Sessions were 60 minutes, five times a week for 4 weeks (20 hours total training time). Each circuit included ten 5-minute workstations Sessions were delivered by a physical therapist in groups of up to four subjects *Comparison group*: Blennerhassett, 2004a: lower limb attention control, Blennerhassett 2004b: upper limb attention control	Outcomes recorded at baseline, which was approx. 6 weeks post-stroke (range 54–74 days), and at 4 weeks and 6 months after training *Upper limb function*: MAS upper arm, MAS hand, Jebsen Taylor Test of Hand Function *Lower limb function*: 6MWT, TUG, Step Test	No significant differences reported at baseline 3% lost to follow-up at end of treatment phase Outcome assessors blinded to group allocation No likely intervention-related withdrawals Average attendance was approx. 80%, with no significant difference between the groups

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
de Sèze, 2001[76]	Single-centre, pilot RCT Randomisation table used. No details of allocation concealment process	France 20 participants: ten experimental, ten control Subjects recruited from admissions to a neurorehabilitation unit in 1998 *Inclusion criteria*: Hemiplegia caused by a single stroke occurring at least 1 month previously. Static imbalance of the trunk resulting from the stroke *Exclusion criteria*: Multiple cerebral lesions, disorders of the locomotor system, a severe visual or auditory deficit, a severe deficit of executive functions, or deterioration in general health *Mean age*: Experimental group 63.5 years (SD 17), control group 67.7 years (SD 15) 55% male *Stroke details*: First stroke: 35% ischaemic, 25% right hemiparesis *Time since stroke*: Experimental group 36.8 days (SD 25), control group 27.7 days (SD 15) *Preintervention functional ability level*: Lack of postural balance	*Experimental intervention*: Postural training using the Bon Saint Côme device, a custom-moulded orthosis that holds a pointing device, used by the subject to point to targets on a vertical panel, which emit light and sound when activated. The subject performs exercises of locating and pointing by controlling trunk movement Intervention was during rehabilitation and additional to usual care Usual care consisted of a Bobath-inspired approach and functional therapy for 1 hour per day, plus a session of occupational therapy 5 days a week Sessions were 60 minutes (unclear whether 5 or 7 days per week), for 4 weeks = 20–28 hours Sessions were delivered individually, by a physical therapist *Comparison group*: Conventional rehabilitation for 2 hours per day	Outcomes recorded at baseline, post-intervention (4 weeks) and at 2 months *Limb-specific function*: Sitting Equilibrium Index, Upright Equilibrium Index, FAC *Motor performance*: Trunk Control Test, Motricity Index, Ashworth Scale *ADL*: FIM	At baseline, postural deficit and unilateral neglect tended to be more severe in the device group, although not significant. Trunk Control Test: device group 36.6 (SD 32.3), control group 50.4 (SD 31.9), Upright Equilibrium Index Device group 0.8 (SD 0.9), control group 1.2 (SD 1.0). 0% lost to follow-up at end of treatment phase Outcome assessors blind to treatment group No intervention related reasons for withdrawal All subjects completed training

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Dean, 1997[66]	Single-centre RCT Randomisation was blocked. Subjects allocated by drawing a card from a box of ten experimental and ten control cards	Australia 20 participants: ten experimental, ten control. Subjects were recruited from stroke clubs around Sydney, Australia *Inclusion criteria*: Diagnosis of stroke resulting in hemiplegia at least 12 months previously, discharged from all rehabilitation services, ability to understand instructions and give informed consent, no orthopaedic problem that would interfere with seated reaching, ability to sit unsupported for 20 minutes *Exclusion criteria*: None stated *Mean age*: 66.9 years (SD 8.2) 70% male *Stroke details*: Not stated whether first or recurrent stroke. 42% right hemiparesis *Time since stroke*: Experimental group 6.7 years (SD 5.8), control group 5.9 years (SD 2.9) *Preintervention functional ability level*: 6MWT: mean 207 m (SD 128)	*Experimental intervention*: Training designed to improve sitting balance and involving emphasis on appropriate loading of the affected leg while practising reaching tasks using the unaffected hand to grasp objects located beyond arm's length Intervention was after discharge from all rehabilitation programmes Sessions were 30 minutes, 5 days per week for 2 weeks = 5 hours Sessions were delivered by a physical therapist in the person's own home *Comparison group*: Upper extremity attention control: performance of cognitive manipulative tasks while seated at a table	Outcomes recorded at baseline and at 2 weeks (post-treatment) *Limb-specific function*: Reaching distance, reaching speed, walking speed (6MWT)	No significant differences reported at baseline 5% loss to follow-up at end of treatment phase Outcome assessors blind to treatment group No intervention-related reasons for withdrawal

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Dean, 2000[67]	Pilot RCT Subjects grouped into matched pairs based on walking speed, then randomised by drawing cards from a box. Cards drawn by a person independent from the study	Canada 12 participants: six mobility intervention, six upper limb attention control group Subjects recruited from a rehabilitation research group database *Inclusion criteria*: First stroke, at least 3 months post-stroke, discharged from all rehabilitation services, able to attend a rehabilitation centre three times a week for 4 weeks, able to walk 10 m *Exclusion criteria*: Any medical condition that would prevent participation *Mean age*: Experimental group 66.2 years (7.7), control group 62.3 years (6.6) 58% male *Stroke details*: Not stated whether first or recurrent stroke. 58% right hemiparesis *Time since stroke*: Mobility group 2.3 years (SD 0.7), upper limb attention-control group 1.3 years (SD 0.9) *Preintervention functional ability level*: 6MWT mean 235 m (SD 139)	*Mobility intervention*: Lower limb circuit training of ten workstations including sitting reach, sit-to-stand, stepping, heel lifts, standing balance, leg strengthening, treadmill walking, obstacle walking, slope and stair walking, plus participation in walking races and relays Intervention was after discharge from all rehabilitation programmes Sessions were 60 minutes, three times a week for 4 weeks = 12 hours Sessions were delivered to a group of six subjects by two physical therapists, in a rehabilitation centre setting *Upper extremity intervention*: Circuit programme designed to improve function of the affected upper limb	Outcomes recorded at baseline, at 4 weeks (post-treatment) and 2 months after completion of training *Limb-specific function*: 6MWT, 10MWS (with and without assistive device), Step Test, TUG *Other*: Satisfaction with programme	No significant difference in walking velocity at baseline for total group, but after withdrawals, measures of walking speed and distance favoured the control group. 6MWT: mobility group 207.9 m (SD 119), upper limb group 259.6 m (SD 154.6); walking speed with assistive device: mobility group 70.7 cm/s (SD 41.8), upper limb group 86.1 cm/s (SD 52.6) 25% loss to follow-up at end of treatment phase Outcome assessors blinded to group allocation, but may have been inadvertently unmasked. 6MWT undertaken by one of the investigators Intervention-related reasons for withdrawal: two subjects withdrew before training (one owing to transport costs) Nine participants attended at least nine out of 12 sessions

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Higgins, 2006[52]	See Salbach, 2004[51]				
Howe, 2005[77]	Two-centre, pilot RCT Group allocation via randomised permuted blocks, with the project manager holding details of assignment until allocation by a therapist	UK 35 participants: 18 experimental, 17 control Subjects recruited from admissions to an acute stroke unit between 2001 and 2002 *Inclusion criteria*: Aged 18 and over, acute vascular stroke presenting with hemiplegia, medically stable, able to cooperate, previously independently mobile, and independent in ADLs *Exclusion criteria*: History of conditions or medication affecting balance, dementia, impaired consciousness levels, concomitant medical illness or musculoskeletal condition, serious perceptual problems *Mean age*: Experimental group: 71.5 years (SD 10.9), control group 70.7 years (SD 7.6) 51% male *Stroke details*: Unknown whether recurrent stroke included, 47% right hemiparesis *Time since stroke*: Experimental group 26.5 days (SD 15.7), control group 23.1 days (SD 17.5) *Preintervention functional ability level:* Rivermead Mobility Index 24	*Experimental group*: Usual care plus exercises aimed at improving lateral weight transference in sitting and standing. This included repetition of self-initiated goal-orientated activities in various postures. 16 tasks in total, with ten repetitions of each exercise Sessions were 30 minutes, three times a week, for 4 weeks = 6 hours Sessions were delivered by trained physiotherapy assistants *Comparison group*: Usual care: no details given	Outcomes recorded at baseline, post-treatment (4 weeks) and at 8 weeks post-baseline *Limb-specific function*: Sit-to-stand, stand-to-sit (time in seconds), lateral reach test (time to return to quiet sitting)	No significant differences reported at baseline 6% lost to follow-up at end of treatment phase Outcome assessors blind to treatment group No intervention-related reasons for withdrawal Subjects completed 10.6 sessions on average

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Kwakkel, 1999[53]	Multicentre RCT Restricted randomisation (permuted blocks of nine) was applied, using random number tables for each of three participating hospitals. Allocation was concealed by use of sealed envelopes 12% lost to follow-up at end of treatment phase	Netherlands 101 participants: 31 leg training group, 33 arm training group, 37 control Participants recruited from seven hospitals in The Netherlands, 1994–1997 *Inclusion criteria*: Primary first ever stroke in the territory of the middle cerebral artery, confirmed by CT or MRI, aged 30–80, impaired motor function of the arm and leg, inability to walk at first assessment *Exclusion criteria*: Complicating medical history or severe deficits in communication, memory or understanding *Mean age*: Arm training group 69 years (SD 9.8), leg training group 64.5 years (SD 9.7), control group 64.1 years (SD 15) 43% male *Stroke details*: First ever stroke (TACI 61%, PACI 33%, LACI 6%), 41% right hemiparesis *Time since stroke*: Arm training group 7.2 days (SD 2.8), leg training group 7.0 days (SD 2.5), control group 7.5 days (SD 2.9) *Preintervention functional ability level*: BI of 9 or lower	*Leg training group*: Sitting, standing and weight-bearing exercise, emphasis on achieving stability and improving gait velocity. Treadmill training was used if available *Arm training group*: Functional exercise to facilitate forced arm and hand activity such as leaning, punching a ball, grasping, reaching, dressing, hair-combing and moving objects *Both groups*: If treatment at disability level not possible, strengthening exercises were used Intervention was additional to basic rehabilitation of 15 minutes each arm and leg rehabilitation and 1.5 hours per week of ADL training by an occupational therapist Sessions were 30 minutes, 5 days a week for 20 weeks = 45 hours. Sessions were delivered individually by a physiotherapist *Comparison groups*: Control group: immobilisation of the paretic arm and leg by means of an inflatable pressure splint	Outcomes recorded at baseline, weekly between weeks 1 and 10, and every 2 weeks between weeks 11 and 26. Post-intervention measures were at week 20. Final measurements were at 26 weeks. Results are presented for baseline, weeks 6, 12, 20 and 26 *Lower limb function*: FAC, walking speed (comfortable and maximum) *Upper limb function*: ARAT *Global ADL*: BI *Health status/quality of life*: NHP	No significant differences reported at baseline Assessors were blind to group allocation. Treatment assignment was unintentionally disclosed for ten subjects (one leg training, four arm training, five control group) No likely intervention-related reasons for withdrawal, although two patients refused the splint control treatment Compliance with delivery of intended amounts of training was monitored and achieved

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Langhammer, 2000[68]	Stratified, single-centre RCT Subjects randomised and stratified according to gender and hemisphere site. No details of randomisation	Norway 61 participants: 33 experimental, 28 control Subjects recruited from patients attending hospital in Norway, 1996–1997 *Inclusion criteria*: First ever stroke with hemiparesis verified clinically and by CT *Exclusion criteria*: More than one stroke incident, subarachnoid bleeding, tumours of the brain, other severe medical conditions in combination with stroke, 5 or more points on each of the scores on the MAS *Mean age*: 78 years (SD 9) (range 49–75) 59% male *Stroke details*: First stroke, 56% right hemiparesis *Time since stroke*: Baseline measures taken within 3 days of admission *Preintervention functional ability level*: BI mean 51	*Experimental group*: Motor Relearning Programme as per Carr and Shepherd, 1987.[18] Functional task training in ordinary settings, with ordinary tasks, using the principles of maximal repetition, task and setting variation Experimental intervention was instead of usual care Sessions were 40 minutes minimum per session, 5 days a week for as long as hospitalised, and continuing into the community, although receipt of physiotherapy in community settings was variable Sessions were delivered by hospital and outpatient physiotherapists. After discharge, some subjects received therapy in their own homes, at rehabilitation centres or private outpatient departments, dependent on need *Comparison group*: Bobath programme, as per Bobath, 1990[144]	Outcomes recorded at baseline, and at 2 weeks, 3 months, 1 year and 4 years post-stroke *Limb-specific function*: MAS, SMES – subscale for trunk/balance/gait, Berg Balance Scale (1 year only) *Motor performance*: SMES – subscales for leg function and arm function *Global function*: BI, NHP. *Other measures*: Length of stay, use of wheelchair, discharge destination	Control group slightly more dependent at entry (baseline), but no significant difference in MAS, SMES or BI Data available for 87% at 3 months Blinding stated, but no description given No intervention-related reasons for withdrawal Does not state monitoring of time spent in therapy

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
McClellan, 2004[78]	Double-blind RCT Randomisation by numbered, sealed, opaque envelopes	Australia 26 participants: 15 experimental, 11 control Subjects recruited on discharge from physiotherapy services in six hospitals in one region *Inclusion criteria*: Stroke within the past 18 months, 45 years and older, living in the community, score >0 and <6 on MAS, score <6 on item 7 or 8 of the MAS *Exclusion criteria*: Unable to consent, uncontrolled cardiac symptoms or other medical conditions that limited exercise, or with a pacemaker *Mean age*: Experimental group 69 years (SD 13), control group 72 years (SD 9) 50% male *Stroke details*: Unclear whether first or recurrent stroke, 50% right hemiparesis *Time since stroke*: Experimental group median 6.5 months (IQR 5.5), control group median 4.5 months (IQR 3) *Preintervention functional ability level*: All subjects could walk, but with difficulty	*Experimental group*: Home-based exercise programme aimed at improving mobility in standing balance and walking, based on a list of 23 activities arranged hierarchically on their challenge to balance. The home programme used video self-modelling prepared on a baseline visit to the clinic to prescribe the exercise programme, telephone monitoring to encourage compliance, and two clinic visits for programme review Sessions were prescribed 60 minutes per day over 6 weeks = 42 hours. Subjects were required to keep a record of practice *Comparison group*: Home-based exercise programme for improving upper limb function, starting from basic movement through to functional activity, using the same self-instructional video, self and telephone monitoring and clinic visits as the experimental group	Outcomes recorded at baseline, post-treatment (6 weeks) and at 14 weeks *Limb-specific function*: Functional Reach Test (cm), MAS walking	No baseline comparisons reported 19% lost to follow-up by end of treatment phase Assessors and subjects blind to group allocation No likely intervention-related reasons for withdrawal Subjects self-reported 75% compliance with prescribed exercises

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Salbach, 2004;[51] Higgins, 2006[52]	Stratified, multicentre RCT Participants stratified into three groups based on comfortable walking speed. Sequence of random assignments computer generated in randomly ordered blocks of 2 and 4 for each stratum. Allocation maintained in sealed, opaque envelopes, prepared before recruitment by persons not involved in the study, and unveiled after baseline assessment and stratification	Canada 91 participants: 44 mobility, 47 arm training group Subjects were recruited from nine hospitals and two rehabilitation centres in Montreal or Quebec *Inclusion criteria*: First or recurrent stroke, under 1 year post-stroke at recruitment, able to walk 10 m but with residual walking deficit from most recent stroke, mental competency and ability to comprehend instructions, discharged from physical rehabilitation and resident in the community *Exclusion criteria*: Resident in permanent care facility, co-morbidity precluding participation *Mean age*: 72 years,(range 38–91) 61.5% male *Stroke details*: First or recurrent stroke, 83% ischaemic, 56% right hemiparesis, 43% left hemiparesis, 1% bilateral *Time since stroke*: mean 228 days (SD 78) *Preintervention functional ability level*: 6MWT mean 207 m (SD 128)	*Mobility intervention*: Ten walking-related tasks designed to strengthen the lower extremities and enhance walking balance, speed and distance in a progressive manner *Upper extremity intervention*: Functional tasks such as manipulating cards, using a keyboard and writing while seated Intervention was after discharge from physical rehabilitation Sessions were 60 minutes, three times a week for 6 weeks = 18 hours Sessions were delivered individually by a physical or occupational therapist in a hospital outpatient or rehabilitation setting *Comparison group*: Salbach, 2004:[51] upper extremity training, Higgins, 2006:[52] lower extremity training	Outcomes recorded at baseline and at 6 weeks *Limb-specific function*: 6MWT, 5-m walk at comfortable and maximum speed, TUG, Berg Balance Scale, Activities Specific Balance Confidence Scale *Global ADL*: BI	No report of significant differences at baseline Intervention-related reasons for withdrawal: one unwilling to travel, one experienced the onset of groin pain; two wanted the other intervention Full intention-to-treat analysis used, with post-intervention values for subjects imputed Assessors were blind to group allocation. Unblinding occurred for 18/42 in the mobility group and 16/43 of the upper extremity training group, but did not bias the estimated effect as evaluated by multiple linear regression model 86% of mobility group subjects attended 17 or more sessions out of 18. 72% of upper extremity attended 17 or more sessions 344 people were evaluated for participation but 73% refused because they could not tolerate the travel required for attendance

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Turton, 1990[69]	Single-centre, quasi-randomised trial Subjects were assigned in alternate runs of five	UK 22 participants: 12 experimental, ten in the control Subjects recruited from stroke patients discharged from inpatient care at one hospital, 1986–1987 *Inclusion criteria*: Some impairment of function of the affected upper limb (i.e. less than 95% performance on a peg transfer task), able to understand instructions, lives within 25 miles (15.5 km) of hospital *Exclusion criteria*: None stated *Mean age*: Experimental group 59 years (SD 11.97), control group 58 years (SD 6.86) 55% male *Stroke details*: Unclear whether first or recurrent stroke, 56% right hemiparesis *Time since stroke*: Experimental group 24 weeks (SD 25.8), control group 16 weeks (SD 6.1) *Preintervention disability level*: 12.5/20 on Southern Motor Assessment Scale	*Experimental group*: Usual outpatient care plus home-based exercise programme for the upper limb, based on motor relearning principles. Exercises included movement and task-related reach, grasp and grip. Subjects were visited by an occupational therapist at home, and given exercises and repetitions. Exercises were detailed in a booklet. Subjects were visited every 2–4 weeks for review. Carers were involved if able and willing Subjects were assigned two to three practice sessions per day (approx. 1 hour), 7 days a week for 8–11 weeks = 63 hours approx. Sessions were self-managed by the subject and their carers at home, with two to three home visits by an occupational therapist for programme review *Comparison group*: Usual outpatient care (some had therapy, but others did not)	Outcomes recorded at baseline and post-treatment (8–11 weeks) *Limb-specific motor performance*: Sitting part of the upper limb activity assessment – Southern Motor Group Assessment, 10HPT	Baseline differences: Difference in time since stroke: experimental group mean of 24 weeks, and usual care mean of 16 weeks. 10HPT performance: experimental group more disabled, home therapy group had more carers living at home No loss to follow-up at end of treatment phase Outcome assessor not blinded to treatment group No intervention-related reasons for withdrawal Self-reported rates of compliance: mean 68% (SD 25). Three out of 12 subjects rated less than 50%

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Van Vliet, 2005[70]	Single-centre RCT Randomisation was by computer-generated random sequence provided by an independent person. Blocked randomisation was used. Allocations were provided in envelopes and opened after initial assessment	UK 120 participants: 60 experimental, 60 control Subjects were recruited from people admitted to a stroke rehabilitation ward over a period of 21 months *Inclusion criteria*: Diagnosis of stroke, referral to physiotherapy *Exclusion criteria*: More than 2 weeks post-stroke, unconscious on admission, unable to toilet independently prior to stroke, living more than 25 km from hospital, unable to tolerate more than 30 minutes of physical tasks required in initial assessment *Mean age*: Experimental group 75 years (SD 9.1), control group 73.3 years (SD 10.4) 50% male *Stroke details*: Unclear whether first or recurrent stroke. 51% right hemiparesis, 46% left hemiparesis, 3% bilateral *Time since stroke*: Within 14 days *Preintervention functional ability level*: Rivermead Motor Assessment gross function subscale: median (IQR) experimental group 2 (1–6), control group 1 (1–4)	*Movement science therapy*: Based on the principle that skill in performance is a direct function of the amount of practice. Programme involved use of everyday objects for functional training, and practice outside delivered sessions Intervention was instead of usual care Subjects received a median 23 minutes of treatment by a physiotherapist per week day (IQR 13–32 m). Median total number of minutes of treatment was 365 (IQR 140–1160), equating to approx. 6 hours' total training time Treatment was delivered by physiotherapists, occupational therapists and physiotherapy assistants, in hospital, and as an outpatient after discharge. Treatment was delivered for as long as needed *Comparison group*: Bobath-based therapy	Outcomes recorded at baseline, 4 weeks, 3 months and 6 months *Limb-specific function*: RMA Scale, MAS, 6MWS, 10HPT *Global function*: BI, Extended Activities of Daily Living	At baseline, control group had higher median scores for Rivermead gross function, and leg and trunk subscales, and for supine to side lying, supine to sitting, balanced sitting, and sit-to-stand sections of the MAS. Experimental group had higher median scores for the upper arm section of the MAS Data available for 71% at 3 months Outcome assessors blind to treatment allocation. Blinding assessed as successful Intervention-related reasons for withdrawal: seven subjects refused outcome measurement at 3 months, 5 in the experimental group and two in the control group, but reasons are not known

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Winstein, 2004[71] (only FTP and usual-care control group data included)	Stratified, single-centre pilot RCT Subjects were randomised to groups within severity strata, using Orpington Prognostic Scale (1.6–4.1 = more severe, 4.2–6.8 = less severe), using a blocking factor not identified to study personnel. Sealed envelopes delivered by independent person, and opened on enrolment of next eligible subject	USA 64 participants: 22 functional task practice (FTP), 21 strength training, 21 usual care (UK) Subjects were recruited from new admissions to a neurorehabilitation services centre *Inclusion criteria*: Aged 29–76, first time stroke. Stroke onset 2–35 days before study entry, FIM score of 40–80, widened to include a broader range early in recruitment phase *Exclusion criteria*: Conditions that interfered with arm movements, cardiac disease limiting function, brain injury, severe aphasia, neglect, agitation or depression that could limit participation *Mean age*: Experimental group <35 years = 2, 35–75 years = 18, control group <35 years = 0, 35–75 years = 19, >75 years = 1 52.5% male (FTP + UC groups) *Stroke details*: First stroke, 85% ischaemic stroke, 62% right hemiparesis *Time since stroke*: Experimental group 15.5 days (SD 6), control group 15.4 days (SD 5.5) *Preintervention disability level*: Orpington Score 1.6–4.1	*Functional task practice group*: Usual care plus task-specific functional training based on the principles of motor relearning, focusing on systematic and repetitive practice of tasks. Tasks were randomly ordered, and progressed in difficulty Sessions were 1 hour per day, 5 days per week, for 4 weeks = 20 hours additional to usual care Sessions were delivered by a physical therapist in hospital, and in an outpatient setting when discharged *Comparison group*: Usual care, delivered primarily by occupational therapists, which could include muscle facilitation exercises emphasising the neurodevelopmental treatment approach, neuromuscular electrical stimulation, stretching exercises and ADLs	Outcomes recorded at baseline, post-treatment (4–6 weeks) and 9 months after stroke *Limb-specific function*: FTHUE *Motor performance*: FM *ADL*: FIM	No significant differences reported at baseline 7% loss to follow-up at end of treatment phase Outcome assessors not blinded to group allocation Intervention-related reasons for withdrawal: one participant in the experimental group lost interest Compliance reported as near perfect, except for one person in the experimental group who, after discharge, and because of travel distance, completed only 15 of the 20 hours' training

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Yen, 2005[72]	Single-centre RCT No details of randomisation method	Taiwan 30 participants: 13 experimental, 17 control Subjects recruited from a department of neurology *Inclusion criteria*: Single stroke resulting in hemiparesis, minimum of 20 degrees of active wrist extension and 10 degrees of active finger extension, aged 18–80, no severe aphasia or cognitive impairment *Exclusion criteria*: Other diseases that would confound the study such as Parkinson's disease, shoulder subluxation, recurrent stroke during the training period *Mean age* 68 years (range 47–80) 46% male *Stroke details*: First stroke, 60% right hemiparesis *Time since stroke*: Experimental group 8.4 months (SD 8), control group 6.2 months (SD 7.9) *Preintervention functional ability level*: baseline mean 3.28 seconds per item on the WMFT	*Experimental intervention*: Practice of 15–20 tasks selected from a battery of 50 tasks, with task shaping, consisting of verbal feedback for small improvements, task selection based on needs of individual, and performance assistance in the initial stages if unable to perform independently Intervention was instead of usual care Sessions were 6 hours per day. It is unclear whether there were five or seven sessions per week. Treatment duration was 2 weeks = 60–84 hours Sessions were delivered by a physical therapist. It is unclear whether sessions were group based or individual *Comparison group*: Regular programme of physical therapy including gait training, facilitation, balance training or occupational therapy. It is unclear how much time the control group spent in therapy	Outcomes recorded at baseline and post-treatment (2 weeks) *Limb-specific function*: Mean time taken to complete individual items on the WMFT. Results for items 8–15 are only presented for subjects able to complete them within 2 minutes	No baseline differences reported No loss to follow-up at end of treatment phase Blinding stated, but no description given No intervention-related reasons for withdrawal No report of attendance

CT, computed tomography; FM, Fugl–Meyer; FTP, functional task practice; LACI, lacunar infarction; MI, myocardial infarction; NHP, Nottingham Health Profile; PACI, partial anterior circulation infarction; TACI, total anterior circulation infarction; UC, usual care.

Appendix 2

Included studies: constraint-induced movement therapy

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Alberts, 2004[83]	RCT Randomisation procedure not described	USA Ten participants: five intervention, five control Participants recruited from subacute stroke patients (3–9 months post-stroke) who were participating in EXCITE trial *Inclusion criteria:* Only one stroke, at least 20 degrees active wrist extension, 10-degree active finger extension, minimum passive range of motion of 90 degrees for shoulder flexion and abduction, score of at least 24 on MMSE and not receiving any other therapy at time of study *Exclusion criteria*: None stated Mean age: 64.1 years (range 41–84) 50% male *Stroke details*: First stroke only, 20% right hemiparesis, % ischaemic stroke not stated *Mean time since stroke*: 6 months, (range 3–9) *Mean FM score pre-intervention*: Overall 39.9 (SD 12.5), intervention 34.4 (SD 7.6), control 45.4 (SD 14.0)	*Experimental group*: constraint-induced movement therapy in which less affected hand was placed in a mitten. Mitten worn for approx. 90% of waking hours Constraint-induced movement therapy training sessions attended 5 days per week for up to 6 hours per day for 2 consecutive weeks. Shaping, or adaptive task practice and repetitive task practice techniques used during training sessions. All training was one-on-one with rehabilitation specialist *Comparison group*: Delayed group scheduled to receive constraint-induced movement therapy 1 year later. During intervention period did not participate in formal rehabilitation programmes	Outcomes recorded pre- and post-intervention. *Limb-specific function*: WMFT *Motor impairment*: FM (arm and hand section)	Allocation concealment stated, but method unclear Blinded outcome assessment No loss to follow-up at end of treatment phase

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Atteya, 2004[79]	RCT Randomisation procedure not described	Saudi Arabia Six participants: two intervention, two traditional therapy, two control *Inclusion criteria*: Stroke 4 weeks to 6 months ago, age 18–75, discharged from rehabilitation, 10-degree active extension in fingers, motivated, willing to follow intervention guidelines *Exclusion criteria*: Significant cognitive impairment haemorrhagic or bilateral lesions, lesions in the primary sensory or motor cortical areas, significant spasticity, significant pain in the affected upper limb, involvement in any other experimental rehabilitation or drug studies *Mean age*: 54.3 years (range 45–67) 50% male *Stroke details*: Unclear whether first or subsequent stroke, 50% right hemiparesis, % ischaemic stroke not stated *Mean time since stroke*: 4.7 months (range 2.3–5.8) *Mean amount of use of affected arm at baseline (measured by MAL)*: constraint-induced movement therapy group 2, traditional therapy group 1, control group 3 (5 is highest rating)	*Experimental intervention*: constraint-induced movement therapy with restraint of lower arm and hand every weekday for 5 hours using a cotton Bobath sling. Patients participated in 30 minutes of physical therapy and 30 minutes of occupational therapy on an outpatient basis three times per week for 10 weeks. Interventions included 'shaping', operant conditioning method in which a behavioural objective is approached in small steps of progressively increasing difficulty Patients discharged from rehabilitation *Setting*: Outpatient clinic *Comparison group*: traditional therapy: as above, but without restraint Control group received no therapy during 10-week period	Outcomes recorded pre- and post-intervention *Limb-specific function*: ARAT, WMFT, MAL *Motor impairment*: FM	Allocation concealment unclear No loss to follow-up at end of treatment phase

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Boake, 2006[84]	RCT Method of randomisation not stated	USA 23 participants: ten intervention, 13 control *Inclusion criteria*: Ischaemic or haemorrhagic stroke within 14 days of entering trial, score 1–3 on item 5 (arm motor) of the NIHSS, 10 degrees of active movement in thumb and two fingers of the affected hand, total NIHSS score ⩽14 if right-sided and ⩽19 if left-sided stroke, ability to provide informed consent, no previous stroke, no neglect or speech comprehension that would prevent participation in study *Exclusion criteria*: NIHSS arm motor score criterion excluded patients with no arm movement at all, or no detectable shoulder weakness *Mean age*: 60.7 years, (range not stated) 65% male *Stroke details*: Unclear whether first or subsequent stroke, 48% right hemiparesis, 78% ischaemic stroke *Mean time since stroke*: within 14 days *Mean NIHSS total score at baseline*: CIMT group 4.9 (SD 1.8), traditional group 5.3 (SD 3.4)	*Experimental intervention*: CIMT for up to 3 hours per day, for 14–15 days at a frequency of 6 days per week, excluding Sundays. Interventions included performing tasks with the affected upper extremity including reaching, grasping, lifting and placing. Task difficulty progressively increased using behavioural techniques of shaping and successive approximation. Participants wore mitten on unaffected hand for 90% of waking hours Intervention delivered by licensed therapists and therapy assistants including occupational and physical therapists Group size not stated *Setting*: inpatient rehabilitation unit and outpatient rehabilitation clinic	Outcomes recorded post-treatment and 3–4 months after stroke *Limb-specific function*: Grooved Pegboard Test, MAL *Motor impairment*: FM	States random allocation, but no description of procedure given Blinded outcome assessors

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Dromerick, 2000[81]	Pilot RCT Table of random numbers	USA 23 participants: 11 intervention, nine control Patients recruited from inpatient facility *Inclusion criteria*: Admission to inpatient rehabilitation within 14 days of ischaemic stroke, persistent hemiparesis leading to impaired upper extremity function as indicated by score of 1–2 on NIHSS, evidence of preserved cognitive function as indicated by 0–1 on the consciousness, communication and neglect items of the NIHSS, presence of protective response, no upper extremity injury or conditions that limited use before stroke *Exclusion criterion*: Haemorrhagic stroke *Mean age*: 66.0 years (range 47–83) 55% male *Stroke details*: Unclear whether first or subsequent stroke, 69.6% right hemiparesis, 100% ischaemic stroke *Mean time since stroke*: Not stated, but all participants within 14 days of stroke *NIHSS score at baseline*: Intervention 10.2 ± 9.4, control 7.5 ± 2.8	*Experimental intervention*: CIMT involving wearing padded mitten for at least 6 hours per day during 14-day treatment period, with 20 hours' training. Interventions included occupational therapy treatment focused on ADLs, upper extremity training and CIMT circuit training Treatment supervised by occupational therapist in both groups Group size not stated *Setting*: Inpatient *Comparison group*: Standard occupational therapy treatment including compensatory techniques for ADLs, upper extremity strength, range of motion and positioning Participants received equivalent time and intensity of treatment directly supervised by occupational therapist	Outcomes recorded pre- and post-intervention *Limb-specific function*: ARAT *Global ADL*: BI, FIM	Attempt at concealment, but real chance of disclosure of assignment before formal entry Blinded outcome assessment Loss to follow-up: 13% (n = 3)

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Page, 2001[80]	RCT Randomisation procedure not described	USA Six participants: two intervention, two traditional rehabilitation, two control *Inclusion criteria*: Stroke experienced between 4 weeks and 6 months before study enrolment, score of 70 or higher on Modified MMSE, no haemorrhagic or bilateral lesions or lesions in the primary sensory or motor cortical areas, age 18–95, no excessive spasticity, no excessive pain in the affected upper limb, completely discharged from all forms of physical rehabilitation, not participating in any experimental rehabilitation or drug studies *Exclusion criteria*: None stated *Mean age*: 55.8 years (range 44–77) 50% male *Stroke details*: Unclear whether first or subsequent stroke, 66.7% right hemiparesis, % ischaemic stroke not stated *Mean time since stroke*: 4.6 months (range 2–5.5) *Mean FM scores pre-intervention*: Intervention 40 (SD 7), traditional rehabilitation 56.5 (SD 3.5), control 58.5 (SD 3.5)	*Experimental intervention*: mCIMT comprising 30 minutes of physical therapy and 30 minutes of occupational therapy three times per week for 10 weeks. 80% of each physical and occupation therapy session focused on neuromuscular facilitation techniques, with emphasis on ADL tasks whenever possible, and 20% focused on compensatory techniques using the unaffected side (i.e. reaching and performing tasks with unaffected arm). Lower arms and hands restrained for 5 hours initially using cotton Bobath sling Group size not stated *Setting*: Outpatient *Comparison group*: Traditional rehabilitation group received the above with no restraint. Control group received no therapy during the same 10-week period	Outcomes recorded pre- and post-intervention *Limb-specific function*: ARAT, WMFT, MAL *Motor impairment*: FM	States random allocation but no description of procedure given Blinded outcome assessment No loss to follow-up

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Page, 2002[61]	RCT Randomisation procedure not described	USA 14 participants: four intervention, five traditional rehabilitation, five control *Inclusion criteria*: Stroke between 4 weeks and 6 months before study enrolment, 10-degree finger extension, and 20 degrees at the wrist, score of 70 or higher on Modified MMSE, no haemorrhagic or bilateral lesions or lesions in the primary sensory or motor cortical areas, age 18–95, no excessive spasticity, no excessive pain in more affected upper limb, discharged from all forms of rehabilitation, not participating in any experimental rehabilitation or drug studies *Exclusion criteria*: None stated *Mean age*: 64.8 years (range 45–83) 64% male *Stroke details*: Unclear whether first or subsequent stroke, 42.9% right hemiparesis, % ischaemic stroke not stated *Mean time since stroke*: 4.4 months (range 4–6) *Mean FM score at baseline*: mCIMT 31.0, traditional rehabilitation 51.4, control 37.0	*Experimental intervention*: mCIMT consisting of participation in 30 minutes of physiotherapy and 30 minutes of occupational therapy three times per week for 10 weeks. Intervention included PT concentration on affected upper limb stretching, dynamic stand/balance activities and gait training. 'Shaping' techniques applied. Less affected limb restrained every weekday for 5-hour period Group size not stated *Setting*: Subacute outpatient clinic *Comparison groups*: (1) Traditional rehabilitation participants received the same amount of occupational and physical therapy sessions; treated according to neuromuscular facilitation principles with some compensatory techniques taught (2) Control participants did not participate in any interventions for the 10-week period	Outcomes recorded pre- and post-intervention *Limb-specific function*: ARAT, MAL *Motor impairment*: FM	States random allocation, but no description of procedure given Blinded outcome assessment No loss to follow-up

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Page, 2004[62]	RCT Computer-generated random numbers table	USA 17 participants: seven intervention, four traditional rehabilitation, six control *Inclusion criteria*: Ability to extend at least 10 degrees at the metacarpophalangeal and interphalangeal joints and 20 degrees at the wrist, stroke more than 1 year before study, score of 70 or higher on Modified MMSE, no haemorrhagic lesions, age 18–95, no excessive spasticity, no excessive pain in more affected upper limb, discharged from all forms of rehabilitation, not participating in any experimental rehabilitation or drug studies *Exclusion criteria*: None stated *Mean age*: 59.2 years (range 37–76) 82% male *Stroke details*: Unclear whether first or subsequent stroke, 58.8% right-hemiparesis, % ischaemic stroke not stated *Mean time since stroke*: 32.3 months (range 14–74) *Mean FM score at baseline*: mCIMT 31.3, traditional rehabilitation 29.3, control 31.8	*Experimental intervention*: mCIMT consisting of participation in 30 minutes of physiotherapy and 30 minutes of occupational therapy three times per week for 10 weeks. Intervention included physical therapy concentration on lower limb activities (e.g. dynamic stand and balance activities, gait training) with some time spent on upper limb stretching to facilitate ADLs. Less affected limb restrained every weekday for a 5-hour period Group size not stated *Setting*: Outpatient clinic *Comparison groups*: (1) Traditional rehabilitation participants received the same amount of occupational and physical therapy sessions, treated according to neuromuscular facilitation principles with some compensatory techniques taught (2) Control participants did not participate in any interventions for the 10-week period	Outcomes recorded pre- and post-intervention *Limb-specific function*: ARAT, MAL *Motor impairment*: FM	Attempt at concealment, but real chance of disclosure of assignment before formal entry Blinded outcome assessment No loss to follow-up

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Page, 2005[82]	RCT Random numbers table	USA Ten participants: five intervention group, five traditional rehabilitation *Inclusion criteria*: 10-degree finger extension, and 20 degrees at the wrist, ischaemic stroke fewer than 14 days before study enrolment, score of 70 or higher on Modified MMSE, age 18–95, no excessive spasticity, no excessive pain in more affected upper limb, more affected limb non-use (amount of use score of <2.5 on MAL), discharged from all forms of rehabilitation, not participating in any experimental rehabilitation or drug studies *Exclusion criteria*: None stated *Mean age*: 60.4 years (range 46–72) 80% male *Stroke details*: Unclear whether first or subsequent stroke, 80% right hemiparesis, 100% ischaemic stroke *Mean time since stroke*: 4.4 days (range 2–9) *Mean FM score at baseline*: mCIMT 33.6, traditional rehabilitation 34.8	*Experimental intervention*: mCIMT consisting of participation in 30 minutes of physiotherapy and 30 minutes of occupational therapy three times per week for 10 weeks, all administered by the same therapist. Intervention included concentration on more affected limb use in three ADLs chosen by participant and therapist (approx. 25 minutes); 5 minutes of therapy spent on affected limb range of motion. 'Shaping' techniques used with three ADLs. Less affected limb restrained every weekday for a 5-hour period Group size not stated *Setting*: Rehabilitation hospital *Comparison group*: Traditional rehabilitation group received standard therapy for 30 minutes 3 days a week for 10 weeks. Sessions included stretching of the affected limb, weight bearing with the affected limb and manual dexterity exercises	Outcomes recorded pre- and post-intervention *Limb-specific function*: ARAT, MAL *Motor impairment*: FM	Attempt at concealment, but real chance of disclosure of assignment before formal entry Blinded outcome assessment No loss to follow-up

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Suputtitada, 2004[64]	RCT 'Table of randomisation'	Thailand 69 participants: 33 intervention, 36 control *Inclusion criteria*: Age 18–80 years, history of a single stroke, duration of stroke before start of study between 1 and 10 years, minimum of 20 degrees active wrist extension and 10 degrees of finger extension, ARAT score <51, able to walk indoors without a stick indicating no major balance problems, no severe aphasia, no sensory disorder, no severe cognitive impairments *Exclusion criteria*: None stated *Mean age*: 59.4 years (range not stated) 68% male *Stroke details*: First stroke only, 92.8% right hemiparesis, 66.7% ischaemic stroke *Mean time since stroke*: Not possible to calculate, but mostly (81.2%) within 1–3 years *Total ARAT at baseline*: Intervention median 41.0 (range 26–51), control median 43.5 (range 10–51)	*Experimental intervention*: Participants received treatment for 2 consecutive weeks, 5 days a week for 6 hours a day. Healthy hand covered by a glove Participants treated in groups of three or four *Setting*: Outpatient clinic *Comparison group*: Participants treated according to neurodevelopmental therapy method. All activities performed bimanually	Outcomes recorded pre- and post-intervention *Limb-specific function*: ARAT	Attempt at concealment, but real chance of disclosure of assignment before formal entry Blinded outcome assessment No loss to follow-up

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Taub, 1993[73]	RCT Randomisation procedure not described	USA Nine participants: four intervention, five control *Inclusion criteria (expressed as exclusion criteria by authors)*: Stroke experienced more than 1 year ago, 10-degree finger extension and 20 degrees at the wrist, no balance problems, inability to make extensive use of involved upper extremity so that significant further improvement could not be expected, no serious cognitive deficits, no excessive spasticity, no serious uncontrolled medical problems, less than 75 years of age, no left arm dominance or left hemiplegia *Age*: intervention median 65 years, comparison median 63 years 22% male *Stroke details*: Unclear whether first or subsequent stroke, 100% right hemiparesis, % ischaemic stroke not stated *Mean time since stroke*: Not stated (range 1.2–18 years) *Mean functional ability on Emory test at baseline*: Intervention 3.2 (estimated), control 3.3 (estimated)	*Experimental intervention*: Unaffected arm secured in resting hand splint and sling; restraint device worn for 14 days for well over 90% of waking hours. One each weekday, patients spent 7 hours at rehabilitation centre and were given a variety of tasks, e.g. throwing a ball, playing dominoes, pushing a broom No details given of intervention providers Group size not stated *Setting*: Rehabilitation centre *Comparison group*: Attention control: procedures designed to focus attention on the involved extremity, but involved limb not given any experience of or training for active movement	Outcomes recorded pre- and post-intervention *Limb-specific function*: Emory Motor Function Test, Arm Motor Activity Test, MAL	States random allocation, but no description of procedure given No mention of blinded outcome assessment No loss to follow-up

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Wittenberg, 2003[74]	RCT Random numbers table. Randomisation performed in pairs, if possible, or in individuals, but never more than two subjects receiving intervention. Both members of pair assigned to same arm to avoid subjects observing therapy in other arm	USA 16 participants: nine intervention, seven control *Inclusion criteria*: Single, subcortical infarction more than 12 months before entry to the study, significant functional impairment of the affected side (indicated by a score of <2.7 on the MAL), voluntary extension of at least 10 degrees of the affected fingers and 20 degrees of the wrist *Exclusion criteria*: Patients without voluntary extension of at least 10 degrees of the affected fingers or 20 degrees of the wrist *Mean age*: 64 years (range 41–81) 81% male *Stroke details*: First stroke only, % right hemiparesis not stated, 12.5% had infarcts affecting non-dominant side, % ischaemic stroke not stated *Mean time since stroke*: 33 months (range 12–86) *WMFT at baseline*: intervention 6.7 (SD 2.0), control 5.5 (SD 2.6)	*Experimental intervention*: Restraint of the upper extremity during waking hours and task-orientated therapy of the affected upper extremity on 10 continuous inpatient days for 6 hours a day (4 hours a day on weekends). Therapy involved progressively improving motor task performance by a successive approximation procedure during combined physical, occupational and recreational therapy No details given of intervention providers Group size not stated *Setting*: Clinical centre *Comparison group*: Designed to be less intense (3 hours a day on weekdays and no treatment on weekends), but also aimed to improve task performance with the unaffected side	Outcomes recorded pre- and post-intervention and at 6 months post-intervention *Limb-specific function*: WMFT, MAL *Motor impairment*: Assessment of Motor and Process Skills	Attempt at concealment, but real chance of disclosure of assignment before formal entry Blinded outcome assessment No loss to follow-up

MMSE, Mini-Mental State Examination; NIHSS, National Institutes of Health Stroke Scale.

Appendix 3

Included studies: treadmill training

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Ada, 2003[87]	Randomised, placebo-controlled clinical trial Participants ranked in descending order according to walking speed and organised into consecutive pairs. Participants randomly allocated by coin toss	Australia 29 participants: 14 intervention, 15 control Volunteer sample recruited via advertisement and stroke clubs *Inclusion criteria*: >6 months post-stroke, <5 years post-stroke, first stroke, presented with hemiparesis, aged 50–85, can walk 10 m independently with a speed of <1.2 m/s *Exclusion criteria*: Cardiovascular problems that would preclude participation in training, severe cognitive deficits such that participants could not follow instructions *Mean age*: 66 years (SD 11) 70% male *Stroke details*: First stroke *Time since stroke*: Experimental 28 months (SD 17), control 26 months (SD 20) *Preintervention functional ability*: Mean walking speed (m/s) experimental 0.62 (SD 0.24), control 0.53 (SD 0.30)	*Experimental intervention*: Treadmill walking (without bodyweight support) and overground whole-task practice of walking of various types. The proportion of treadmill walking decreased by 10% each week from 80% in week 1 to 50% in week 4 Participants were treated as outpatients in a community setting for three 30-minute sessions per week for 4 weeks = 6 hours. Two subjects trained concurrently, with training provided by a physiotherapist *Comparison group*: Home exercise programme consisting of exercises to lengthen/strengthen lower limb muscles, train balance and coordination. Participants were also encouraged to walk every day. The aim was to provide a sham programme to control for the effect of placebo. Participants were instructed to carry out the programme three times a week for 4 weeks. Participants were telephoned once a week and exercises were progressed accordingly	Outcomes recorded pre- and post-intervention and at 3 months after the cessation of intervention *Limb-specific function*: 10MWS, 6MWT *Motor impairment*: Step length of both the affected and unaffected leg, cadence, step width over 10 m	Allocation concealment adequate No significant differences in baseline characteristics Blinded outcome assessment Loss to follow-up at end of treatment phase: 7% No intervention-related withdrawals Attendance: Transport was provided if necessary. On average, subjects in the experimental group attended 11 out of 12 sessions

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Da Cuhna, 2002[86]	RCT pilot study Participants were randomised to groups using random numbers to preassign participants based on recruitment order	USA 15 participants: seven intervention, eight control Participants recruited from inpatient rehabilitation *Inclusion criteria*: Within 6 weeks of stroke, gait speed of 0.6 m/s or less and score 0–2 on the Functional Ambulation category, sufficient cognition to participate, able to stand and to take at least one step with assistance, stable medical condition *Exclusion criteria*: Co-morbidity or disability that would preclude gait training, cardiac illness, uncontrolled health condition for which exercise is contraindicated, e.g. diabetes, hypertension, lower extremity joint disease, bodyweight over 110 kg, cognitive impairment, history of bilateral cerebrovascular accident *Mean age*: 57.80 years (SD 5.50) intervention, 58.90 (SD 12.90) control (not including dropouts) 100% male *Stroke details*: 92% ischaemic stroke *Time since stroke*: Experimental 15.7 days (SD 7.7), control 19 days (SD 12.7) *Prevention functional ability:* Mean walking speed (m/s): intervention 0.36 (SD 0.25), control 0.12 (SD 0.15) (not including drop-outs)	*Experimental intervention*: Participants received regular rehabilitation but without the usual gait training. In place of usual gait training was treadmill training with bodyweight support. Participants walked on a treadmill with support using a harness of up to 30% bodyweight. Support was progressively decreased as participants acquired greater self-support Participants were treated as inpatients for five 20-minute sessions per week for 3 weeks = 5 hours. Training was delivered individually by a physiotherapist *Comparison group*: Regular rehabilitation: daily sessions of physiotherapy, kinesiotherapy and occupational therapy over 3 hours. Physiotherapy focused on strengthening, function and mobility activities including gait training. Occupational therapy related to ADLs	Outcomes recorded pre- and post-intervention *Limb-specific function*: FAC, fast walking speed over 5 m, 5MWT *Motor impairment*: Gait energy expenditure, gait energy cost	Allocation concealment unclear No significant differences in baseline characteristics Blinding of outcome assessors not stated *Intervention-related withdrawals*: one subject dropped from the study because he did not complete at least nine sessions *Loss to follow-up at end of treatment phase*: 13% No details given of attendance

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Eich, 2004[89]	RCT Randomisation by independent person using sealed envelopes	Germany 50 participants: 25 intervention, 25 control Participants recruited from inpatient rehabilitation unit *Inclusion criteria*: Age range from 50–75 years, first-time supratentorial stroke, less than 6 weeks post-stroke, able to walk a minimum distance of 12 m with either intermittent help or standby while walking, BI ranging from 50–80, participation in a 12-week comprehensive rehabilitation programme, cardiovascularly stable, no other neurological or orthopaedic disease impairing walking, able to understand the purpose and content of the study *Mean age*: 62.4 years (SD 4.8) intervention, 64.0 years (SD 6.0) control 66% male *Stroke details*: First stroke. 100% ischaemic stroke *Time since stroke*: Experimental 6.1 weeks (SD 2.2), control 6.32 weeks (SD 6) *Preintervention functional ability*: Mean walking speed (m/s): intervention 0.40 (SD 0.17), control 0.44 (SD 0.22)	*Experimental intervention*: Aerobic treadmill training with bodyweight either not supported or supported to a maximum of 15% using a harness. Intervention also included other individual physical therapy. Treadmill training was graded to a defined training heart rate. If necessary, one or two therapists provided help with setting the paretic limb, assisting weight shifting and hip extension Treated as inpatients for five 60-minute sessions consisting of 30 minutes' treadmill training and 30 minutes' individual physical therapy per week for 6 weeks *Comparison group*: Bobath-orientated individual physiotherapy exclusively concentrated on walking rehabilitation. Included tone-inhibiting and gait preparatory manoeuvres and walking practice on the floor and stairs	Outcomes recorded pre- and post-intervention and at 12 weeks after the cessation of the treatment *Limb-specific function*: 10MWS, 6MWT gross motor function including walking ability using the RMA score, walking quality assessed with a customised score, adapted from the Los Ranchos Los Amigos Gait Analysis Handbook	Allocation concealment adequate No significant differences in baseline characteristics Outcome observers may not have been totally blind in the given clinical setting No loss to follow-up at end of treatment phase No intervention-related withdrawals No adverse events

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Macko, 2005[88]	RCT Participants were randomised to groups using a computer-based system that was stratified by deficit severity and age	USA 61 participants: 32 intervention, 29 control Participants recruited from chronic stroke participants with hemiparetic gait (>6 months) *Inclusion criteria*: Chronic hemiparetic stroke (more than 6 months), aged 45 years or more, residual mild to moderate hemiplegic gait deficits, achievement of adequate exercise intensity without signs of myocardial ischaemia or other contraindications to training *Exclusion criteria*: Heart failure, unstable angina, peripheral arterial occlusive disease, aphasia, dementia, untreated major depression and other medical conditions precluding participation in exercise *Mean age*: 63 years (SD 10) intervention, 64 years (SD 8) control 71% male *Stroke details*: Unclear whether first or recurrent stroke *Time since stroke*: Experimental group 35 months (SD 29), control 39 months (SD 59) *Preintervention functional ability*: Mean walking speed (m/s): intervention 0.82 (SD 0.08), control 0.9 (SD 0.10)	*Experimental intervention*: Treadmill training at target aerobic intensity of 60–70% heart-rate reserve. Training started at low intensity (40–50%) for 10–20 minutes and increased every 2 weeks as tolerated. Task-orientated training administered according to a progressive aerobic exercise formula. No bodyweight support was provided Treated as outpatients for three 40-minute sessions per week for 6 months Training was delivered by exercise physiologists under the supervision of a physician *Comparison group*: Matched duration exposure to staff implementing common components of conventional therapy. Participants completed supervised stretching movements and 5 minutes of low-intensity treadmill walking at 30–40% heart-rate reserve without bodyweight support	Outcomes recorded pre- and post-intervention *Limb-specific function*: Walking speed over 30 feet (9.1 m), 6MWT, Rivermead Mobility Index *Impairment*: Walking Impairment Questionnaire. Economy of gait Vo_2 peak	Allocation concealment unclear No significant differences in baseline characteristics Blinding of outcome assessors to group allocation for ambulatory measures and functional mobility. Treadmill exercise testing not blinded Loss to follow-up at end of treatment phase: 27% Intervention-related withdrawals: three out of 25 subjects were lost from both the experimental and control groups for compliance reasons No adverse events stated

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Pohl, 2002[85] (Details on groups supplemented from Moseley, 2005[20])	RCT Participants randomised to groups by block randomisation stratified by walking speed over 10 m without assistance	Germany 69 participants: 25 group 1, 22 group 2, 22 control (from Moseley, 2005[20]) Participants recruited from inpatient rehabilitation *Inclusion criteria*: Hemiparesis caused by ischaemic stroke or intracerebral haemorrhage, impaired gait, duration of hemiparesis > 4 weeks, no or slight spasticity, able to walk without personal assistance, time required to walk 10 m >5 seconds and <60 seconds *Exclusion criteria*: Previous treadmill training, class C/D exercise risk (American College of Sports Medicine criteria), cognitive deficits, movement disorders, orthopaedic and other gait influencing disease *Mean age*: Group 1: 58.2 years (SD 10.5), group 2: 57.1 years (SD 13.9), group 3: 61.6 years (SD 10.6) 71.6% male *Stroke details*: 70% ischaemic stroke *Time since stroke*: Experimental 16.8 weeks (SD 20.5), control 16.1 weeks (SD 18.5) *Preintervention functional ability*: Mean walking speed (m/s): group 1 0.61 (SD 0.32), group 2 0.66 (SD 0.39), group 3 0.66 (SD 0.42)	*Experimental intervention*: Trial included two intervention–control pairs: speed-dependent, and limited progressive treadmill training. The limited progressive intervention–control comparison was used Intervention group 2 consisted of limited progressive treadmill training. Participants walked on a treadmill with the training speed increased by no more than 5% of the maximum initial walking speed each week. Physical therapists directly assisted participants in the walking cycle. Bodyweight support allowed only in the first three training sessions Treated as inpatients for three 30-minute sessions per week for 4 weeks. Intervention was additional to conventional physiotherapy received by all groups *Comparison group*: Conventional gait training: physiotherapeutic gait therapy based on neurophysiological techniques. Three 45-minute sessions per week for 4 weeks. Additional to conventional physiotherapy received	Outcomes recorded pre- and post-intervention *Limb-specific function*: Fastest comfortable walking speed over 10 m using gait aids if required, FAC *Motor impairment*: Cadence, stride length	Allocation concealment unclear No significant differences in baseline characteristics Blinded outcome assessment Loss to follow-up at end of treatment period: 10% No intervention-related withdrawals No adverse events reported

continued

Author and year	Study details	Country and participants	Intervention	Outcomes	Notes
Scheidtmann, 1999[63] (Description taken from translation and supplemented by details given in Moseley, 2005[20])	Cross-over group design Participants randomised to groups (method of randomisation and concealment not stated)	Germany 15 participants allocated to experimental then control group, and 15 participants allocated to control then experimental group *Inclusion criteria*: Hemiparesis, stroke (infarct or haemorrhage), at least 4 weeks post-stroke, not able to walk, able to stand for 20 seconds *Exclusion criteria*: Cardiovascular problems or infections with a decrease in general health *Age*: 57.7 (SD 11) 52% male *Stroke details*: 69% ischaemic stroke *Time since stroke*: 58.2 days (SD 28.6) *Preintervention ability level*: Able to stand for up to 20 seconds	*Experimental intervention*: Treadmill training combined with physiotherapy with bodyweight support. Participants walked on a treadmill with partial bodyweight support provided by a harness for 30 minutes and completed 30 minutes of usual physiotherapy per day Treated as in-participants for five 1-hour sessions per week for 3 weeks *Comparison group*: Participants completed two 30-minute sessions of physiotherapy per day	Outcomes assessed at baseline, at cross-over (3 weeks) and after treatment phase (at 6 weeks) *Limb-specific function*: RMA Scale, walking speed over 10 m (item 6 of the RMA), comfortable or maximum Personal assistance, supervision and gait aid use were not reported *Motor impairment*: Self-developed gait scale based on clinical assessment	Allocation concealment unclear Blinding of outcome assessors to group allocation not reported No dropouts at end of first treatment phase No intervention-related withdrawals Adverse events not stated

Appendix 4

Characteristics of excluded studies

Study	Not functional, or no functional outcome	Mixed intervention, or main focus on exercise rather than function	Not repetition, or unable to determine amount of practice	Passive movement	Compared against another repetitive functional intervention	Method or reporting reasons	Comment
RTT							
Bagley, 2005[145]			x				
Brown, 2002[146]	x						
Carey, 2002[147]	x						
Chan, 2006[148]					x		
Chang, 2000[149]		x					
Cirstea, 2003[150]					x		
Desrosiers, 2005[151]		x					
Duncan, 2003[152]		x					
Eng, 2003[153]		x					
Feys, 1998[154]	x						
Gelber, 1995[155]	x						
Hanlon, 1996[156]						x	No baseline measures for function
Husemann, 2004[157]				x			
Inaba, 1973[158]			x				
Katz-Leurer, 2006[159]	x						
Kayhan, 1996[160]						x	Unable to contact author
Khanna, 2003[161]						x	Study did not start
Kilbreath, 1997[162]						x	Study information not available
Krutulyte, 2004[163]						x	Unable to determine whether randomised
Li, 2005[164]	x						
Liao, 2006[165]		x					
Mudie, 2002[166]	x						
Nelles, 2001[167]						x	Not designed to evaluate intervention
Pang, 2006[168]		x					
Platz, 2001[169]						x	No subgroup data
Pollock, 2002[170]	x						
Sunderland, 1992[171]		x					
Theilman, 2004[172]					x		
Wellmon, 1997[173]	x						
Xiao, 2002[174]			x				
Yang, 2005[175]		x					
CIMT							
Ploughman, 2004[176]					x		
Ro, 2006[177]						x	Subgroup of Boake, 2006[84]
Sterr, 2002[178]						x	Not RCT
Van der Lee, 1999[179]					x		

continued

Study	Not functional, or no functional outcome	Mixed intervention, or main focus on exercise rather than function	Not repetition, or unable to determine amount of practice	Passive movement	Compared against another repetitive functional intervention	Method or reporting reasons	Comment
TM							
Jaffe, 2004[180]		x					
Kosak, 2000[181]					x		
Nilsson, 2001[182]					x		
Laufer, 2001[183]					x		
Liston, 2000[184]					x		
Richards, 1993[185]		x					
Richards, 2004[186]		x					
Visintin, 1998[187]					x		Bodyweight support comparison
Werner, 2002[188]					x		

Appendix 5

Characteristics of ongoing studies

Study	Trial name	Participants	Interventions	Outcomes	Starting date	Notes
RTT						
Allison, 2005[90]	Pilot randomised control trial to assess the impact of additional supported standing practice on functional ability post-stroke	0–3 months post-stroke	Standing practice plus usual care	RMA, Trunk Control Test, Berg Balance Scale	2001	Trial complete and being submitted for publication
Askim, 2005[91]	Does intensive task specific training improve balance after acute stroke?	0–3 months post-stroke	Balance training plus usual care	Balance, sit-to-stand, walking speed, ADL, falls, lower limb function	2005 2012	Trial due to complete
English, 2005[93]	Is task-related circuit training an effective means of providing rehabilitation to acute stroke patients?	0–3 months post-stroke	Task-related circuit training	Balance, MAS, gait speed and endurance, NHP, patient satisfaction	2003	Trial complete and being submitted for publication
Harris, 2006[92]	Evaluation of a repetitive practice scheme to improve sit-to-stand performance following stroke	0–3 months post-stroke	Repetitive sit-to-stand training	Sit-to-stand	2005	Trial due to complete 2006
Langhammer, 2005 (personal communication)	Stroke: reduction of physical performance post-stroke: inactivity or secondary complications?	Post-acute rehabilitation	Motor relearning	Physical endurance, strength, balance	2003	Trial closed intake autumn 2005
Miller, 2002[95]	Early intensive task-specific sensory and motor training of the upper limb after acute stroke: a pilot study	0–3 months post-stroke	Task-specific training of the upper limb, emphasising unimanual and bimanual functional activities	MAS, Chedoke McMaster Impairment Inventory, Sickness Impact Profile, hand dexterity	2002	PhD due to complete in 2007
Sherrington, 2005[94]	A randomised controlled trial to evaluate task-related exercise classes for older people with impaired mobility	173 older people, 90 with neurological problems	Circuit designed to provide repetitive, functional, task-related exercise	Balance, gait, sit-to-stand, walking endurance	2005	Publication submitted. Subgroup data available 2008
CIMT						
Noser, 2004[96]	Constraint-induced movement therapy after subacute stroke	4–10 days post-stroke	CIMT	Arm and hand function	2000	Trial due to complete June 2007

Appendix 6

Criteria for subgroup analyses

Study	Task practice amount[a]	Time since stroke[b]	Intervention delivery[c]	Allocation concealment[d]	Comparison group[e]	Therapy time[f]	Trial size[g]
RTT							
Blennerhassett, 2004[50]	1	3	2	A	AC	EQ	2
Dean, 1997[66]	1	3	1	B	AC	EQ	1
Dean, 2000[67]	1	3	2	A	AC	EQ	1
de Sèze, 2001[76]	1	2	1	B	UC	EQ	2
Howe, 2005[77]	1	2	1	A	UC	EQ	2
Kwakkel, 1999[53]	2	1	1	A	AC	EQ	2
Langhammer, 2000[68]	1	1	1	B	UC	EQ	2
McClellan, 2004[78]	2	3	3	A	AC	EQ	2
Salbach, 2004[51]	1	3	2	A	AC	EQ	2
Turton, 1990[69]	2	2	3	B	UC	ADD	1
Van Vliet, 2005[70]	1	1	1	A	UC	EQ	2
Winstein, 2004[71]	1	1	1	A	UC	ADD	2
Yen, 2005[72]	2	3	1	B	UC	EQ	2
TM							
Ada, 2003[87]	1	3	1	A	AC	EQ	2
da Cuhna, 2002[86]	1	2	1	B	UC	EQ	1
Eich, 2004[89]	1	2	1	A	ALT	EQ	2
Macko, 2005[88]	2	3	1	B	ALT	EQ	2
Pohl, 2002[85]	1	2	1	B	UC	EQ	2
CIMT							
Alberts, 2004[83]	2	2	1	B	NT	ADD	1
Atteya, 2004[79]	2	2	1	B	NT	ADD	1
Boake, 2006[84]	2	1	1	B	UC	EQ	1
Dromerick, 2000[81]	1	1	1	B	UC	EQ	1
Page, 2001[80]	2	2	1	B	NT	ADD	1
Page, 2005[82]	1	1	1	B	UC	ADD	1
Taub, 1993[73]	2	3	1	B	AC	EQ	1
Wittenberg, 2003[74]	2	3	1	B	AC	ADD	1

[a] 1 = ⩽20 hours, 2 = >20 hours.
[b] 1 = 1–14 days, 2 = 15 days to 6 months, 3 = >6 months.
[c] 1 = individual therapy, 2 = group, 3 = self – home.
[d] A = adequate, B =inadequate/unclear.
[e] AC = attention control, UC = usual care, ALT = alternative treatment, NT = no treatment.
[f] EQ = equal time, ADD = additional time.
[g] 1 = <25 participants, 2 = ⩾25 participants.

Appendix 7

Summary of baseline characteristics of patients from the cohort in the patient data set who survived to 3 years

Age (years) median (IQR)	69.5 (64 to 77)
Gender female, *n* (%)	58 (39)
Lesion type, *n* (%)	
IC	108 (72)
Primary intracerebral haemorrhage	17 (11)
Haemorrhagic transformation of IC	4 (3)
No scan	21 (14)
Side, *n* (%)	
Left	52 (35)
Right	64 (42)
No bilateral signs	34 (23)

IC, ischaemic infarction.

Appendix 8

Numbers of patients and costs in the baseline and new groups

		Baseline groups		New groups		
Barthel category	**Average cost**	***n***	**Total cost**	***n*[a]**	**Total cost**	**Difference**
⩽10	£4,398	28	£123,154	25.5	£111,958	
11–14	£6,874	34	£233,727	28.0	£192,793	
15–17	£4,914	33	£162,169	30.5	£149,883	
18 or 19	£2,153	25	£53,819	23.5	£50,589	
20	£1,610	30	£48,291	42.5	£68,412	
Total		150	£621,159	150	£573,636	£47,523
Average			£4,141		£3,824	£317

[a] Approximate.

Appendix 9

Cost-effectiveness at 3 years per QALY gained for RFTP on outcome measures that were significant in the systematic review

Analysis[a]	Outcome	Overall[b]	Arm function[c]	ADL[c]	Walking distance[d]	Functional ambulation[d]	Sit-to-stand[d]
1	SMD	£10,870	£15,185	£11,009	£4,187	£10,187	£5,708
	SMD lower limit CI	£23,947	£77,821	£49,983	£16,539	£83,239	£19,010
	SMD upper limit CI	£6,039	£6,237	£3,942	£658	£3,025	£1,596
2	SMD: BI; 0.2:1.0	£10,870	£15,185	£11,009	£4,187	£10,187	£5,708
	SMD: BI; 0.2:0.8	£15,011	£20,405	£15,185	£6,658	£14,157	£8,558
	SMD: BI; 0.2:0.6	£21,913	£29,104	£22,144	£10,775	£20,774	£13,309
	SMD: BI; 0.2:0.4	£35,716	£46,503	£36,064	£19,010	£34,008	£22,810
	SMD: BI; 0.2:0.2	£77,126	£98,700	£77,821	£43,713	£73,711	£51,315
3	BI: EQ-5D; 1:0.05	£10,870	£15,185	£11,009	£4,187	£10,187	£5,708
	BI: EQ-5D; 1:0.04	£13,587	£18,981	£13,761	£5,234	£12,734	£7,135
	BI: EQ-5D; 1:0.03	£18,116	£25,308	£18,348	£6,979	£16,978	£9,513
	BI: EQ-5D; 1:0.02	£27,175	£37,962	£27,523	£10,469	£25,467	£14,269
	BI: EQ-5D; 1:0.01	£54,349	£75,924	£55,045	£20,937	£50,935	£28,538
4	£35 per hour	£9,143	£12,712	£9,031	£3,283	£8,734	£4,664
	£40 per hour	£10,870	£15,185	£11,009	£4,187	£10,187	£5,708
	£45 per hour	£12,597	£17,657	£12,987	£5,092	£11,640	£6,751
	£50 per hour	£14,323	£20,129	£14,965	£5,996	£13,093	£7,794
	£55 per hour	£16,050	£22,602	£16,943	£6,900	£14,546	£8,837
	£60 per hour	£17,777	£25,074	£18,921	£7,804	£15,999	£9,880
5	Discount = 0%	£10,228	£14,543	£10,367	£3,545	£9,545	£5,065
	Discount = 3.5%	£10,870	£15,185	£11,009	£4,187	£10,187	£5,708
	Discount = 6.0%	£11,301	£15,616	£11,440	£4,619	£10,618	£6,139
6	Discount = 0%	£9,191	£13,068	£9,316	£3,186	£8,577	£4,552
	Discount = 3.5%	£10,870	£15,185	£11,009	£4,187	£10,187	£5,708
	Discount = 6.0%	£12,227	£16,895	£12,377	£4,997	£11,488	£6,642

[a] 1, Base case; 2, varying the association between the SMD and the BI (shaded cells are base case); 3, varying the association between the BI and the EQ-5D (shaded cells are base case); 4, varying the cost per hour of client contact with therapist (shaded cells are base case); 5, varying the discount rate on cost (shaded cells are base case); 6, varying the discount rate on outcome (shaded cells are base case).
[b] Cost per QALY gained, where the cost of the intervention is £1265 (based on the average cost of RTT, CIMT and TM).
[c] Cost per QALY gained, where the cost of the intervention is £1126 (based on the average cost of RTT and CIMT).
[d] Cost per QALY gained, where the cost of the intervention is £999 (based on the average cost of RTT and TM).

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Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor, Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster, Consumer member, HTA – Expert Advisory Network

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The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Alpha House, Enterprise Road
Southampton Science Park
Chilworth
Southampton SO16 7NS, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@hta.ac.uk
http://www.hta.ac.uk

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