Caregiver-mediated exercises after stroke

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Chapter 1

General introduction

Stroke is the third cause of disability in the world with about 25 million stroke survivors worldwide.[1] Stroke is classically characterized as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage.[2] While the incidence of stroke is declining in most Western countries, the prevalence of persons living with the consequences of stroke is increasing due to the ageing population and improved quality of health care.[3] The number of people living with stroke in Europe is expected to increase by one million between 2015 and 2035, reaching 4,631,050.[4] In the Netherlands, stroke ranks second in terms of disease burden with approximately 477,800 persons living with the consequences of stroke (including transient ischemic attack).[5] The socioeconomic impact of stroke is estimated at €45 billion in Europe in 2015.[4, 6] In The Netherlands costs of care for stroke is estimated €2.3 billion in 2011.[7] These costs are expected to increase in the next decades.

Intensity of exercise therapy

Stroke recovery is heterogeneous and may range from complete neurological recovery within days to persisting neurological deficits after 6 months.[8] Impaired body functions such as strength, sensory function, communication, and cognition can affect mobility, activities of daily living (ADL) and quality of life. Stroke recovery is a complex process of poorly understood mechanisms of spontaneous neurobiological recovery[8, 9] and learning-dependent processes including behavioral restitution and compensation.[8, 10] Currently, strong evidence is available favoring high repetitive task-orientated and task-specific training for improving motor function in all phases poststroke.[11, 12] In addition, meta-analyses suggest that increased intensity of exercise training by applying more repetitions of task-specific training leads to better functional outcome in stroke patients in terms of mobility and basic ADL.[11, 13]

Like the other parts in the western world, resources (mostly staff) for rehabilitation after stroke are becoming increasingly scarce and it proves to be difficult to apply sufficient dose of exercise therapy in the Netherlands.[14] It is therefore important to find new ways to augment the intensity of exercise therapy. In recent years, innovative technologies have been introduced in stroke services to augment exercise therapy such as upper and lower limb robotics,[15, 16] tele-rehabilitation services[17-19] and virtual reality training.[20] In addition, help of therapy assistants[21, 22] and self-training[23] can be used to increase the intensity of exercise therapy. However, the added value of these interventions above usual care is limited. Realizing the unmet needs by lack of staff, inspired by literature[24] and by families in the rehabilitation centre who already tried to exercise with their loved one with stroke, we became interested in the concept of caregiver-mediated exercises (CME) as an alternative method to increase the intensity of exercise therapy and thereby improve outcomes after stroke. With CME,

the patient with stroke and a caregiver are trained to perform exercises together to increase intensity of exercise training for the patient after stroke. The caregiver can for example be a partner, family member, neighbour or friend.

In order to determine current evidence, we first performed a systematic review of the literature according to the guidelines of Cochrane in **chapter 2**.

CME and early supported discharge

A better functional outcome with CME may facilitate early supported discharge (ESD) and lead to a significant reduction in length of inpatient stay (LOS) in the first months poststroke. Especially when the exercises focus on improving sitting and standing balance, transfers and gait performance, because these aspects are important mobility criteria for discharge from an inpatient facility to outpatient rehabilitation in the community setting.[25] ESD is defined by The National Institute for Health and Care Excellence in the United Kingdom as 'an intervention for adults after stroke that allows their care to be transferred from an inpatient environment to a community setting. It enables people to continue their rehabilitation therapy at home, with the same intensity and expertise that they would receive in hospital' (page 25).[26] However, the content of the support given by ESD may vary considerably between countries and regions.[27] The Stroke Alliance For Europe (SAFE) recommends adequate management of discharge planning in order to keep the quality of services in the community at the same level as provided during the inpatient care in hospitals and rehabilitation wards. They describe a current shortage of ESD services in all European countries and defined as target for 2030 to provide ESD to at least 20% of all stroke survivors living in Europe.[4] In our opinion, the support given by CME might have an added value in ESD by providing the possibility to continue exercising at home and by empowering patient and caregiver to cope with the transition from inpatient care to their own home setting.[28-32]

The costs of inpatient rehabilitation are significantly higher when compared to outpatient rehabilitation services. Consequently, reducing LOS can significantly decrease the costs per patient.[33] Therefore, CME aimed at reducing LOS in a hospital, nursing home and/or rehabilitation centre may be an innovative way to improve health-related quality of live and reduce costs in health care.

Involvement of the caregiver

Being a caregiver of a stroke patient is associated with persistent psychological distress and burden.[34, 35] At first sight, CME might be yet another burden for caregivers in already stressful

times. However, the importance of involving the caregiver in stroke rehabilitation[36-38] and their role in (early supported) discharge has been emphasized previously.[39, 40] CME might even empower the caregiver and increase caregiver's awareness and understanding about the physical and cognitive abilities of the patient with stroke. Indeed, several studies showed that involving a caregiver in exercise or skill training did not increase, and even decreased caregiver strain.[24, 41] More information is needed about the effects of CME on the caregiver. In addition, previous studies on CME report little to nothing about how many caregivers are available, willing and suitable for CME. To learn about implementation possibilities this information needs to be collected.

E-health and tele-rehabilitation

While CME have already shown to be feasible and promising,[24] theoretically, the combination with e-health including tele-rehabilitation services may further support the caregiver and patient to do their exercises. In the present thesis, a distinction can be made between e-health and tele-rehabilitation services. E-health can be defined as 'the use of Information and Communication Technologies (ICT) for health'.[42] Tele-rehabilitation services is often defined as 'the delivery of rehabilitation services using telecommunication technology'.[43] The definition of e-health is therefore broader than that of tele-rehabilitation alone. Tele-rehabilitation includes technology which uses telecommunication such as phone or video conferencing for support in health services. At the time we developed our ideas to combine CME with e-health, studies investigating the added value of e-health within stroke rehabilitation were just emerging.[17] In recent years, e-health is increasingly used to support rehabilitation interventions. Two updated systematic reviews show that evidence of cost-effectiveness is limited but that e-health can be a suitable alternative when compared to usual rehabilitation care.[18, 19] In addition, Cramer et al recently compared activity-based training via home-based telerehabilitation to traditional inpatient rehabilitation. They found that both interventions produced substantial gain in arm motor function regardless of how the training was provided.[44] Our hypothesis is that support for patient and caregiver during CME by using an application with instructional videos and the possibility to contact the therapist using tele-rehabilitation services, may be an innovative way to improve mobility, monitor improvement, allow remote coaching of patients and their caregiver, and improve engagement[45] of the patient-caregiver couple.

Developing and describing a CME program

We developed a program for patients with stroke, with the acronym CARE4STROKE, in which CME and e-health are combined aimed at improving functional outcome by increasing intensity of exercise therapy. At that time one well-designed trial investigating a CME program of Galvin and colleagues was published (the FAME trial).[24] They showed that an 8-week CME program in addition to usual care aimed to increase intensity of exercise therapy was feasible. We therefore used some components of their program and refined the program further, among other things by combining CME with e-health. CARE4STROKE is an 8-week program by which patients with stroke can exercise together with their caregiver, in addition to usual care. The exercises are presented in instructional videos which can be viewed in a stand-alone application on a tablet or smartphone. To make sure the program follows training principles like patient engagement, goal setting and an incremental training regimen,[8] the exercises in the CARE4STROKE program are patient-tailored and weekly progressive. In addition, safety during CME is of utmost importance. A caregiver should be physically able to support a patient during mobility exercises to prevent adverse events. Therefore, special attention was given to developing a reliable strategy for participant selection, securing safety during exercising and monitoring strain of patients and caregivers. All exercises were developed in collaboration with rehabilitation physicians, movement scientists, therapists, physiotherapy students and patient-caregiver couples. In **chapter 3**, all key elements of the CARE4STROKE program are systematically described in detail using the Template for Intervention Description and Replication (TIDieR) checklist.[46-48] allowing replication of the CME program in the future.

CARE4STROKE trial

To investigate the (cost)effectiveness, the CARE4STROKE program was compared to usual care alone in an observer blinded, proof-of-concept, randomized controlled trial. Patient-caregiver couples were included in a rehabilitation centre, nursing home or hospital in the Amsterdam region. The program continued at home if discharge was before the end of the intervention period. It was hypothesized that the CARE4STROKE program would lead to better functional outcome in terms of self-reported mobility and reduced costs as reflected by the primary outcome measures, the mobility domain of the Stroke Impact Scale (SIS, version 3.0) and LOS. For transparency, the design of the study is described in detail in **chapter 4**. The recruitment for the CARE4STROKE trial ran from April 2014 until July 2016 and was funded by ZonMw (grant no: 837001408 and grant no: 606300098012). The results of this trial are presented in **chapter 5**.

Experiences of participants with CME

To give more meaning to our results and gain information about facilitators and barriers for possible future implementation of CME, the perspectives and experiences of the participants with the CARE4STROKE program were studied using qualitative research techniques. To date, only one previous study asked participants about their experiences with exercising with a family member after stroke.[31] They found that individuals with stroke as well as their families felt that their rehabilitation was enhanced by the active role of the family members. However, they did not specifically study the interaction between patient and caregiver and possible additional effects. **Chapter 6** presents the results a qualitative study aimed at how patient-caregiver couples exercise together and what exercising together brings about, besides more hours of practice.

This thesis ends with a general discussion (**chapter 7**) in which a brief overview of the main findings of chapters 2–6 is presented. In addition, a reflection on our results, implications and recommendations for further research will be provided.

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Chapter 2

Caregiver-mediated exercises for improving outcomes after stroke

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Cochrane Database of Systematic Reviews 2016;12:CD011058

Abstract

Background:

Stroke is a major cause of long-term disability in adults. Several systematic reviews have shown that a higher intensity of training can lead to better functional outcomes after stroke. Currently, the resources in inpatient settings are not always sufficient and innovative methods are necessary to meet these recommendations without increasing healthcare costs. A resource efficient method to augment intensity of training could be to involve caregivers in exercise training. A caregiver-mediated exercise programme has the potential to improve outcomes in terms of body function, activities, and participation in people with stroke. In addition, caregivers are more actively involved in the rehabilitation process, which may increase feelings of empowerment with reduced levels of caregiver burden and could facilitate the transition from rehabilitation facility (in hospital, rehabilitation centre, or nursing home) to home setting. As a consequence, length of stay might be reduced and early supported discharge could be enhanced.

Objectives:

To determine if caregiver-mediated exercises (CME) improve functional ability and health-related quality of life in people with stroke, and to determine the effect on caregiver burden.

Search methods:

We searched the Cochrane Stroke Group Trials Register (October 2015), CENTRAL (the Cochrane Library, 2015, Issue 10), MEDLINE (1946 to October 2015), Embase (1980 to December 2015), CINAHL (1982 to December 2015), SPORTDiscus (1985 to December 2015), three additional databases (two in October 2015, one in December 2015), and six additional trial registers (October 2015). We also screened reference lists of relevant publications and contacted authors in the field.

Selection criteria:

Randomised controlled trials comparing CME to usual care, no intervention, or another intervention as long as it was not caregiver-mediated, aimed at improving motor function in people who have had a stroke.

Data collection and analysis:

Two review authors independently selected trials. One review author extracted data, and assessed quality and risk of bias, and a second review author cross-checked these data and assessed quality. We determined the quality of the evidence using GRADE. The small number of included studies limited the pre-planned analyses.

Main results:

We included nine trials about CME, of which six trials with 333 patient-caregiver couples were included in the meta-analysis. The small number of studies, participants, and a variety of outcome measures rendered summarising and combining of data in meta-

analysis difficult. In addition, in some studies, CME was the only intervention (CME-core), whereas in other studies, caregivers provided another, existing intervention, such as constraint-induced movement therapy. For trials in the latter category, it was difficult to separate the effects of CME from the effects of the other intervention.

We found no significant effect of CME on basic ADL when pooling all trial data post intervention (4 studies; standardised mean difference (SMD) 0.21, 95% confidence interval (CI) -0.02 to 0.44; *P*=0.07; moderate-quality evidence) or at follow-up (2 studies; mean difference (MD) 2.69, 95% CI -8.18 to 13.55; *P*=0.63; low-quality evidence). In addition, we found no significant effects of CME on extended ADL at post intervention (two studies; SMD 0.07, 95% CI -0.21 to 0.35; *P*=0.64; low-quality evidence) or at follow-up (2 studies; SMD 0.11, 95% CI -0.17 to 0.39; *P*=0.45; low-quality evidence). Caregiver burden did not increase at the end of the intervention (2 studies; SMD -0.04, 95% CI -0.45 to 0.37; *P*=0.86; moderate-quality evidence) or at follow-up (1 study; MD 0.60, 95% CI -0.71 to 1.91; *P*=0.37; very low-quality evidence).

At the end of intervention, CME significantly improved the secondary outcomes of standing balance (3 studies; SMD 0.53, 95% CI 0.19 to 0.87; *P*=0.002; low-quality evidence) and quality of life (1 study; physical functioning: MD 12.40, 95% CI 1.67 to 23.13; *P*=0.02; mobility: MD 18.20, 95% CI 7.54 to 28.86; *P*=0.0008; general recovery: MD 15.10, 95% CI 8.44 to 21.76; *P*<0.00001; very low-quality evidence). At follow-up, we found a significant effect in favour of CME for Six-Minute Walking Test distance (1 study; MD 109.50 m, 95% CI 17.12 to 201.88; *P*=0.02; very low-quality evidence). We also found a significant effect in favour of the control group at the end of intervention, regarding performance time on the Wolf Motor Function test (2 studies; MD -1.72, 95% CI -2.23 to -1.21; *P*<0.00001; low-quality evidence). We found no significant effects for the other secondary outcomes (i.e. patient: motor impairment, upper limb function, mood, fatigue, length of stay and adverse events; caregiver: mood and quality of life).

In contrast to the primary analysis, sensitivity analysis of CME-core showed a significant effect of CME on basic ADL post intervention (2 studies; MD 9.45, 95% CI 2.11 to 16.78; *P*=0.01; moderate-quality evidence).

The methodological quality of the included trials and variability in interventions (e.g. content, timing, and duration), affected the validity and generalisability of these observed results.

Authors' conclusions:

There is very low- to moderate-quality evidence that CME may be a valuable intervention to augment the pallet of therapeutic options for stroke rehabilitation. Included studies were small, heterogeneous, and some trials had an unclear or high risk of bias. Future high-quality research should determine whether CME interventions are (cost-)effective.

BACKGROUND

Description of the condition

Stroke is a major cause of long-term disability in adults with effects on activities of daily living (ADL) and quality of life (QoL). Although most people leave the rehabilitation setting with some level of independent walking, many have residual walking disabilities and it has been reported that following rehabilitation, only 7% of stroke survivors can walk at a level commensurate with community participation (Ada 2009). Twelve months after stroke about 28% of people with stroke remain dependent in their basic ADLs, such as dressing, toileting, and indoor mobility (Ullberg 2015). Pettersen and colleagues reported that 32% of people with stroke living at home after three years were inactive in extended ADL (Pettersen 2002). Any treatment that improves functional outcome can potentially reduce the burden of this illness for the person, their caregivers, and society.

Description of the intervention

Several systematic reviews have shown that a higher intensity of training in terms of time spent on exercise therapy can lead to better functional outcome in people with stroke in terms of ADL and functional performance (French 2010; Galvin 2008a; Kwakkel 2004; Kwakkel 2006; Langhorne 2011; Lohse 2014; Veerbeek 2011; Veerbeek 2014). One resourceefficient method to increase intensity of training could be to involve caregivers in exercise training (De Weerdt 2002). We define caregiver-mediated exercises (CME) as the person with stroke performing exercises together with a caregiver under the auspices of a physical or occupational therapist. "Under the auspices" means that the therapist is involved as a coach by instructing both patient and caregiver on how to perform the exercises, and evaluating them on a regular basis. Hereby, the exercises are aimed at improving ADL including mobility, such as making transfers, standing, and walking.

How the intervention might work

Performing exercises together with a caregiver has the potential to augment the intensity of practice without increasing healthcare costs. This could improve outcomes in terms of body functions, activities, and participation as well as cost effectiveness in people with stroke. In addition, caregivers are more actively involved in CME than in the usually applied rehabilitation services, which may increase feelings of empowerment with reduced levels of caregiver burden (Brereton 2002; Smith 2004a). CME could lead to a reduced length of inpatient stay or outpatient treatment in hospitals, rehabilitation, and nursing settings,

and may improve outcomes in self-management, empowerment, and QoL of patients and caregivers.

Why it is important to do this review

Several systematic reviews have indicated that additional exercise therapy and repetitive task training have a significant, favourable effect on functional outcome after stroke, and concluded that the more time spent on exercise therapy (Galvin 2008a; Kwakkel 2004; Kwakkel 2006; Lohse 2014; Veerbeek 2011), and the higher the number of repetitions, the better the outcome (French 2010; Langhorne 2011; Veerbeek 2014). Therefore, clinical guidelines recommend that people who are in a rehabilitation setting should have the opportunity to train intensively (ESO 2008; NICE 2013; SIGN 2010; Veerbeek 2014). For example, the stroke guideline in the UK recommends a daily dose of 45 minutes of exercise therapy (NICE 2013). Currently, the resources in inpatient settings are not sufficient to meet these recommendations. Most people admitted to stroke units, rehabilitation wards, and nursing homes spend most of their waking time during the working week inactive (Bernhardt 2004; Smith 2008; West 2012), and on weekends, rehabilitation services (including exercise therapy) in most hospital and rehabilitation settings are not available (Otterman 2012). Therefore, it is important to find innovative methods, such as CME, to enhance intensity of training after stroke, without increasing costs. However, the caregiver taking the role of a therapist (instead of a family role) may burden the caregiver with yet another task (Gordon 2004). Therefore, it is important to study the mood, burden, and QoL of caregivers when involving them in CME systematically. No systematic review has yet been conducted to evaluate the effect of caregiver participation in exercise training on functional outcome after stroke, or to evaluate the effect on mood and burden of the caregiver when involved in CME.

OBJECTIVES

To determine if caregiver-mediated exercises (CME) improve functional ability and health-related quality of life in people with stroke, and to determine the effect on caregiver burden.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), including cluster-RCTs. One group of the trial must have received CME and we considered this group as the experimental group for this review. The other (control) group could have received usual treatment, no treatment, or any other type of rehabilitation intervention or attention-control as long as it was not caregiver-mediated. We accepted usual treatment when it was described as usual care in the setting of the participant.

Types of participants

People, at least 18 years old, who had had a stroke. Stroke is defined by the World Health Organization as "a clinical syndrome typified by rapidly developing signs of focal or global disturbance of cerebral functions, lasting more than 24 hours or leading to death, with no apparent causes other than of vascular origin" (WHO 1989). We included RCTs regardless of timing after stroke and setting.

Types of interventions

One group of the RCT must have included CME, whereas the caregiver involvement was not explicitly asked for in the other group of the RCT. We included trials in which the patient and their caregiver were trained or instructed together, as well as trials in which the caregiver was trained or instructed alone. There was no limit to the number of sessions or to the frequency of delivery. We included all types of exercises as long as they were aimed at improving patients' abilities to perform daily activities. Therefore, we excluded RCTs of speech, swallowing, or cognitive interventions done together with a caregiver. We defined a caregiver or carer as an unpaid or partially paid person who voluntarily helped an impaired person with his or her ADL. In other words, the mediated services were not applied by a professional in health care but in most cases, someone who was close to the patient and voluntarily offered his or her services. This may have been a partner, family member, or friend, but it can also have been a volunteer. We argued that this person was 'not a professional' such as a 'therapy assistant'. When a professional in health services applied the mediated exercises, we excluded the RCT. We included interventions delivered at any location, for example at home, in hospital, or in a rehabilitation setting. Because a caregiver can be the provider of an intervention, we did not exclude trials that combined CME with an existing intervention. However, we did

differentiate between trials in which CME was the only intervention (CME-core) and trials in which a caregiver was used to deliver another, existing intervention. We contacted trial authors when it was unclear whether a trial met our definition.

Types of outcome measures

Primary outcomes

- Patient: basic ADL measures, such as the Barthel index (BI) (Collin 1988; Mahoney 1965), Functional Independence Measure (FIM) (Dodds 1993), modified Rankin Scale (mRS) (De Haan 1995; Dromerick 2003); extended ADL measures, such as the Nottingham Extended Activities of Daily Living (NEADL) Index (Nouri 1987), or Frenchay Activities Index (FAI) (Wade 1985). When found, we combined scales with the same construct.
- Caregiver: measures of burden, for example Caregiver Strain Index (CSI) (Robinson 1983). When found, we combined scales with the same construct.

When possible we distinguished between caregivers who were family or friends and other types of caregivers, such as volunteers, for the above-mentioned measures of outcome.

Secondary outcomes

- Measures of motor impairment: Motricity Index (MI) (Collin 1990), Fugl-Meyer Assessment (FMA) (Duncan 1983; Sanford 1993; Shelton 2001).
- Gait and gait-related measures: walking speed, walking distance, Timed-Up-and-Go test (TUG) (Collen 1990; Flansbjer 2005), Rivermead Mobility Index (RMI) (Collen 1991; Hsieh 2000; Hsueh 2003), Berg Balance Scale (BBS) (Berg 1992; Berg 1995; Mao 2002; Stevenson 2001).
- Measures of upper limb activities or function, for example, Action Research Arm Test (ARAT) (Chen 2012; Hsieh 1998; Platz 2005).
- Measures of mood and QoL of the patient, for example, measured by the Stroke Impact Scale (SIS) (Duncan 1999; Duncan 2002; Duncan 2003), and Hospital Anxiety and Depression Scale (HADS) (Aben 2002; Bjelland 2002; Herrmann 1997; Zigmond 1983).
- Measures of fatigue of the participant, for example, measured by the Fatigue Severity Scale (FSS) (Valko 2008).
- Length of stay in hospital, rehabilitation centre, or nursing home, or treatment in an outpatient clinic.
- Adverse outcomes, for example, pain, injury, or falls. When possible, we compared the total number of falls between groups, and the number of patients experiencing at least one fall between groups.

- Caregiver: measures of mood and QoL, for example, HADS (Aben 2002; Bjelland 2002; Herrmann 1997; Zigmond 1983), or CarerQoL (Brouwer 2006; Hoefman 2011).

When we found scales measuring the same construct, we combined them. If studies reported outcome measures other than the ones mentioned above, we verified if they measured the same construct. If this was the case, we pooled them; if they did not measure the same construct, we reported these outcomes separately.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We searched for trials in all languages and arranged translation of papers where necessary. Due to time limitations, we were unable to perform the review within one year after the first search (April 2014). Therefore, it was necessary to update our search in October 2015. We used the same search strategy but due to different availability of Information Specialists and providers of databases, we adjusted the search strategies accordingly: Embase.com instead of Ovid/Embase, and EBSCO/AMED instead of Ovid/AMED. We limited the update searches between 2014 and 2016.

Electronic searches

We searched the following databases and trials registers.

- Cochrane Stroke Group Trials Register (last searched October 2015).
- Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2015, Issue 10).
- Cochrane Database of Systematic Reviews (CDSR) (the Cochrane Library, last searched October 2015).
- Cochrane Methodology Register (CMR) (the Cochrane Library, last searched October 2015).
- Database of Abstracts of Reviews of Effects (DARE) (the Cochrane Library, last searched October 2015).
- Health Technology Assessment Database (HTA) (the Cochrane Library, last searched October 2015).
- NHS Economic Evaluation Database (NHS EED) (the Cochrane Library, last searched October 2015).
- MEDLINE (Ovid) (from 1946 to October 2015).
- Embase (Ovid from 1980 to April 2014 and Embase.com from 2014 to December 2015).

- CINAHL (Cumulative Index of Nursing and Allied Health Literature) (EBSCO) (from 1982 to December 2015).
- SPORTDiscus (EBSCO) (from 1985 to December 2015).
- AMED (Alternative and Complementary Medicine) (Ovid from 1985 to April 2014 and EBSCO from 1985 to December 2015).
- Physiotherapy Evidence Database (PEDro) (from 1929 to October 2015) (www.pedro.org.au/).
- REHABDATA (from 1956 to October 2015) (www.naric.com/?q=en/REHABDATA).
- ClinicalTrials.gov (www.clinicaltrials.gov/).
- EU Clinical Trials Register (www.clinicaltrialsregister.eu).
- Stroke Trials Registry (www.strokecenter.org/trials/).
- Current Controlled Trials (www.controlled-trials.com).
- World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp/en/).
- Australian New Zealand Clinical Trials Registry (www.anzctr.org.au/).

See Textbox 2.1 for the MEDLINE search strategy. The other search strategies can be found in the article or can be obtained from the author.

Searching other resources

To identify further published, unpublished, and ongoing studies we:

- searched the reference lists of all included articles;
- contacted experts and authors in the field;
- used Science Citation Index Cited Reference Search for forward tracking of important articles.

Data collection and analysis

Selection of studies

Two review authors (JV, MM) independently screened the titles of records obtained from the electronic searches and excluded obviously irrelevant studies. Subsequently, we screened the remaining abstracts and excluded those that were irrelevant. Finally, we obtained the full-text articles for the remaining studies and the same two review authors selected studies for inclusion in the review based on the inclusion criteria described previously. We resolved any disagreement by discussion and, where necessary, in consultation with a third review author (EvW).

Textbox 2.1 MEDLINE search strategy (Ovid).

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp intracranial arteriovenous malformations/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or vasospasm, intracranial/ or vertebral artery dissection/ or brain injuries/ or brain injury, chronic/
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$)).tw.
5. hemiplegia/ or exp paresis/
6. (hempar$ or hemipleg$ or brain injur$).tw.
7. Gait Disorders, Neurologic/
8. or/1-7
9. caregivers/ or friends/ or exp parents/ or spouses/ or visitors to patients/
10. voluntary workers/ or hospital volunteers/ or home health aides/ or exp parent-child relations/ or exp interpersonal relations/
11. family/ or exp family characteristics/ or family relations/ or intergenerational relations/
12. family therapy/ or family health/
13. (carer$ or caregiver$ or care giver$ or care-giver$).tw.
14. (family$ or families or spous$ or parent or parents or father$ or mother$ or friend or friends or husband$ or wife or wives or partner or partners or neighbour or neighbours).tw.
15. next of kin.tw.
16. ((non-professional or non professional or informal or volunteer$ or relative or relatives) adj5 (exercise$ or rehabilitat$ or therap$ or train$)).tw.
17. or/9-16
18. rehabilitation/ or "activities of daily living"/ or exp exercise therapy/ or occupational therapy/ or physical therapy modalities/ or exp exercise movement techniques/ or exp Exercise/ or Physical Fitness/ or physical endurance/ or early ambulation/ or walking/ or exp "Physical and Rehabilitation Medicine"/
19. (rehabilitat$ or activities of daily living or ADL or exercis$ or physiotherap$ or occupational therap$ or physical therap$ or physical fitness or physical endurance or ambulat$ or walk$ or progressive resist$).tw.
20. (muscle adj5 strengthen$).tw.
21. 18 or 19 or 20
22. 8 and 17 and 21
23. cerebrovascular disorders/rh or exp basal ganglia cerebrovascular disease/rh or exp brain ischemia/rh or exp carotid artery diseases/rh or exp intracranial arterial diseases/rh or exp intracranial arteriovenous malformations/rh or exp "intracranial embolism and thrombosis"/rh or exp intracranial hemorrhages/rh or stroke/rh or exp brain infarction/rh or vasospasm, intracranial/rh or vertebral artery dissection/rh or brain injuries/rh or brain injury, chronic/rh or hemiplegia/rh or exp paresis/rh or Gait Disorders, Neurologic/rh
24. 17 and 23
25. 22 or 24
26. Randomized Controlled Trials as Topic/
27. random allocation/

Textbox 2.1 ***Continued*****.**

28. Controlled Clinical Trials as Topic/
29. control groups/
30. clinical trials as topic/
31. double-blind method/
32. single-blind method/
33. cross-over studies/
34. Therapies, Investigational/
35. Research Design/
36. randomized controlled trial.pt.
37. controlled clinical trial.pt.
38. clinical trial.pt.
39. (random$ or RCT or RCTs).tw.
40. (controlled adj5 (trial$ or stud$)).tw.
41. (clinical$ adj5 trial$).tw.
42. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
43. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
44. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
45. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
46. (cross-over or cross over or crossover).tw.
47. trial.ti.
48. (assign$ or allocate$).tw.
49. or/26-48
50. 25 and 49
51. exp animals/ not humans.sh
52. 50 not 51.

Data extraction and management

Two review authors (JV, MM) conducted data extraction and reviewed risk of bias of the eligible trials. The review authors were not blinded to study authors, journals, or outcomes. We resolved any disagreement about risk of bias by discussion. If we could not reach consensus, a third review author (EvW) made the final decision. One review author (JV) extracted data and a second review author (MM) cross-checked the extracted data using a standard checklist, including randomisation method, study population, intervention methods and delivery, outcome measures, and follow-up.

Assessment of risk of bias in included studies

We used the tool for assessing risk of bias in included RCTs as described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We assessed allocation (selection bias), blinding (performance and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential sources of bias, such as management of dropouts (no intention-to-treat analysis). We presented the results in 'Risk of bias' tables. We provided our judgement ('low risk', 'high risk' or 'unclear risk') for each entry, followed by a description of the judgement. We made our judgements transparent, and used comments or quotes when necessary.

Measures of treatment effect

We extracted means and standard deviations (SDs) of post-intervention scores and follow-up scores. Where available, we also extracted means and SDs of change from baseline.

For continuous outcomes using similar measurement scales, we used the mean difference (MD) with 95% confidence intervals (CIs). If similar outcomes were measured on different scales, we used Hedges' g, calculated the 95% CI and standard mean difference (SMD).

We reported the direction of the effect for every scale to align the treatment effects between outcome scales. For scales in which a low score reflected a favourable outcome and a high score an unfavourable outcome, we multiplied scores by -1.

We used Review Manager 5 for all quantitative analyses (RevMan 2014).

Unit of analysis issues

We took into account that studies can apply different randomisation methods, for example, at the level of a participant or at the level of a group of participants (cluster randomisation).

In selected studies with multiple intervention groups, we made multiple pair-wise comparisons between all possible pairs of intervention groups. We made sure that participants were not double-counted in the analysis.

Dealing with missing data

If data were missing or were not in a form suitable for quantitative pooling, we contacted the trial authors to request additional information.

Assessment of heterogeneity

We assessed the impact of heterogeneity in the meta-analysis for each outcome with the I^2 statistic (Higgins 2011). When there was substantial statistical heterogeneity (I^2 greater than 50%) we used a random-effects model, otherwise we used a fixed-effect model for meta-analysis.

Assessment of reporting biases

Because we identified fewer than 10 studies, we did not assess reporting bias by a funnel plot in which effect estimates and precision (standard error) of individual RCTs are plotted, as we had planned.

Data synthesis

We performed a meta-analysis of the comparison CME versus control group (usual care, no intervention, or any other intervention) where there were two or more RCTs with a low risk of bias in which study population, intervention, and outcome measures were the same. We determined the quality of evidence using GRADE levels of evidence.

We included a 'Summary of findings' table using the Cochrane template, and included the following seven outcomes: ADL measures, burden of the caregiver, walking speed, walking distance, mood of the patient, length of stay, and adverse events (falls) (see Summary of findings table). For each outcome, we included the number of participants, the overall quality of the evidence using GRADE levels of evidence, the magnitude of the effect, a measure of burden of the outcome, and comments (Guyatt 2008a; Guyatt 2008b).

In the text and tables, we have systematically described those studies that could not be included in the meta-analysis. In the same way, we systematically reported other outcome measures that we could not include in a meta-analysis because they did not measure the same construct as our predefined outcome measures.

We used Review Manager 5 for the analyses (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

Where two or more studies per subgroup were available, we performed subgroup analysis for:

- interventions with a higher dose of training in the intervention group than the control group versus interventions with a same dose of training in intervention and control groups;
- interventions within six months after stroke and interventions beyond six months after stroke;

- interventions aimed at the upper extremity and interventions aimed at the lower extremity.

Sensitivity analysis

A caregiver could be a provider of an existing intervention, for example constraint-induced movement therapy (CIMT). We included trials investigating this form of CME. However, in these trials, it was difficult to separate the effects of CME from the effects of the intervention. In the other trials, CME itself was considered as the only intervention under study. Therefore, we performed a sensitivity analysis in which only these trials were included (CME-core). A priori, we did not plan this sensitivity analysis, but decided afterwards to include this analysis in light of the type of studies that we identified. In this sensitivity analysis, we also repeated the subgroup analyses.

Where we applied a fixed-effect model, we subsequently applied a random-effects model to assess the robustness of the results to the method used.

RESULTS

Description of studies

See Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies tables.

Results of the search

Through electronic searches we found 8107 citations. In addition, one potentially relevant trial was already known to us, but not found through electronic searches (Wall 1987). After removing duplicates, we screened 5640 citations. Based on screening of titles, we excluded 5201 obviously irrelevant studies and screened the remaining 439 abstracts. Subsequently, we excluded 307 studies based on the abstract. Finally, we assessed 132 full-text articles or trial registry entries for eligibility.

After an extensive search, we still could not obtain full-text articles for four studies ("THE DAYS AFTER"; "Family boosts results of poststroke therapy"; Liu 2012; Wang 2014). We identified 11 relevant systematic reviews, which we screened for trials (Bakas 2014; Brereton 2007; Glasdam 2010; Klinke 2015; Lawler 2013; Legg 2011; Morris 2014; Parke 2015; Pollock 2014a; Pollock 2014b; Warner 2015). In total, we identified 46 potentially relevant trials. The results of the search are summarised in Figure 2.1. We were able to include nine trials for

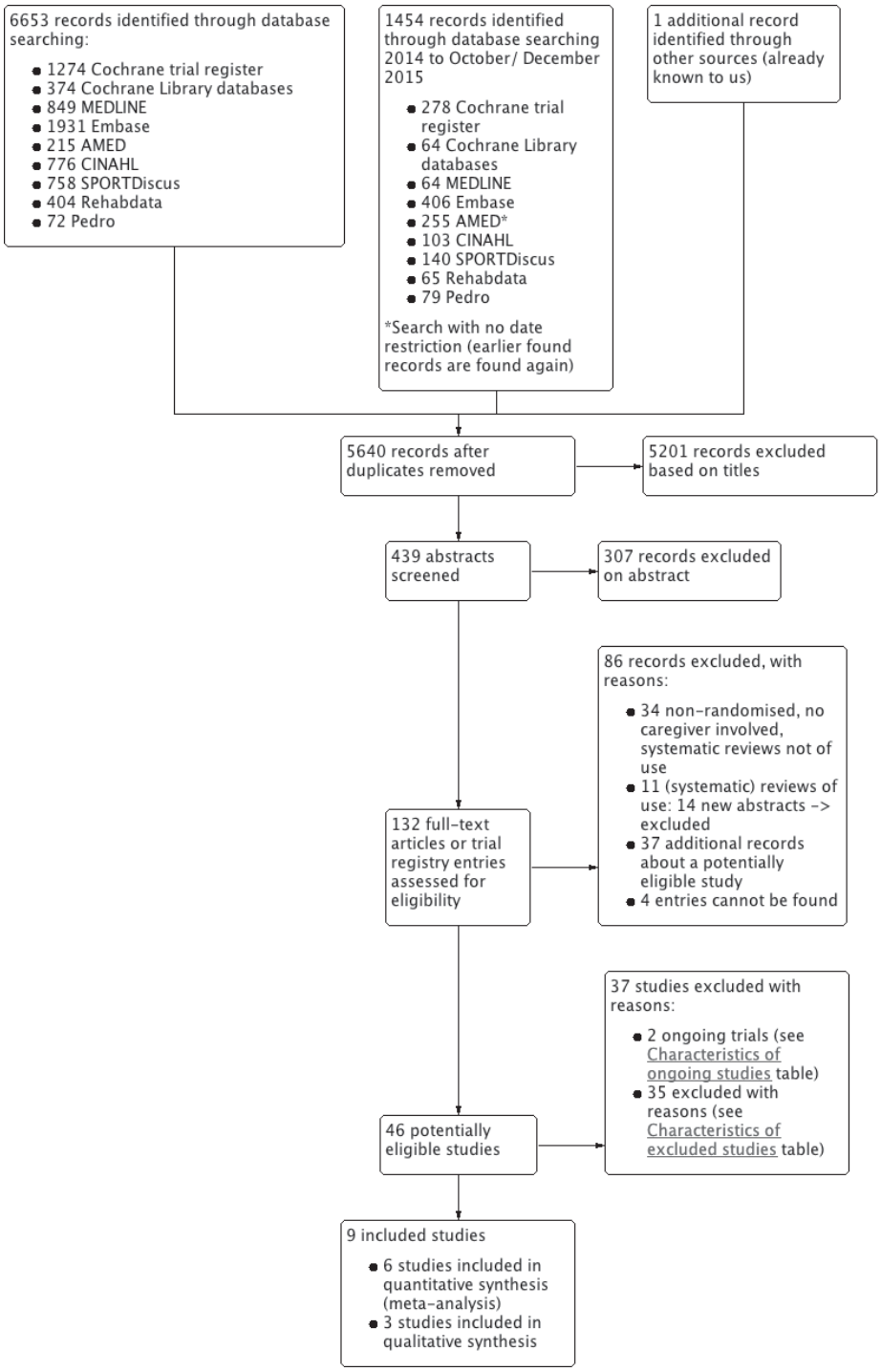

Figure 2.1 Study flow diagram.

final analysis (see Characteristics of included studies table), and we included six trials in the meta-analysis (Abu Tariah 2010; Barzel 2015; Dai 2013; Galvin 2011; Wall 1987; Wang 2015).

We excluded three trials from the meta-analysis because of poor methodological quality (Agrawal 2013; Gómez 2014) or no reporting of required data (i.e. means or SDs, or both, of outcome measures) (Agrawal 2013; Gómez 2014; Souza 2015), or both. We had no success contacting the corresponding authors to request the necessary data.

We excluded 37 trials, 35 with reasons given in the Characteristics of excluded studies table. Two trials are ongoing (see Characteristics of ongoing studies table).

Included studies
Participants

Characteristics

In the nine included studies, 456 stroke survivors and their caregivers were randomised to CME or control interventions. A total of 342 people with stroke-caregiver couples were included in the six trials included in the meta-analysis. In these six trials, nine patient-caregiver couples were not analysed according to intention-to-treat principles and no information about these withdrawals was published. Therefore, we have presented information about 333 stroke survivors and their caregivers (ranging from 18 to 156 patient-caregiver couples per trial) in the meta-analysis.

The mean age in all studies was around 60 years. The mean time since onset of symptoms ranged from 15 days to 10 years. One trial did not report mean time since onset of symptoms (Gómez 2014).

Three studies defined inclusion or exclusion criteria for the caregiver, for example "willing to participate", "medically stable and physically able" (Galvin 2011), "being defined as primary caregivers" (Dai 2013), and "caregivers were excluded if they were in poor physical health, had mental or behavioural disorders" (Wang 2015).

Four studies described an inclusion criterion for the patient about the caregiver: "live with family caregiver at home" (Abu Tariah 2010), "patients with family support" (Gómez 2014), "had a caregiver who was prepared to be a nonprofessional coach (e.g., family member)" (Barzel 2015), and "availability of a family member to supervise home exercises" (Souza 2015). Two studies gave information about the caregiver: "about 50% of the caregivers were nursing attendants" (Dai 2013), and "majority were patients' spouse" (Wang 2015).

Sample size

Five trials included fewer than 50 participants: 20 participants (Abu Tariah 2010; Wall 1987), 24 participants (Souza 2015), 30 participants (Agrawal 2013), and 40 participants (Galvin 2011). Four trials included more than 50 participants: 51 participants (Wang 2015), 55 participants (Dai 2013), 60 participants (Gómez 2014), and 156 participants (Barzel 2015).

Interventions

The content of the training and the timing was different between trials. Details of each intervention are summarised in Table 2.1. Two trials were aimed at the lower body (Galvin 2011; Wall 1987), five at the upper body (Abu Tariah 2010; Agrawal 2013; Barzel 2015; Gómez 2014; Souza 2015), and two at both upper and lower body (Dai 2013; Wang 2015). Four studies included patients within six months after stroke (Agrawal 2013; Dai 2013; Galvin 2011; Gómez 2014), three studies included patients beyond six months after stroke (Barzel 2015; Wall 1987; Wang 2015), one study included patients from two months after stroke or later (Abu Tariah 2010), one study included patients if they had a stroke in the last 24 months (Souza 2015). The task of the caregiver ranged across trials from supervision, guidance, encouragement, to physical help. In four trials, usual care continued, so CME were applied in addition to usual care (Agrawal 2013; Dai 2013; Galvin 2011; Gómez 2014). The frequency, duration, and programme length differed between studies, with training frequencies ranging from twice a week (Wall 1987; Wang 2015), to every day (Abu Tariah 2010; Galvin 2011), with a duration per session ranging from 30 minutes (Dai 2013), to three hours (Souza 2015), and a programme length ranging from 14 days (Gómez 2014), to six months (Wall 1987). In four trials, patients had weekly contact with the supervising therapist (Agrawal 2013; Barzel 2015; Galvin 2011; Wang 2015). Two trials planned two to four sessions with a therapist (Abu Tariah 2010; Dai 2013). One trial had 10 sessions with a therapist in 22 days (Souza 2015). One trial consisted of four groups, the amount of contact with the therapist differed between trial groups (Wall 1987). The frequency and duration of one trial was not clearly reported (Gómez 2014). Three trials were carried out at home (Abu Tariah 2010; Barzel 2015; Wang 2015), one trial was carried out in an inpatient setting (Gómez 2014), three trials were carried out when patients were inpatient, outpatient, or at home (Galvin 2011; Souza 2015; Wall 1987), and two trials were unclear about the location of the intervention (Agrawal 2013; Dai 2013).

Two trials had more than one trial group. The study by Agrawal 2013, which was not included in meta-analysis, had two experimental trial groups with different duration of intervention (60 and 90 minutes, five days a week) and one control group. Wall 1987 had two intervention groups (CME, CME plus physiotherapy) and two control groups (physiotherapy,

Table 2.1 Outline of included studies

Study ID	Form of training	Upper or lower body	Timing since stroke	Task caregiver	Routine care continued	Control group	Programme (length -frequency- duration)	Contact with therapist	Place
Abu Tariah 2010	CIMT	Upper	>2 months	Carried out the intervention with support of therapists	No	Neurodevelopmental training, same intensity	2 months - daily - 2 hours	3 or 4 sessions	Home
Agrawal 2013	Exercise therapy	Upper	"Sub-acute stroke"	Encouragement, participating, and help	Yes	Usual care	4 weeks -5 days/week - 60 to 90 minutes	Weekly	Inpatient?
Barzel 2015	CIMT	Upper	>6 months	Supervision, help, and maintaining training diary	No	Usual care, frequency of seeing a therapist was the same	4 weeks every weekday (not weekend) - 2 hours	5 x 60 minutes	Home
Dai 2013	Vestibular rehabilitation	Both	<6 months	Guidance and supervision (in third and fourth week)	Yes	Usual care	4 weeks - 10 sessions per 2 weeks - 30 minutes	2 to 4 sessions in first 2 weeks	Inpatient?
Galvin 2011	Exercise therapy	Lower	Assessment 2 weeks after stroke onset	Encouragement and help	Yes	Usual care	8 weeks -every day - 35 minutes	Weekly	Inpatient or at home

Gómez 2014	CIMT	Upper	<6 months	Monitoring and supervising	Yes	Usual care	14 days - every day* - 5.5 hours*	1.5 hours per day*	Inpatient
Souza 2015	CIMT: 1.5 hours with therapist and 1.5 hours with caregiver	Upper	<24 months**	Supervision and making notes	No	CIMT: 3 hours with therapist	22 days - 10 sessions - 3 hours	10 x 90 minutes	Outpatient and home
Wall 1987	Exercise therapy	Lower	After discharge of rehabilitation	Supervision	No	No intervention	6 months - twice a week - 1 hour	1 group: twice a week 1 group: once a week 1 group: 'monitoring'	Outpatient or at home
Wang 2015	Exercise programme aimed at body functions, activities, and participation	Both	>6 months	Encouragement and help	No	Usual care	12 weeks - minimal twice a week, if possible every day - minimal 50 to 60 minutes	Weekly 90 minutes	Home

CIMT = constraint-induced movement therapy.
* Details of the intervention are not completely clear, contact with the authors was not successful.
** But mean time since stroke was 27 and 35 months since stroke, unclear why.

no intervention). We decided to combine the intervention groups and the control groups into one comparison because of the small total number of participants (20).

Compliance

Five studies recorded compliance: "frequency of training and tasks completed was recorded" (Wang 2015), "the amount of training was noted in a diary by patients' families" (Abu Tariah 2010), "compliance with therapy time was documented through the use of an exercise diary, in which the number of exercises completed and time taken to complete the exercises were recorded daily" (Galvin 2011), "a log sheet per participant to record the total number of minutes completed per day" (Agrawal 2013), and "compliance was assessed in all participants via a form (standard therapy group) or a training diary (home CIMT group)" (Barzel 2015). Two trials reported these outcomes in the results. Galvin 2011 reported that 245 minutes of additional exercise therapy was planned for each participant and that a mean of 227 minutes was actually delivered. Barzel 2015 reported a mean exercise time of 27.7 hours within the four-week intervention. They also noted 12 cases of participants not adhering to the protocol. In Souza 2015, compliance about wearing of the sling was reported in the results, but no information about compliance to the CME was provided. Agrawal 2013 mentioned "inability to monitor patient's compliance with the home exercise programme which might have influenced the study".

Comparisons

Interventions consisted of CME in addition to usual care (Agrawal 2013; Dai 2013; Galvin 2011; Gómez 2014), or instead of usual care (Abu Tariah 2010; Barzel 2015; Souza 2015; Wall 1987; Wang 2015). Two studies included a control intervention (Abu Tariah 2010; Souza 2015), seven included usual care as control (Agrawal 2013; Barzel 2015; Dai 2013; Galvin 2011; Gómez 2014; Wall 1987; Wang 2015), one had no control intervention (Wall 1987). Furthermore, there were different forms of interventions in terms of type of exercise therapy, duration of the intervention, and timing of the intervention.

Outcome measures

All trials reported outcome measures at the end of intervention. Five trials reported outcome measures after three to six months' follow-up (Abu Tariah 2010; Barzel 2015; Galvin 2011; Souza 2015; Wall 1987). Two trials reported outcome measures during the intervention period (Dai 2013; Wall 1987). Some outcome measures were not reported at baseline, but only at post intervention and at follow-up. In some instances there were no SDs of outcome measures given, for which we imputed other SDs from the same study when possible (i.e. Galvin 2011:

no SD at post intervention for NEADL Index, CSI and Reintegration to Normal Living Index was available and follow-up SD was used; Abu Tariah 2010: no SD at post intervention or follow-up for Wolf Motor Function test - performance time was given and SD from baseline was used). Walking speed was reported in different units and were converted to metres/second. Where available, we also extracted mean changes from baseline (Abu Tariah 2010; Barzel 2015; Galvin 2011; Wang 2015), and in those cases where postintervention scores were not available, we used the mean change from baseline. Abu Tariah 2010 and Wang 2015 gave no SDs, but provided CIs. We calculated the SDs for these outcomes using the Z-score.

One trial reported two outcome measures for extended ADL (Galvin 2011). Based on that, the NEADL Index is developed for people with stroke and widely used in stroke research, we restricted to NEADL Index in the main analysis.

Insufficient information was available regarding the type of caregiver, rendering it impossible to distinguish between caregivers who were family or friends and other (voluntary) caregivers for the different outcome measures. One study mentioned that "about 50% of the caregivers were nursing attendants" (Dai 2013), and one study included four paid workers (Wang 2015). We did not take this professional background into account during the analyses.

The trials used a variety of outcome measures. Some outcome measures were identical, but most differed between trials. We combined outcome measures when they appeared to measure the same construct.

Excluded studies

We excluded 35 articles based on the full texts because they did not meet the inclusion criteria (Adie 2014; Araujo 2015; Barzel 2009; Baskett 1999; Bertilsson 2014; Cameron 2015; Chang 2015; Chinchai 2010; El-Senousey 2012; Evans 1984; Forster 2013; Goldberg 1997; Grasel 2005; Harrington 2010; Harris 2009; Hebel 2014; Hirano 2012; Jones 2015; Kalra 2004; Koh 2015; Larson 2005; Lin 2004; Maeshima 2003; Marsden 2010; McClellan 2004; Mudzi 2012; NCT00908479; Osawa 2010; Parker 2012; Redzuan 2012; Schure 2006; Shyu 2010; Smith 2004b; Van de Port 2012; Walker 1996). See Characteristics of excluded studies table.

The most common reasons for exclusion were: interventions were educational for patient and caregiver but they performed no, or minimal, exercises together (Chinchai 2010; El-Senousey 2012; Evans 1984; Forster 2013; Harrington 2010; Larson 2005; Marsden 2010; Mudzi 2012; Parker 2012; Schure 2006; Shyu 2010; Smith 2004a); caregivers were involved and encouraged to participate but caregiver participation was not mandatory (Adie 2014; Baskett 1999; Bertilsson 2014; Harris 2009; Jones 2015; Lin 2004; McClellan 2004; NCT00908479; Van de Port 2012; Walker 1996); and the intervention concerned 'skill training' (Araujo 2015;

Chang 2015; El-Senousey 2012; Forster 2013; Grasel 2005; Hebel 2014; Kalra 2004; Mudzi 2012). Skill training is primarily aimed at training of the caregiver in performing ADL and mobility together with the patient to improve functioning together in the home situation. Skill training is given to the caregiver in a limited number of sessions by a professional, like a therapist or a nurse, but it is not considered progressive training to improve functioning of the patient.

Furthermore, there are some non-randomised studies about CME (Barzel 2009; Hirano 2012; Maeshima 2003; Osawa 2010). Because of their relevance for the topic of this review they are listed in Characteristics of excluded studies table. However, it is important to note that our search was not aimed at identifying non-randomised studies and, therefore, we may not be complete in reporting these studies.

Risk of bias in included studies

Assessments for 'Risk of bias' in individual studies are shown in the Characteristics of included studies table. See also Figure 2.2 and Figure 2.3 for a summary of the results.

Allocation (selection bias)

All trials used random allocation to an intervention or control group, of which four adequately described how the randomisation procedure took place and provided sufficient information to determine that the allocation procedure was concealed (Abu Tariah 2010; Barzel 2015; Galvin 2011; Wang 2015). One study was unclear about the randomization procedure, but did provide sufficient information about allocation procedure (Souza 2015). The other four studies did not describe the randomisation procedure sufficiently (Agrawal 2013; Dai 2013; Gómez 2014; Wall 1987).

Blinding (performance bias and detection bias)

Participant blinding

Due to the nature of the intervention, participants included in the trials could not be blinded for treatment allocation.

Investigator blinding

Six studies blinded the outcome assessors to treatment allocation (Abu Tariah 2010; Barzel 2015; Dai 2013; Galvin 2011; Souza 2015; Wang 2015). Three studies did not report anything about an outcome assessor (Agrawal 2013; Gómez 2014; Wall 1987). Five studies used participant-reported outcomes (questionnaires, report of number of falls) (Barzel 2015; Dai

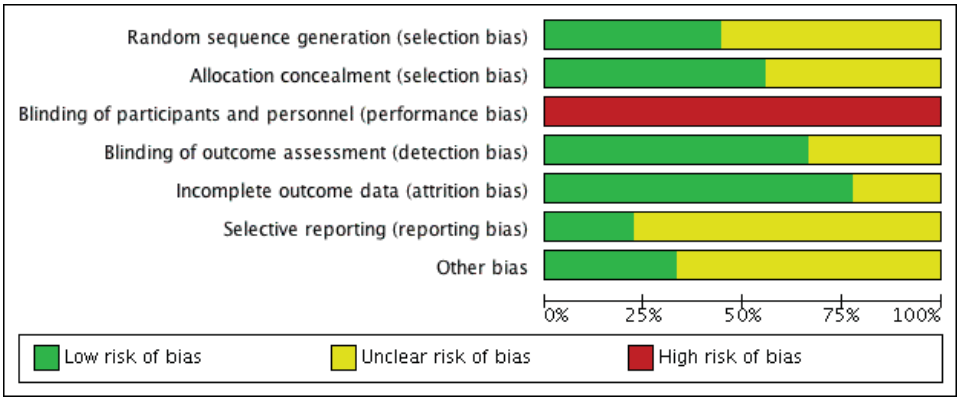

Figure 2.2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

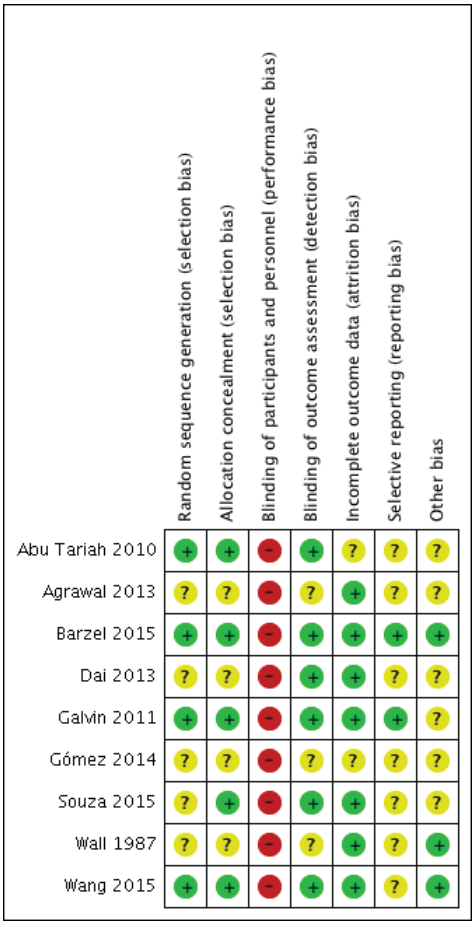

Figure 2.3 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

2013; Galvin 2011; Souza 2015; Wang 2015). For these outcomes, the assessor (patient or caregiver) was aware of the treatment allocation. This may have biased the results.

Incomplete outcome data (attrition bias)

Three studies had no withdrawals and, therefore, reported complete outcome data (Agrawal 2013; Wall 1987; Wang 2015). Four studies had withdrawals, but reasons were well described and comparable in the intervention and control group (Barzel 2015; Dai 2013; Galvin 2011; Souza 2015). One study reported only withdrawals in the control group (Abu Tariah 2010). Reasons for withdrawal were not documented by the participants, making the risk of bias unclear. One trial did not describe withdrawals, making the risk of bias unclear (Gómez 2014).

Selective reporting (reporting bias)

For two included trials (Barzel 2015; Galvin 2011), we identified a trial registry (NCT00666744) and published protocol (Barzel 2013; Galvin 2008b). Galvin 2011 reported no exclusion criteria in the trial paper in contrast to the protocol paper (Galvin 2008b) and trial registration (NCT00666744). Not all outcome measures that were reported in the protocol paper of Barzel 2013 were reported in the trial paper (Barzel 2015), such as the EQ-5D and healthcare costs. There were an insufficient number of studies (fewer than 10) to reliably examine the effects of risk of bias on estimates of effect and thus we generated no funnel plots.

Other potential sources of bias

Three trials did not perform an intention-to-treat analysis. This could be a potential source of bias (Abu Tariah 2010; Dai 2013; Souza 2015). Three trials did not report means or SDs for (a part of) the study outcomes (Agrawal 2013; Galvin 2011; Souza 2015). In one trial, means and SDs for outcome measures were not given, the included outcomes were insufficiently described, and intervention and timing of measurements needed clarification (Gómez 2014). We identified no other potential sources of bias for the remaining trials (Barzel 2015; Wall 1987; Wang 2015).

Grading the quality of the evidence

We determined the quality of the evidence using GRADE levels of evidence. We downgraded effects based on one trial by two levels of evidence and effects based on a small total number of participants (fewer than 200 participants) (BMJ Clinical Evidence 2012) by one level. When half, or more, of the included trials for an outcome measure were of unclear or high risk of bias, we downgraded the level of evidence by one level. When we found substantial

unexplained statistical heterogeneity or clinical heterogeneity, we also downgraded the level of evidence by one level. In addition, when we found publication bias, we downgraded the level of evidence by one level.

Effects of interventions

Caregiver-mediated exercises versus control (Comparison 1 and 2): primary outcomes

Patient: activities of daily living measures

End of intervention

Three trials assessed the BI (100-point version) (Barzel 2015; Galvin 2011; Wang 2015). We found no significant summary effect (mean difference (MD) 5.09, 95% CI -2.88 to 13.07; *P*=0.21; Table 2.2). One trial used the FIM (Dai 2013). The effect of CME on the FIM was not significant (MD 11.04, 95% CI -1.59 to 23.67; *P*=0.09; Table 2.2). Overall, we found no significant summary effect on basic ADL (standardised mean difference (SMD) 0.21, 95% CI -0.02 to 0.44; *P*=0.07; Analysis 1.1). The quality of evidence for effects on basic ADL was moderate; it was downgraded one level due to clinical heterogeneity between studies.

Two trials assessed extended ADL (Barzel 2015; Galvin 2011). We found no significant effects of CME on the NEADL Index (MD 5.50, 95% CI -5.83 to 16.83; *P*=0.34; Table 2.2) or on the Instrumental Activities of Daily Living (IADL) (MD 0.02, 95% CI -0.72 to 0.76; *P*=0.96; Table 2.2). Overall, we found no significant summary effect on extended ADL (SMD 0.07, 95% CI -0.21 to 0.35; *P*=0.64; Analysis 1.2). This effect was based on two trials with low risk of bias, but with clinical heterogeneity between studies and a small total number of participants for this outcome measure, resulting in a low quality of evidence.

Follow-up

Two trials assessed basic ADL and extended ADL at three months' follow-up (Galvin 2011) and six months' follow-up (Barzel 2015). We found no significant summary effect of CME on basic ADL (MD 2.69, 95% CI -8.18 to 13.55; *P*=0.63; Analysis 2.1). This effect was based on two trials with low risk of bias, but with clinical heterogeneity between studies and a small total number of participants for this outcome measure, resulting in a low quality of evidence. The substantial statistical heterogeneity between trials (I2=69%), can be explained by different timing post stroke (within six months versus beyond six months) and thus there was no reason to downgrade the level of evidence further. The effect of CME on extended ADL measured with the NEADL Index (MD 9.50, 95% CI -1.83 to 20.83; *P*=0.10; Table 2.2), or measured with the IADL (MD 0.02, 95% CI -0.77 to 0.81; *P*=0.96; Table 2.2) was

Table 2.2 (Standard) Mean differences which are not reported in section 'data and analysis'

Outcome	Outcome measure	Fixed-effect or random-effects model	Mean difference	Confidence interval	Heterogeneity	P value
1.1 Patient: ADL measures - Combined	1.1.1 Barthel Index	Random-effects	5.09	-2.88 to 13.07	58%	0.21
	1.1.2 Functional Independence Measure	Fixed-effect	11.04	-1.59 to 23.67	-	0.09
1.2 Patient: ADL measures - extended ADL	1.2.1 Nottingham Extended Activities of Daily Living Index	Fixed-effect	5.50	-5.83 to 16.83	-	0.34
	1.2.2 IADL	Fixed-effect	0.02	-0.72 to 0.76	-	0.96
1.3 Caregiver: burden	1.3.1 Caregiver Strain Index	Fixed-effect	-0.50	-1.81 to 0.81	-	0.46
	1.3.2 Caregiver Burden Scale	Fixed-effect	1.30	-4.88 to 7.48	-	0.68
1.6 Gait and gait-related measures: balance	1.6.1 Berg Balance Scale	Fixed-effect	6.35	1.64 to 11.06	0%	0.008
	1.6.2 Postural Assessment for Stroke patients	Fixed-effect	3.50	-0.52 to 7.52	-	0.09
2.2 Patient: ADL measures - extended ADL	2.2.1 Nottingham Extended Activities of Daily Living Index	Fixed-effect	9.50	-1.83 to 20.83	-	0.10
	2.2.2 IADL	Fixed-effect	0.02	-0.77 to 0.81	-	0.96
3.1 Patient: ADL measures - combined	3.1.1 <6 months	Fixed-effect	0.44*	0.01 to 0.86	0%	0.04
	3.1.2 >6 months	Random-effects	4.90	-7.56 to 17.36	77%	0.44
8.1 Patient ADL measures - extended ADL - end of intervention	8.1.1 Reintegration to normal living Index	Fixed-effect	0.20	-3.76 to 4.16	-	0.92
	8.1.2 IADL	Fixed-effect	0.02	-0.72 to 0.76	-	0.96
8.2 Patient ADL measures - extended ADL - end of follow-up	8.2.1 Reintegration to normal living Index	Fixed-effect	4.50	0.54 to 8.46	-	0.03
	8.2.2 IADL	Fixed-effect	0.02	-0.77 to 0.81	-	0.96

ADL = activities of daily living; IADL = instrumental activities of daily living. *Standardised mean difference.

not significant. Overall, there was no significant summary effect of CME on extended ADL (SMD 0.11, 95% CI -0.17 to 0.39; *P*=0.45; Analysis 2.2). The quality of evidence was low, based on two trials with low risk of bias, but with clinical heterogeneity between studies and a small total number of participants for this outcome measure.

Caregiver: measures of burden

End of intervention

One trial used the CSI to assess caregiver burden (Galvin 2011); we found no significant effect (MD –0.50, 95% CI -1.81 to 0.81; *P*=0.46; Table 2.2). Another trial used the Caregiver Burden Scale (Wang 2015), and again we found no significant effect (MD 1.30, 95% CI -4.88 to 7.48; *P*=0.68; Table 2.2). Overall, we found no significant summary effect of CME on caregiver strain (SMD -0.04, 95% CI -0.45 to 0.37; *P*=0.86; Analysis 1.3). These findings were based on two trials with low risk of bias, but with a small total number of participants for this outcome measure, resulting in moderate quality of evidence.

Follow-up

One study reported follow-up of caregiver burden by using the CSI, three months after termination of the intervention (Galvin 2011). We found no significant effect of CME on caregiver strain compared with the control group (MD 0.60, 95% CI -0.71 to 1.91; *P*=0.37; Analysis 2.3). The quality of the evidence for this finding was very low, since it is based on only one trial with a small number of participants.

Caregiver-mediated exercises versus control (Comparison 1 and 2): secondary outcomes

Measures of motor impairment

One study assessed the FMA lower extremity score (Galvin 2011). We found no significant effect after the intervention (MD 3.10, 95% CI -2.02 to 8.22; *P*=0.24; Analysis 1.4) or at follow-up (MD 3.40, 95% CI -1.74 to 8.54; *P*=0.19; Analysis 2.4). These findings were based on one trial with a small number of participants, resulting in a very low quality of evidence.

One study assessed the FMA upper extremity score (Abu Tariah 2010). We found no significant effect of CME at the end of intervention (MD 4.43, 95% CI -2.09 to 10.95; *P*=0.18; Analysis 1.5) or at follow-up (MD 2.75, 95% CI -8.24 to 13.74; *P*=0.62; Analysis 2.5). These findings were based on only one trial with a small number of participants. Therefore, the quality of evidence was very low.

Gait and gait-related measures

Balance

Two trials reported the BBS (Galvin 2011; Wang 2015). We found a significant summary effect (MD 6.35, 95% CI 1.64 to 11.06; *P*=0.008; Table 2.2). One study assessed the Postural Assessment Scale for Stroke Patients (Dai 2013), and found no significant effect of CME (MD 3.50, 95% CI -0.52 to 7.52; *P*=0.09; Table 2.2). Overall, we found a significant summary effect of CME on standing balance performance at the end of the intervention (SMD 0.53, 95% CI 0.19 to 0.87; *P*=0.002; Analysis 1.6). These findings were based on a small total number of participants and there was clinical heterogeneity between studies resulting in a low quality of evidence. One trial was of unclear risk of bias (Dai 2013), but more than half of the trials were of low risk of bias (Galvin 2011; Wang 2015), and thus there was no reason to downgrade the level of evidence further.

Only one trial assessed standing balance performance at three months' follow-up (Galvin 2011). There was no significant effect (MD 8.40, 95% CI -1.04 to 17.84; *P*=0.08; Analysis 2.6). This effect was based on one trial with a small number of participants resulting in a very low quality of evidence.

Walking distance

Two trials used the Six-Minute Walk Test to assess walking distance (Galvin 2011; Wang 2015). We found no significant summary effect of CME at the end of the intervention period (MD 30.98 m, 95% CI -20.22 to 82.19; *P*=0.24; Analysis 1.7). These findings were based on two trials with a low risk of bias, but with a small total number of participants for this outcome measure, resulting in a moderate quality of evidence.

Only one trial assessed the Six-Minute Walk Test at three months' follow-up (Galvin 2011). There was a significant effect in favour of CME (MD 109.50 m, 95% CI 17.12 to 201.88; *P*=0.02; Analysis 2.7). This finding was based on one trial with a small number of participants, resulting in a very low quality of evidence.

Walking speed

Two trials reported comfortable walking speed (Wall 1987; Wang 2015). We found no significant summary effect of CME on walking speed (MD 0.08 m/s, 95% CI -0.03 to 0.18; *P*=0.17; Analysis 1.8). This effect was based on one trial with low risk of bias (Wang 2015) and one trial with an unclear risk of bias (Wall 1987). In addition, there was a small total number of participants. Therefore, the quality of evidence was low.

Only Wall 1987 reported follow-up data three months after termination of the intervention. We found no significant effect of CME on walking speed (MD 0.10 m/s, 95% CI -0.02 to 0.22; *P*=0.10; Analysis 2.8). The quality of evidence was very low, because the effect was based on only one trial of unclear risk of bias with a small total number of participants.

Measures of upper limb activities or function

Two trials with low risk of bias used the Wolf Motor Function test and the Motor Activity Log (Abu Tariah 2010; Barzel 2015). However, there may be publication bias, because all studies excluded for meta-analysis were about upper limb training (Agrawal 2013; Gómez 2014; Souza 2015). In addition, there was a small total number of participants for these outcome measures and we detected substantial unexplained statistical heterogeneity between trials. We graded the quality of the evidence as very low, except the Wolf Motor Function test - performance time and the Motor Activity Log - amount of use at the end of intervention, and the Motor Activity Log - quality of movement at both end of intervention and follow-up. We did not detect any substantial statistical heterogeneity in these cases and, therefore, we graded the quality of evidence as low.

We found no significant summary effect of CME on the Wolf Motor Function test - functional ability (end of intervention: MD 0.02, 95% CI -0.52 to 0.55; *P*=0.95; Analysis 1.9; follow-up four to six months after termination: MD 0.08, 95% CI -0.46 to 0.61; *P*=0.77; Analysis 2.9), the Motor Activity Log - amount of use (end of intervention: MD 0.01, 95% CI -0.36 to 0.38; *P*=0.96; Analysis 1.11; follow-up four to six months after termination: MD 0.21, 95% CI -0.65 to 1.08; *P*=0.63; Analysis 2.11), and Motor Activity Log - quality of movement (end of intervention: MD 0.08, 95% CI -0.26 to 0.42; *P*=0.64; Analysis 1.12; follow-up four to six months after termination: MD -0.03, 95% CI -0.43 to 0.37; *P*=0.89; Analysis 2.12).

For the Wolf Motor Function test - performance time, we found a significant summary effect in favour of the control group post intervention (MD -1.72, 95% CI -2.23 to -1.21; *P*<0.00001; Analysis 1.10), but not at follow-up (MD 1.85, 95% CI -8.78 to 12.48; *P*=0.73; Analysis 2.10).

One trial used the Nine Hole Peg test (Barzel 2015). We found no significant effect post intervention (MD -0.04, 95% CI -0.11 to 0.03; *P*=0.26; Analysis 1.13) or at follow-up (MD -0.05, 95% CI -0.12 to 0.02; *P*=0.17; Analysis 2.13). This evidence was based on one trial with a small number of participants, resulting in a very low quality of evidence.

Measures of mood and quality of life of the patient

One trial assessed QoL of the patients with the SIS 3.0 at the end of the intervention (Wang 2015), and one trial assessed only SIS hand function (Barzel 2015).

The effect of CME was significant for the composite physical scale (MD 12.40, 95% CI 1.67 to 23.13; *P*=0.02; Analysis 1.14), mobility scale (MD 18.20, 95% CI 7.54 to 28.86; *P*=0.0008; Analysis 1.17), and general recovery scale (MD 15.10, 95% CI 8.44 to 21.76; *P*<0.00001; Analysis 1.23).

For SIS hand function at follow-up (Barzel 2015), we found no significant effect (MD -2.20, 95% CI -12.46 to 8.06; *P*=0.67; Analysis 2.14). These findings were based on one trial with a small number of participants resulting in a very low quality of evidence. The reported effects on SIS hand function were based on two trials with low risk of bias, but with clinical heterogeneity between studies, resulting in a moderate quality of evidence.

Measures of fatigue of the patient

None of the trials reported on effects of CME on fatigue of the patient after intervention or at follow-up.

Length of stay

None of the included trials reported length of stay as an outcome measure. However, Galvin 2011 did state that mean length of hospital stay for the intervention group was 35.7 days (SD 10.5) and for the control group was 40.1 days (SD 15). Mean length of stay in a rehabilitation unit was 40.3 days (SD 9.6) for the intervention group and 52.3 days (SD 40) for the control group. Patients were recruited in a hospital and a rehabilitation unit. We found no significant differences for length of stay in a hospital (MD 4.40 days, 95% CI -3.91 to 12.71; *P*=0.30; Analysis 1.24) or length of stay in a rehabilitation unit (MD 12.0 days, 95% CI -10.88 to 34.88; *P*=0.30; Analysis 1.25). These effects were based on one trial, and length of stay was reported for a small number of participants (n=20). Therefore, we graded the quality of the evidence as very low.

Adverse outcomes

One trial reported falls among participants (Dai 2013). We found no significant effect of CME on the number of falls reported (MD 0.04, 95% CI -0.10 to 0.18; *P*=0.57; Analysis 1.26). There was no follow-up in this trial. This effect was based on one trial with unclear risk of bias and a small number of participants, resulting in a very low quality of evidence.

Caregiver: measures of mood and quality of life

None of the included trials reported measures of mood or QoL of the caregiver.

Other outcomes

See Table 2.3.

Wall 1987 reported on gait parameters such as duration of single support phase and asymmetry ratio. We did not summarise these findings because they were beyond the scope of this review.

Table 2.3 Results 'other outcomes' (not included in meta-analysis)

	Control group (mean (SD))			Intervention group (mean (SD))		
Outcome	Baseline	Post intervention	Follow-up	Baseline	Post intervention	Follow-up
Behavioural Inattention Test Conventional (Dai 2013)	48.79 (44.64)	68.83 (44.72)	-	49.71 (39.63)	88.71 (44.56)	-
Motor Assessment Scale (Galvin 2011)	29.7 (12.9)	34.5 (11.6)	35.2 (10.8)	24.3 (11.1)	36.1 (10.2)	37.9 (9.7)

SD = standard deviation.

Dose of training

In three trials, the dose of training was comparable between the intervention and control groups (Abu Tariah 2010; Souza 2015; Wall 1987). In six trials, the dose of training in the intervention group was higher than the dose of training in the control group (Agrawal 2013; Barzel 2015; Dai 2013; Galvin 2011; Gómez 2014; Wang 2015). In four of these trials, there was as higher dose of training in the intervention group because the intervention was additional to usual care and the control group received only usual care (Agrawal 2013; Dai 2013; Galvin 2011; Gómez 2014). In one trial, the intensity of training in the intervention group was higher due to the differences between interventions in the intervention and control groups (Wang 2015). The study compared a 90-minute visit of a therapist and performing activities at least twice weekly, and if possible, every day in the intervention group, with a weekly visit or telephone call of the therapist and maintaining daily routines in the control group. In one trial, daily CIMT, which is a high-intensity training intervention, was compared with usual care (Barzel 2015). With that, the intensity of training in the intervention group was higher than the dose of training in the control group.

We could not perform subgroup analysis for dose of training (higher dose of training versus same dose of training). For most outcome measures, all included trials had a higher dose of training in the intervention group, so no comparison could be made. For walking speed and upper arm function (Wolf Motor Function test and Motor Activity Log), one included trial was in the higher dose of training group and one included trial was in the same dose of training group. Because there was only one study per subgroup for these outcome measures, we did not perform a subgroup analysis.

Timing post stroke (Comparison 3)

We performed subgroup analyses for trials that included patients within six months after stroke (Agrawal 2013; Dai 2013; Galvin 2011; Gómez 2014) versus trials that included patients beyond six months after stroke (Barzel 2015; Wall 1987; Wang 2015). One trial included patients from beyond two months after stroke (Abu Tariah 2010), and another included patients directly after stroke (Souza 2015); however, the reported mean time since stroke was about nine months after stroke in the Abu Tariah 2010 study and 30 months after stroke in the Souza 2015 study. Therefore, we included both trials in the chronic phase group.

Because of the low number of included trials, we could only perform a subgroup analysis for the outcome measure basic ADL at the end of intervention. We found no difference between trials that included participants within six months after stroke when compared with trials that included patients beyond six months after stroke (P=0.21; Analysis 3.1). The quality of evidence for this comparison was low, due to clinical heterogeneity between studies and a small total number of participants per subgroup.

For all other outcome measures, the number of included trials per subgroup was too low to test for subgroup differences.

Upper and lower extremity

Five trials were aimed at the upper extremity (Abu Tariah 2010; Agrawal 2013; Barzel 2015; Gómez 2014; Souza 2015), and four of these trials were about CIMT (Abu Tariah 2010; Barzel 2015; Gómez 2014; Souza 2015). However, Agrawal 2013, Gómez 2014, and Souza 2015 were not included in meta-analysis. Two trials were specifically aimed at the lower extremity (Galvin 2011; Wall 1987).

Basic and extended ADL were the only outcome measures in common when comparing upper and lower extremity trials. Due to the low number of trials per subgroup, we could not perform a subgroup analysis.

Reported mean changes (Comparison 4)

Mean change from post intervention to follow-up

Galvin 2011 reported mean change at follow-up (three months after termination of the intervention) from post intervention, using the outcome measures BI, CSI, NEADL Index, Reintegration to Normal Living Index, FMA lower extremity score, BBS, Six-Minute Walk Test, and the Motor Assessment Scale.

This study found a significant effect in favour of CME for the Reintegration to Normal Living Index, CSI and the Six-Minute Walk Test. The other mean changes were not significantly different. This result was based on one trial with a small number of participants, resulting in a very low quality of evidence.

Sensitivity analysis (Comparisons 5 and 6)

CME-core

In five trials, CME was the only intervention (CME-core) (Agrawal 2013; Galvin 2011; Souza 2015; Wall 1987; Wang 2015). Four trials studied the effect of another, existing intervention provided by the caregiver (Abu Tariah 2010; Barzel 2015; Dai 2013; Gómez 2014). In these four trials, it was difficult to separate the effects of CME from the effects of the other intervention (e.g. CIMT). Therefore, we performed a sensitivity analysis that included only CME-core trials.

Three CME-core trials were suitable for meta-analyses (Galvin 2011; Wall 1987; Wang 2015). We found a significant summary effect for basic ADL post intervention in favour of CME (2 studies; MD 9.45, 95% CI 2.11 to 16.78; *P*=0.01; Analysis 5.1). This effect was based on two studies with low risk of bias, but with a small total number of participants for this outcome measure, resulting in a moderate quality of evidence.

We found no significant effect at follow-up (1 study; MD 9.00, 95% CI -1.29 to 19.29; *P*=0.09; Analysis 6.1). This effect was based on one study with a small number of participants, resulting in a very low quality of evidence.

For extended ADL, we found no significant summary effect post intervention (1 study; MD 5.50, 95% CI -5.83 to 16.83; *P*=0.34; Analysis 5.2) or at follow-up (1 study; MD 9.50, 95% CI -1.83 to 20.83; *P*=0.10; Analysis 6.2). These effects were based on one study with a small number of participants resulting in a very low quality of evidence. For outcome measures relating to caregiver burden, we found no significant differences between the CME and control groups (see Analysis 1.3; moderate quality of evidence; and Analysis 2.3: very low quality of evidence).

For the secondary outcome measures, we found significant effects in favour of CME post intervention for standing balance (2 studies; MD 6.35, 95% CI 1.64 to 11.06; P = 0.008; Analysis 5.3; moderate quality of evidence) and QoL, concerning the composite physical subscale (1 study; MD 12.40, 95% CI 1.67 to 23.13; *P*=0.02; Analysis 1.14; very low quality of evidence), mobility subscale (1 study; MD 18.20, 95% CI 7.54 to 28.86; *P*=0.0008; Analysis 1.17; very low quality of evidence), and general recovery subscale of the SIS (1 study; MD 15.10, 95% CI 8.44 to 21.76; *P*<0.00001; Analysis 1.23; very low quality of evidence). We found a significant effect in favour of CME for walking distance at follow-up (1 study; MD 109.50 m, 95% CI 17.12 to 201.88; *P*=0.02; Analysis 2.7; very low quality of evidence).

The included trials did not report the outcome measures FMA upper extremity, upper limb activities or function, length of stay, and adverse outcome for this sensitivity analysis.

The total number of included trials per subgroup within this sensitivity analysis was too small to test for subgroup differences.

Robustness of the results

In all analyses where we applied a fixed-effect model, we subsequently applied a random-effects model. This did not affect the overall results.

For one study, we combined two intervention groups (CME; CME plus physiotherapy) and two control groups (physiotherapy; no intervention) (Wall 1987). When we made separate comparisons of each intervention group versus each control group, we found no differences in the results (Comparison 7).

One study reported two outcome measures for extended ADL: the NEADL Index and the Reintegration to Normal Living Index (Galvin 2011). To prevent double counting this trial in our meta-analysis, we included the NEADL Index in our primary analysis. We performed a sensitivity analysis in which we replaced the NEADL Index with the Reintegration to Normal Living Index (Comparison 8). Changing the outcome measure did not affect the direction or magnitude of the effect, neither did it affect the significance level of the meta-analysis.

Qualitative synthesis

We could not include three trials in meta-analyses: the various reasons are described in the Results of the search section (Agrawal 2013; Gómez 2014; Souza 2015). All three trials were aimed at the upper extremity, with two trials applying CIMT (Gómez 2014; Souza 2015). For details of these trials, see the Characteristics of included studies table.

Table 2.4 Results Agrawal 2013 (study not included in meta-analysis)

	Control group (mean scores)		GRASP 60 group (mean scores)		GRASP 90 group (mean scores)	
Outcome	Baseline	Post intervention	Baseline	Post intervention	Baseline	Post intervention
Fugl-Meyer Assessment upper extremity	31.3	37.0	32.9	44.0	34.7	48.2
Chedoke Arm and Hand Activities Inventory	20.3	26.8	21.0	30.0	24.4	37.0

Agrawal 2013 comprised exercise training for the upper extremity in addition to usual care for two months. The three groups included a total of 30 participants. The results of each group are separately summarised in Table 2.4.

Gómez 2014 studied CIMT with a caregiver in addition to usual care compared with usual care alone. The trial included a total of 60 participants and the intervention lasted 14 days. The goal of this trial was to determine if family support could increase eligibility for CIMT and to study the influence of social and family support. Reported outcomes were a description of the included participants and their level of social and family support. Furthermore, correlations were calculated between ADL, cognitive functioning, and level of social and family support, and were all found to be significant. Means and SDs were not reported. Gómez 2014 concluded that family can play a crucial role in delivering a CIMT protocol and that social and family support has a positive influence on functional outcome of the patient.

Souza 2015 studied CIMT (partly) performed together with a caregiver versus CIMT performed with a therapist. The trial included a total of 24 participants and had a follow-up of six months. The study authors published effectiveness indexes for the outcome measures Motor Activity Log - quality of movement, FMA upper extremity scale, and Stroke Specific Quality of Life Scale (SSQoL). There were no differences between experimental and control groups and the authors concluded that CIMT therapy (partly) together with a caregiver is equally effective as CIMT therapy with a therapist, but less expensive.

DISCUSSION

Summary of main results

For an overview of the results, see the Summary of findings table.

Effects on outcome measures

This review aimed to determine the effectiveness of CME versus control in people with stroke. We included nine out of 46 potentially relevant trials. The meta-analyses included 333 patient-caregiver couples. Four trials assessed the primary outcome measure of ADL. We found no significant summary effect on basic ADL at the end of intervention (Analysis 1.1; moderate quality of evidence) or at follow-up (Analysis 2.1; low quality of evidence). For extended ADL, there were two trials, in which we found no significant summary effect at the end of intervention (Analysis 1.2; low quality of evidence) or follow-up (Analysis 2.2; low quality of evidence). Two trials assessed the primary outcome measure of caregiver burden at the end of intervention and one trial at follow-up. For both time points, we found no significant summary effects of CME (at the end of intervention: Analysis 1.3; moderate quality of evidence; at follow-up: Analysis 2.3; very low quality of evidence).

With regard to secondary outcome measures, we found a significant effect in favour of CME at the end of intervention for standing balance (three studies; Analysis 1.6; low quality of evidence) and QoL (one study: composite physical (Analysis 1.14), mobility (Analysis 1.17), and general recovery (Analysis 1.23) subscales; very low quality of evidence). The composite physical scale is a sum score of the scales strength, hand function, mobility, and ADL/IADL. We found a significant effect on walking distance at follow-up (one study; Analysis 2.7; very low quality of evidence). On the Wolf Motor Function test - performance time at the end of intervention there was a significant effect in favour of the control group (two studies; Analysis 1.10; low quality of evidence). We found no significant effects for walking distance post intervention or for standing balance at follow-up, and QoL was not reported at follow-up. We found no significant effects for FMA upper and lower extremity scores, walking speed, measures of upper limb activities or function, length of hospital stay, and adverse events (falls) at both post intervention and at follow-up (where assessed). None of the included trials reported on measures of fatigue of the patient or mood and QoL of the caregiver.

Unfortunately, due to the small number of included trials, we could not apply subgroup analyses with respect to the dose of training and focus of CME training aimed at the upper or lower extremity. In the subgroup analysis regarding timing since stroke onset (within six months after stroke versus beyond six months after stroke), we could only make a comparison

for basic ADL at the end of intervention. For the other outcome measures, the number of included studies per subgroup was too small. Timing since stroke did not have an effect on basic ADL at the end of intervention (Analysis 3.1; low quality of evidence).

One trial reported mean changes from post intervention to follow-up. Most reported mean changes were in favour of CME. The mean change of caregiver burden from post intervention to follow-up was significantly in favour of the CME group (Analysis 4.4; very low quality of evidence).

CME-core

We included all trials of CME in the primary analysis. However, several trials used CME as the only intervention (CME-core), where in others a caregiver provided an existing intervention, for example CIMT. In the latter trials, it is difficult to separate the effects of CME from the effects of the other intervention.

Sensitivity analysis with the three trials investigating CME-core showed one important difference compared with the primary analysis. We found a significant effect in favour of CME-core on basic ADL post intervention (Analysis 5.1; moderate quality of evidence). On secondary outcome measures, we found the same significant effects in favour of CME as in the primary analysis at the end of intervention for standing balance (Analysis 5.3; moderate quality of evidence) and QoL (composite physical: Analysis 1.14; mobility: Analysis 1.17; general recovery scale: Analysis 1.23; all very low quality of evidence), and at follow-up for walking distance (Analysis 2.7; very low quality of evidence). We could not perform subgroup analysis.

It is important to note that in the CME-core analysis only lower extremity trials could be included. An ADL outcome, such as the BI, is more sensitive to lower extremity improvement than to upper extremity improvement (Kwakkel 2004).

These positive effects of CME-core on basic ADL and standing balance may suggest improved and earlier independence, similar to early supported discharge interventions.

Importance of the CME-core analysis

There are a limited number of trials and outcome measures included in this meta-analysis. Due to the number of participants in the trial of Barzel (n=156), this trial has a large effect on the results (Barzel 2015). The main affected outcome measures are basic ADL, extended ADL, and measures of upper limb activities or function (Wolf Motor Function test and Motor Activity Log). In this trial, CIMT provided by a caregiver was compared with standard therapy; therefore, this trial is one of the trials in which the effects of CME are difficult to

Summary of findings table

Caregiver-mediated exercises compared with control intervention for people with stroke

Patient or population: people with stroke
Settings: inpatient and outpatient settings
Intervention: caregiver-mediated exercises
Comparison: control, i.e. usual care, other intervention, no intervention

	Illustrative comparative risks* (95% CI)					
	Assumed risk	Corresponding risk	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	
Outcomes	Control intervention	Caregiver-mediated intervention				Comments
Patient: ADL measures Barthel Index. Scale 0 to 100 (follow-up: 2 studies; 3/6 months) FIM. Scale 7 to 126 (no follow-up)	The mean Barthel Index score ranged across control groups from 78 to 84 1 study: The mean FIM score in the control group was 65	The mean Barthel Index score in the intervention groups was 5.09 higher (-2.88 to 13.07 higher) 1 study: The mean FIM score in the intervention group was 11 higher (-1.59 to 23.67 higher)	-	Barthel Index: 247 (3) FIM: 48 (1) Total: 295	⊕⊕⊕⊖ Moderate	Higher scores are better More than half of the studies at low risk of bias (3 low risk of bias, 1 at unclear risk of bias) There was clinical heterogeneity SMD 0.21 (-0.02 to 0.44)
Caregiver: measures of mood, burden and QoL: burden Caregiver Strain Index Scale. 0 to 13 (follow-up 3 months) Caregiver Burden Scale. 22 to 88 (no follow-up)	The mean Caregiver Strain Index score in the control group was 3.4 The mean Caregiver Burden Scale score in the control group was 46.6	The mean Caregiver Strain Index score in the intervention group was 0.50 higher (-0.81 to 1.81 higher) The mean Caregiver Burden Scale score in the intervention group was 1.30 lower (-4.88 to 7.48 lower)	-	Caregiver Strain Index: 40 (1) Caregiver Burden Scale: 51 (1) Total: 91	⊕⊕⊕⊖ Moderate	Lower scores are better Both studies at low risk of bias Small total number of participants SMD -0.04 (-0.45 to 0.37)
Gait and gait-related measures: walking speed in m/s (follow-up: 1 study, 9 months)	The mean walking speed ranged across control groups from 0.26 m/s to 0.46 m/s	The mean walking speed in the intervention group was 0.08 m/s higher (-0.03 to 0.18)	-	71 (2)	⊕⊖⊖⊖ Very low	

Gait and gait-related measures: walking distance measured with the Six-Minute Walk Test in metres walked in 6 minutes (follow-up: 1 study, 3 months)	The mean distance walked ranged across control groups from 157 m to 166 m	The mean distance walked in the intervention groups was 30.98 m higher (-20.22 to 82.19 higher)	-	91 (2)	⊕⊕⊕⊖ Moderate	Lower scores are better 1 study at unclear risk of bias Small total number of participants MD 0.04 (-0.10 to 0.18)
Measures of mood and QoL of the patient: Stroke Impact Scale Stroke Impact Scale mobility scale. Scale 9 to 45. (no follow-up)	The mean Stroke Impact Scale mobility score in the control group was 66.8	The mean Stroke Impact Scale mobility score in the intervention group was 18.2 higher (7.54 to 28.86 higher)	-	51 (1)	⊕⊖⊖⊖ Very low	Higher scores are better 1 study at low risk of bias Small total number of participants MD 18.2 (7.54 to 28.86)
Length of stay: length of stay in rehabilitation unit in days	The mean length of stay in a rehabilitation unit in the control group was 52.3 days	The mean length of stay in a rehabilitation unit in the intervention group was 12 days lower (-10.88 to 34.88)	-	20 (1)	⊕⊖⊖⊖ Very low	Higher scores are better 1 study at low risk of bias and 1 at unclear or high risk of bias Small total number of participants There was clinical heterogeneity MD 0.08 m/s (-0.03 to 0.18)
Adverse outcomes: falls number of falls/patient (no follow-up)	1 study: the mean number of falls/ patient in the control group was 0.08	1 study: the mean number of falls/ patient in the intervention group was 0.04 lower (-0.10 to 0.18 lower)	-	48 (1)	⊕⊖⊖⊖ Very low	Higher scores are better Both studies at low risk of bias Small total number of participants MD 30.98 m (-20.22 to 82.19)

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). ADL = activities of daily living; CI = confidence interval; FIM = Functional Independence Measure; MD = mean difference; QoL = quality of life; RR = risk ratio; SD = standard deviation; SMD = standardised mean difference..

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

separate from the effects of the other intervention (CIMT). Therefore, we believe that the sensitivity analysis, in which only CME-core trials are included, is especially important. The effects found in the analysis of CME-core are probably the most robust to answer the objective of this review.

Activities of daily living

We found no significant effects on basic or extended ADL in the primary analyses. These results were not robust because CME had a significant positive effect on basic ADL at the end of the intervention in the sensitivity analysis of CME-core. There was no positive effect on basic ADL at follow-up. This may be attributed to the ceiling effect of outcome measures of basic ADL (Quinn 2011). Therefore, it is important that measures of extended ADL are included in studies investigating CME.

CME has the potential to increase intensity of training. In most included trials in this review, CME did increase intensity of training (Agrawal 2013; Barzel 2015; Dai 2013; Galvin 2011; Gómez 2014; Wang 2015). Several systematic reviews have shown that a higher intensity of training can lead to better outcome in people with stroke in terms of ADL (French 2010; Galvin 2008a; Kwakkel 2004; Kwakkel 2006; Langhorne 2011; Lohse 2014; Veerbeek 2011; Veerbeek 2014), and, therefore, one may expect favourable outcomes in terms of ADL. However, based on the low number of proof-of-concept trials and moderate-quality evidence, our results are not conclusive yet and more trials assessing ADL are needed.

Caregiver burden

CME are yet another task for the caregiver and, therefore, one could hypothesise that CME will lead to an increase in caregiver burden. However, several authors have argued that caregiver burden could actually decrease during CME, due to concurrent education of both patient and caregiver and increased caregiver support, by providing caregivers with more knowledge about the capabilities of the person with stroke and themselves (Galvin 2011; Kalra 2004; Wang 2015). This may potentially increase feelings of self-efficacy and control of the caregiver (van den Heuvel 2001). When combining data in this review from two trials that assessed caregiver burden, we found no significant effects, that is, there was no increase or decrease in caregiver burden (Galvin 2011; Wang 2015). Quality of the evidence was moderate. Reported mean change on the CSI from post intervention to follow-up was in favour of CME (Galvin 2011).

Veerbeek 2014 did show a significant homogeneous positive significant effect size on caregiver strain in its meta-analysis of trials about CME. The difference with our analysis

is that they included Kalra 2004, which we excluded because we implemented a different definition of CME. Kalra 2004 applied skill training of the caregiver, which strictly speaking is not the same as CME as it is not a progressive training intervention. However, as skill training and CME may be closely related, the current results on the effect of CME on caregiver burden are not robust. So, results on caregiver burden are inconclusive and more trials assessing caregiver burden in CME are needed.

Adherence to safety

Adherence to safety is essential in CME. Only one included trial assessed adverse events in terms of number of falls, and there were no differences between the intervention and control groups. These findings suggest that, at the least, CME are equally safe as usual care. However, the quality of the evidence was very low. Since a caregiver is not a professional therapist, specific screening, training, and instruction are needed to address safety risks (e.g. falling). Therefore, an important part of each CME protocol should be addressing safety during CME.

Dose of training

Veerbeek 2014 found strong evidence in favour of physiotherapy interventions with intensive, high repetitive, taskoriented, and task-specific training in all phases post stroke. This is in line with several other meta-analyses that showed that intensity of training and repetitive task training are crucial aspects of stroke rehabilitation, suggesting that more exercise therapy is better (French 2010; Galvin 2008a; Kwakkel 2004; Kwakkel 2006; Langhorne 2011; Lohse 2014; Pollock 2014a; Veerbeek 2011; Veerbeek 2014). Pollock and colleagues suggested that a dose of 30 to 60 minutes per day, delivered five to seven days per week, has a surplus value in terms of activities. However, no conclusions could be drawn regarding to the total duration of the intervention due to substantial heterogeneity in the analyses (Pollock 2014a).

All trials included in the high-intensity training group had a dose of at least 30 to 60 minutes per day delivered five to seven days per week. In all trials, except for Dai 2013, the intervention group received at least 16 hours of exercise treatment compared with the control group (Kwakkel 2004; Veerbeek 2011). In one trial, the intervention group received an extra 10 hours of treatment compared with the control group (Dai 2013).

Unfortunately, in the present review, we could not perform a subgroup analysis of the augmented dose of training compared to dose-matched trials.

Timing post stroke

The first two months after stroke are considered the optimal time for recovery of function (Cramer 2008; Hankey 2007; Jørgensen 1995; Jørgensen 1999; Kwakkel 2003; van Kordelaar 2014). Pollock 2014a found evidence of greater benefit of an intervention associated with a shorter time since stroke onset. Therefore, increasing intensity of training with CME seems especially meaningful in the first months after stroke. We could only perform one subgroup analysis (basic ADL post intervention), and we found no difference between participants who started the intervention in the first six months after stroke and participants who started the intervention beyond six months after stroke. However, it is not possible to conclude if there are any differences in effect of CME at different time points after stroke due to the low number of included trials in subgroup analyses.

Upper versus lower extremity

Five of the nine included trials were aimed at the upper extremity (Abu Tariah 2010; Agrawal 2013; Barzel 2015; Gómez 2014; Souza 2015), and four of these trials were about CIMT (Abu Tariah 2010; Barzel 2015; Gómez 2014; Souza 2015). CIMT has proven to be an effective therapy (Nijland 2011). However, CIMT can be a time-consuming therapy and asking for the help of a caregiver can decrease the time spent by a therapist, so the intervention is still enforceable. Souza and colleagues performed an important trial by comparing CIMT therapy (partly) together with a caregiver to CIMT therapy done with a therapist. They found no differences between experimental and control groups and concluded that these forms of therapy provision are equally effective, but that training with a caregiver is less expensive when compared to training with a therapist (Souza 2015).

In our primary analysis, we found a significant effect in favour of the control intervention on the performance time of the Wolf Motor Function test at post intervention, but not at follow-up. This result is largely determined by a single study with a large number of participants (Barzel 2015), and should, therefore, be considered with caution.

Only two included trials were specifically aimed at the lower extremity (Galvin 2011; Wall 1987). A disadvantage of interventions aimed at the lower extremity is the safety aspect. The risk of adverse events (e.g. tripping or falling) is much higher when standing or walking is practiced compared with practicing the use of the upper extremity. However, evidence for intensity trials focused on the lower limb showed them to be more effective than those aimed at the upper paretic limb after stroke. This latter finding makes focusing CME on gait and gait-related activities meaningful.

Overall completeness and applicability of evidence

We found a limited number of trials (nine) with substantial variation in type of CME, duration, timing of training (i.e. within six months or beyond six months after stroke), and outcome measures, which hampered summarising and combining data in a meta-analysis. However, for both primary outcome measures we found two or more trials of relative good quality.

Due to the limited number of included studies, not enough good quality trials were available to perform subgroup analyses, with the exception of timing post stroke (i.e. within six months or beyond six months) for the outcome basic ADL.

Two studies included paid as well as unpaid caregivers, which could not be separated in the results (Dai 2013; Wang 2015). Therefore, this review could not compare the effect of paid and unpaid caregivers. The effects of exercising with a paid caregiver may be different compared with exercising with an unpaid caregiver, especially when there is a difference in the relationship between patient and caregiver.

There may be cultural, ethnic, and societal differences between regions and countries that can influence the applicability and effectiveness of CME interventions. Where ethnicity in itself may not be a limitation for individualised CME programmes after stroke, potential facilitators and barriers may be present that relate to the capacity of the professional to navigate cultural and ethnic differences effectively (Norris 2014).

In addition, involving caregivers during the rehabilitation process can be more or less easy to implement and may be more or less accepted as self-evident in certain cultures for several reasons. In some countries, rehabilitation services are not readily available and communities are required to help, so-called 'community-based rehabilitation' (WHO CBR). One of the excluded trials performed CME in both groups (Redzuan 2012). When contacted, the study author explained that caregivers (or paid workers) are often asked to help in Malaysia. Conversely, caregivers in Western cultures, with advanced healthcare systems and different social practices may be more inclined to leave healthcare services to professionals. However, due to constant changes and budget cuts in Western health care, more pressure is put on the family to provide care. Therefore, CME could have very different implications in different cultures.

Quality of the evidence

The risk of bias of the nine included trials was generally low or unclear (Characteristics of included studies table). Unfortunately, there was insufficient data (fewer than 10 trials) to examine the effects of risk of bias on the calculated estimates of effect reliably by funnel plots.

The overall quality of evidence was very low to moderate. Details of GRADE levels of evidence are presented in the Effects of interventions section. The meta-analysis could include only six trials and these included trials were small, considering the number of included participants per trial. Therefore, we downgraded most of the evidence one level due to a small total number of participants (fewer than 200 participants). For some outcome measures (mainly aimed at upper extremity functioning), there was substantial unexplained statistical heterogeneity and we downgraded the level of evidence one level. For other outcome measures, there was substantial clinical heterogeneity. There is substantial variation between type of exercises performed with a caregiver between trials. We differentiated between CIMT trials (Abu Tariah 2010; Barzel 2015), trials with mobility exercises (Galvin 2011; Wall 1987; Wang 2015), and other trials (Dai 2013). When these trials were combined, we downgraded the level of evidence because there was clinical heterogeneity. In addition, there may be publication bias in the comparisons about upper extremity functioning, because all trials not included in meta-analyses were aimed at upper extremity functioning, and, therefore, we downgraded the level of evidence for these outcome measures.

For an overview of the quality of evidence per outcome measure see Summary of findings table.

Potential biases in the review process

In some countries, CME appears to be more necessary or is more accepted, or both, in daily practice due to lack of formal rehabilitation services or because of cultural attitudes. Although speculative, the implementation of CME could, therefore, be different across countries, suggesting that compliance should be systematically measured in CME trials. As we did not identify any completed trials from, for example, Africa, Asia, and South America, information on such cultural differences remains elusive.

In the current review, we made a distinction between CME and skill training of the caregiver, whereby we excluded trials about skill training as skill training does not pertain specifically to a couple performing exercises together. There could potentially be some overlap between these two forms of training. By excluding trials about skill training, potentially useful information from these trials may have been missed. However, we are confident that our current results do adequately reflect the effects of CME.

Regarding the data-analysis, we employed imputation or extrapolation procedures where SDs were not reported or could not be obtained from the study authors. In four analyses, the SDs from the same trial were used, for example from baseline. For mean changes, we

used 95% CI and the Z-score to calculate SDs. Although this could be a potential source of bias, it is unlikely that results were impacted in a major way.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, there is evidence of very low to moderate quality that caregiver-mediated exercises (CME) can improve patients' functional performance in terms of standing balance and quality of life (QoL) at the end of intervention and walking distance at the end of follow-up, with no significant increase or decrease effect on caregiver burden and no significant effects on (extended) activities of daily living (ADL). Separate analyses of only CME-core trials suggest favourable effects in terms of basic ADL at the end of intervention. However, the results should be interpreted with caution since the included phase II trials were small, had potential bias, and had methodological shortcomings including multiple testing. In addition, one outcome measure was in favour of the control group (Wolf Motor function test - performance time), although this result was mainly influenced by one study with a relatively large number of participants.

The findings in this review suggest that CME may be a valuable and resource-efficient intervention to augment intensity of rehabilitation services after stroke. The effect of CME may be explained by, at least in part, an increase in intensity of training. However, due to the small number of included trials, we could not confirm or reject this hypothesis. In addition, CME can be a treatment option when an increase in intensity of training is useful, for example in constraint-induced movement therapy (CIMT). To implement CME, it is essential that study protocols are published explaining in detail the type, intensity, and content of exercises as well as safety instructions. Finally, CME can be used in inpatient settings as well as in outpatient settings and may be used in acute, subacute, and chronic phase after stroke.

Implications for research

Further studies are needed to get a more complete overview of the different aspects of CME such as timing, duration, and frequency, to assess the most suitable target audience, and to assess (long-term) effects. In addition, it is important to study caregiver burden in relation to CME further, and to assess self-efficacy and study empowerment of people with stroke and their caregivers, which may allow stroke patients to return earlier to the community and stay independently at home (van Vliet 2015). At the moment, only nine trials have been

published that use different outcome measures and measurement tools, making it difficult to summarise and combine outcome measures.

In addition, studies about cost-effectiveness are needed. CME have the potential to achieve a higher intensity of training, resulting in better functional outcome, without increasing healthcare costs. One included trial recorded length of stay and showed a positive trend (Galvin 2011). However, more studies are needed to determine if CME can be costeffective by reducing length of stay, supporting early supported discharge, improving outcomes, and therewith reducing direct and indirect healthcare costs.

To visualise exercises, measure compliance, or keep contact with a supporting therapist, the use of e-health appears promising. This could also be a cost-effective method. E-health in combination with CME has not been studied to date, but two similar clinical trials conducted in different countries (i.e. Adelaide, Australia and Amsterdam, the Netherlands) are currently ongoing (Care4Stroke trial 2014). In particular, because of the impact of availability of community-based stroke services as well as cultural differences with respect to the role of the caregiver as a co-therapist, CME cannot be implemented around the world in the same way. Due to these cross-cultural differences, exercising with a caregiver will be interpreted and implemented differently and so it will be necessary to identify these differences before implementation.

In conclusion, future trials should obey the current CONSORT statements for reporting randomised controlled trials (CONSORT 2010). In addition, they should be powered in a more robust way by including more participants and provide larger treatment contrasts of additional (caregiver-mediated) exercises when compared with the control group as suggested in several meta-analyses with respect to intensity of exercise therapy, include a long-term follow-up, use a consensus-based set of clinical outcome measures (particularly with respect to primary outcomes such as basic ADL and extended ADL), as well as perceived burden of the caregiver. Preferably, these trials should include an economical evaluation alongside to investigate the cost-effectiveness of these services.

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DATA AND ANALYSES

1. Caregiver-mediated exercises versus control - end of intervention

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
1.1 Patient: activities of daily living (ADL) measures: combined	4	295	Std. Mean Difference (IV, Fixed, 95% CI)	0.21 [-0.02, 0.44]
1.1.1 Barthel Index	3	247	Std. Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.09, 0.41]
1.1.2 Functional Independence Measure	1	48	Std. Mean Difference (IV, Fixed, 95% CI)	0.49 [-0.09, 1.06]
1.2 Patient: ADL measures: extended ADL: combined	2	196	Std. Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.21, 0.35]
1.2.1 Nottingham Extended Activities of Daily Living Index	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.33, 0.92]
1.2.2 Instrumental Activities of Daily Living (IADL)	1	156	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.31, 0.32]
1.3 Caregiver: burden: combined	2	91	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.45, 0.37]
1.3.1 Caregiver Strain Index	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.85, 0.39]
1.3.2 Caregiver Burden Scale	1	51	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.44, 0.66]
1.4 Measures of motor impairment: Fugl-Meyer Assessment lower extremity	1	40	Mean Difference (IV, Fixed, 95% CI)	3.10 [-2.02, 8.22]
1.5 Measures of motor impairment: Fugl-Meyer Assessment upper extremity	1	18	Mean Difference (IV, Fixed, 95% CI)	4.43 [-2.09, 10.95]
1.6 Gait and gait-related measures: balance: combined	3	139	Std. Mean Difference (IV, Fixed, 95% CI)	0.53 [0.19, 0.87]
1.6.1 Berg Balance Scale	2	91	Std. Mean Difference (IV, Fixed, 95% CI)	0.56 [0.14, 0.98]
1.6.2 Postural Assessment Scale for Stroke Patients	1	48	Std. Mean Difference (IV, Fixed, 95% CI)	0.48 [-0.09, 1.06]
1.7 Gait and gait-related measures: Six-Minute Walk Test	2	91	Mean Difference (IV, Fixed, 95% CI)	30.98 [-20.22, 82.19]
1.8 Gait and gait-related measures: walking speed	2	71	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.03, 0.18]
1.9 Measures of upper limb activities or function: Wolf Motor Function test - functional ability	2	174	Mean Difference (IV, Random, 95% CI)	0.02 [-0.52, 0.55]
1.10 Measures of upper limb activities or function: Wolf Motor Function Test - performance time	2	174	Mean Difference (IV, Fixed, 95% CI)	-1.72 [-2.23, -1.21]

1. Caregiver-mediated exercises versus control - end of intervention – *Continued*

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
1.11 Measures of upper limb activities or function: Motor Activity Log (MAL) - amount of use	2	174	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.36, 0.38]
1.12 Measures of upper limb activities or function: MAL - quality of movement	2	174	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.26, 0.42]
1.13 Measures of upper limb activities or function: Nine Hole Peg test	1	156	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.11, 0.03]
1.14 Measures of mood and quality of life (QoL) of the patient: Stroke Impact Scale (SIS) - composite physical	1	51	Mean Difference (IV, Fixed, 95% CI)	12.40 [1.67, 23.13]
1.15 Measures of mood and QoL of the patient: SIS - strength	1	51	Mean Difference (IV, Fixed, 95% CI)	12.20 [-0.08, 24.48]
1.16 Measures of mood and QoL of the patient: SIS - ADL/IADL	1	51	Mean Difference (IV, Fixed, 95% CI)	11.40 [-1.11, 23.91]
1.17 Measures of mood and QoL of the patient: SIS - mobility	1	51	Mean Difference (IV, Fixed, 95% CI)	18.20 [7.54, 28.86]
1.18 Measures of mood and QoL of the patient: SIS - hand function	2	207	Mean Difference (IV, Fixed, 95% CI)	2.64 [-5.87, 11.15]
1.19 Measures of mood and QoL of the patient: SIS - memory	1	51	Mean Difference (IV, Fixed, 95% CI)	6.30 [-1.65, 14.25]
1.20 Measures of mood and QoL of the patient: SIS - communication	1	51	Mean Difference (IV, Fixed, 95% CI)	3.00 [-2.34, 8.34]
1.21 Measures of mood and QoL of the patient: SIS - emotion	1	51	Mean Difference (IV, Fixed, 95% CI)	2.10 [-4.35, 8.55]
1.22 Measures of mood and QoL of the patient: SIS - social participation	1	51	Mean Difference (IV, Fixed, 95% CI)	6.70 [-1.69, 15.09]
1.23 Measures of mood and QoL of the patient: SIS - general recovery	1	51	Mean Difference (IV, Fixed, 95% CI)	15.10 [8.44, 21.76]
1.24 Length of stay - hospital	1	37	Mean Difference (IV, Fixed, 95% CI)	4.40 [-3.91, 12.71]
1.25 Length of stay - rehabilitation unit	1	20	Mean Difference (IV, Fixed, 95% CI)	12.00 [-10.88, 34.88]
1.26 Adverse outcomes: falls	1	48	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.10, 0.18]

2. Caregiver-mediated exercises versus control - end of follow-up

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
2.1 Patient: activities of daily living (ADL) measures: ADL	2	196	Mean Difference (IV, Random, 95% CI)	2.69 [-8.18, 13.55]
2.1.1 Barthel Index	2	196	Mean Difference (IV, Random, 95% CI)	2.69 [-8.18, 13.55]
2.2 Patient: ADL measures: extended ADL: combined	2	196	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.17, 0.39]
2.2.1 Nottingham Extended Activities of Daily Living Index	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	0.51 [-0.12, 1.14]
2.2.2 IADL	1	156	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.31, 0.32]
2.3 Caregiver: burden	1	40	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.71, 1.91]
2.3.1 Caregiver Strain Index	1	40	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.71, 1.91]
2.4 Measures of motor impairment: Fugl-Meyer Assessment lower extremity	1	40	Mean Difference (IV, Fixed, 95% CI)	3.40 [-1.74, 8.54]
2.5 Measures of motor impairment: Fugl-Meyer Assessment upper extremity	1	18	Mean Difference (IV, Fixed, 95% CI)	2.75 [-8.24, 13.74]
2.6 Gait and gait-related measures: balance	1	40	Mean Difference (IV, Fixed, 95% CI)	8.40 [-1.04, 17.84]
2.6.1 Berg Balance Scale	1	40	Mean Difference (IV, Fixed, 95% CI)	8.40 [-1.04, 17.84]
2.7 Gait and gait-related measures: Six-Minute Walking Test	1	40	Mean Difference (IV, Fixed, 95% CI)	109.50 [17.12, 201.88]
2.8 Gait and gait-related measures: walking speed	1	20	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.02, 0.22]
2.9 Measures of upper limb activities or function: Wolf Motor Function test - functional ability	2	174	Mean Difference (IV, Random, 95% CI)	0.08 [-0.46, 0.61]
2.10 Measures of upper limb activities or function: Wolf Motor Function test - performance time	2	174	Mean Difference (IV, Random, 95% CI)	1.85 [-8.78, 12.48]
2.11 Measures of upper limb activities or function: Motor Activity Log - amount of use	2	174	Mean Difference (IV, Random, 95% CI)	0.21 [-0.65, 1.08]
2.12 Measures of upper limb activities or function: Motor Activity Log - quality of movement	2	174	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.43, 0.37]

2. Caregiver-mediated exercises versus control - end of follow-up – *Continued*

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
2.13 Measures of upper limb activities or function: Nine Hole Peg test	1	156	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.12, 0.02]
2.14 Measures of mood and quality of life of the patient: Stroke Impact Scale (SIS) - hand function	1	156	Mean Difference (IV, Fixed, 95% CI)	-2.20 [-12.46, 8.06]

3. Timing post stroke - end of intervention

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
3.1 Patient: activities of daily living measures: combined	4	295	Std. Mean Difference (IV, Fixed, 95% CI)	0.21 [-0.02, 0.44]
3.1.1 <6 months	2	88	Std. Mean Difference (IV, Fixed, 95% CI)	0.44 [0.01, 0.86]
3.1.2 >6 months	2	207	Std. Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.16, 0.39]

4. Mean change from post intervention - end of follow-up

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
4.1 Patient: activities of daily living (ADL) measures: Barthel Index	1	40	Mean Difference (IV, Fixed, 95% CI)	2.30 [-3.95, 8.55]
4.2 Patient: ADL measures: extended ADL - Nottingham Extended Activities of Daily Living Index	1	40	Mean Difference (IV, Fixed, 95% CI)	4.00 [-0.99, 8.99]
4.3 Patient: ADL measures: extended ADL - reintegration to normal living index	1	40	Mean Difference (IV, Fixed, 95% CI)	4.30 [2.03, 6.57]
4.4 Caregiver: Caregiver Strain Index	1	40	Mean Difference (IV, Fixed, 95% CI)	1.10 [0.45, 1.75]
4.5 Measures of motor impairment: Fugl-Meyer Assessment lower extremity	1	40	Mean Difference (IV, Fixed, 95% CI)	0.30 [-2.21, 2.81]
4.6 Gait and gait-related measures: balance: Berg Balance Scale	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-4.78, 2.98]
4.7 Gait and gait-related measures: Six-Minute Walking Test	1	40	Mean Difference (IV, Fixed, 95% CI)	43.30 [15.11, 71.49]
4.8 Other outcomes: Motor Assessment Scale	1	40	Mean Difference (IV, Fixed, 95% CI)	1.10 [-0.92, 3.12]

5. Sensitivity analysis - caregiver-mediated exercise (CME)-core - end of intervention

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
5.1 Patient: activities of daily living (ADL) measures: Barthel Index	2	91	Mean Difference (IV, Fixed, 95% CI)	9.45 [2.11, 16.78]
5.2 Patient: ADL measures: extended ADL - Nottingham Extended Activities of Daily Living Index	1	40	Mean Difference (IV, Fixed, 95% CI)	5.50 [-5.83, 16.83]
5.3 Gait and gait-related measures: balance: Berg Balance Scale	2	91	Mean Difference (IV, Fixed, 95% CI)	6.35 [1.64, 11.06]

6. Sensitivity analysis - caregiver-mediated exercise (CME)-core - end of follow-up

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
6.1 Patient: activities of daily living (ADL) measures: Barthel Index	1	40	Mean Difference (IV, Fixed, 95% CI)	9.00 [-1.29, 19.29]
6.2 Patient: ADL measures: extended ADL - Nottingham Extended Activities of Daily Living Index	1	40	Mean Difference (IV, Fixed, 95% CI)	9.50 [-1.83, 20.83]

7. Walking speed, different possibilities study of Wall

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
7.1 Walking speed - caregiver-mediated exercises (CME) vs physiotherapy - end of intervention	2	61	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.07, 0.20]
7.2 Walking speed - CME vs physiotherapy - end of follow-up	1	10	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.04, 0.26]
7.3 Walking speed - CME vs no intervention - end of intervention	2	61	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.08, 0.19]
7.4 Walking speed - CME vs no intervention - end of follow-up	1	10	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.04, 0.24]
7.5 Walking speed - CME and physiotherapy vs physiotherapy - end of intervention	2	61	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.06, 0.21]

7. Walking speed, different possibilities study of Wall – *Continued*

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
7.6 Walking speed - CME and physiotherapy vs physiotherapy - end of follow-up	1	10	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.11, 0.31]
7.7 Walking speed - CME and physiotherapy vs no intervention - end of intervention	2	61	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.07, 0.20]
7.8 Walking speed - CME and physiotherapy vs no intervention - end of follow-up	1	10	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.11, 0.29]

8. Extended activities of daily living (ADL) - analyses with Reintegration to Normal Living Index (RNLI)

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
8.1 Patient: ADL measures: extended ADL - combined - end of intervention	2	196	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.27, 0.29]
8.1.1 RNLI	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.59, 0.65]
8.1.2 Instrumental Activities of Daily Living (IADL)	1	156	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.31, 0.32]
8.2 Patient: ADL measures: extended ADL - combined - end of follow-up	2	196	Std. Mean Difference (IV, Random, 95% CI)	0.29 [-0.37, 0.95]
8.2.1 RNLI	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.69 [0.05, 1.33]
8.2.2 IADL	1	156	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.31, 0.32]

CHARACTERISTICS OF STUDIES

Characteristics of included studies

Footnotes: ADL = activities of daily living; CIMT = constraint-induced movement therapy; CT = computerised tomography; IADL = instrumental activities of daily living; ITT = intention-to-treat; MRI = magnetic resonance imaging; NDT = neurodevelopmental treatment; SD = standard deviation; SIS = Stroke Impact Score; VR = vestibular rehabilitation.

Abu Tariah 2010

Methods	Design: randomised trial of CIMT training vs NDT training Study duration: 6 months (2 months' intervention and 4 months' follow-up) Randomisation: 20 participants were randomly numbered from 1 to 20; odd numbers participated in the CIMT group, even numbers in the NDT group. Allocation concealment: not applicable: all participants were randomised at the same time. Blinding: assessors blind for group allocation ITT: no
Participants	Randomised: 20 participants Withdrawals: 2 participants dropped out of the NDT group at an early stage. There were no reasons given by the participants. Intervention: 10 participants; 8 men and 2 women; mean age 54.8 years (SD 10.9); mean time since stroke 9.2 months (SD 5.79) Control: 8 participants; 4 men and 4 women; mean age 60.6 years (SD 4.9); mean time since stroke 9.6 months (SD 4) Inclusion criteria: stroke >2 months ago; aged 40 to 75 years; live with family caregivers at their homes; no balance problem that might risk safety Exclusion criteria: recurrent, bilateral or brain stem stroke; inability to actively extend 10° at metacarpophalangeal and interphalangeal joints, and 20° at wrist; substantial use of the involved upper extremity in their life situation: Motor Activity Log - amount of use scale >2.5; major cognitive deficits (score <24 points on the Folstein Mini-Mental State Examination); excessive spasticity and pain, as determined by clinical judgement
Interventions	Intervention: CIMT: intensive training of the affected arm 2 hours/day, while restraining the unaffected hand with a resting splint, 7 days/week, for 2 months; 2 trained occupational therapists educated and trained stroke survivors and their caregivers at home in 3 or 4 sessions; detailed information about the training activities to be carried out were given; importance of caregiver commitment was discussed; training activities focuses on patient's ADL/IADL/leisure activities; amount of training was noted in a diary by patients' family. Control: NDT: training consisted of weight bearing and facilitation of arm movement based on conventional NDT procedures; 2 hours/day during weekdays in outpatient clinic and a home programme of 2 hours during the weekend for 2 months; once a week a home visit and follow-up telephone calls. Setting: outpatient clinic of a large hospital; intervention done at home
Outcomes	Included outcomes: Wolf Motor Function test, Motor Activity Log, Fugl-Meyer Assessment upper extremity Measurements: baseline assessment, post intervention after 2 months, follow-up 4 months after end of the treatment

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The 20 participants were randomly numbered from 1 to 20; odd numbers in CIMT group, even numbers in NDT group.
Allocation concealment (selection bias)	Low risk	All participants were randomised at the same time.
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel cannot be blind for the intervention.
Blinding of outcome assessment (detection bias)	Low risk	Investigators were blind to the allocation of the group, they provided the evaluation. The investigators were not the therapists who treated the participants.
Incomplete outcome data (attrition bias)	Unclear risk	2 withdrawals in the control NDT group, there were no reasons given by the participants. No withdrawals in intervention group. The effect of withdrawal from the control group was unclear.
Selective reporting (reporting bias)	Unclear risk	No trial registry; nothing stated. Outcomes were described in results.
Other bias	Unclear risk	Small sample size; no ITT analysis

Agrawal 2013

Methods	Design: randomised trial of exercise training of upper extremity in addition to usual care vs usual care; 3 groups: 90 minutes' exercise training, 60 minutes' exercise training, control Study duration: 4 weeks Randomisation: 'randomly assigned', not described how Allocation concealment: not described Blinding: not described ITT: yes
Participants	Randomised: 30 participants Withdrawals: 0 Intervention: Group A (+ 90 minutes): 10 participants; 7 men and 3 women; mean age 55.80 years (SD 4.10); mean time since stroke 3.50 months (SD 1.08) Group B (+ 60 minutes): 10 participants; 5 men and 5 women; mean age 55.70 years (SD 6.24); mean time since stroke 3.70 months (SD 1.34) Group C (control): 10 participants; 7 men and 3 women; mean age 55.20 years (SD 6.12); mean time since stroke 3.50 months (SD 1.08) Inclusion criteria: subacute median carotid artery stroke diagnosed by neuro-physician on CT or MRI scan; Fugl-Meyer Assessment upper extremity scale score between 10 and 57; aged 45 to 65 years Exclusion criteria: Mini-Mental Status Examination score <20; visual/auditory impairments; presence of any other neurological diagnosis other than stroke or any other major comorbidity; unstable cardiovascular status; non-co-operative patients

Agrawal 2013 – *Continued*

Interventions	Intervention: GRASP (Graded Repetitive Arm Supplementary Program) protocol: self-administered upper-limb exercise programme aimed at improving upper-limb recovery; exercise book and kit tailored according to the motor impairment level; exercise book contained written and pictorial instructions; kit contained inexpensive equipment to complete the exercises; each exercise was graded by varying repetitions to meet each participant's need; exercises included strengthening of the arm, range of motion, and gross and fine motor skills. Repetitive goal and tasks-oriented activities were designed to simulate partial or whole skill sets required for ADL; 5 days/week, 90 minutes/day (group A) or 60 minutes/day (group B); help of 1 caregiver; weekly meeting with the therapist; plus the education programme: information on stroke recovery and general health. Control: education programme (information on stroke recovery and general health) and conventional physiotherapy (not described) Setting: rehabilitation unit of a hospital
Outcomes	Included outcomes: Fugl-Meyer Assessment upper extremity scale, Chedoke Arm and Hand Activity Inventory Measurements: baseline assessment, post intervention assessment after 4 weeks
Notes	In results section, SDs were not noted. Contact with authors was unsuccessful.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned"; but not described how.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel cannot be blind for the intervention.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	No withdrawals
Selective reporting (reporting bias)	Unclear risk	No trial registry; nothing stated
Other bias	Unclear risk	None of the SDs in the result section were noted.

Barzel 2015

Methods	Design: cluster-randomised trial of home CIMT vs standard therapy Study duration: 4 weeks Randomisation: practices were stratified by region and randomly allocated by an external biometrician (1:1, block size of 4) using a computer-generated sequence. Allocation concealment: yes, by the computer-generated sequence. Randomisation was per practice and further allocation concealment was not necessary. Furthermore, patients were included in the study before randomisation of practices to minimise differential self-selection. Blinding: assessors blind for group allocation; statistician was also masked. ITT: yes
Participants	Randomised: 156 participants Withdrawals: 5 withdrawals in the intervention group because of death, poor health, and not wanting to continue; 4 withdrawals in the control group because of moving, death, and poor health Intervention: Home CIMT: 85 participants; 51 men and 34 women; mean age 62.55 years (SD 13.73); mean time since stroke 56.57 months (SD 47.36) Standard therapy: 71 participants; 43 men and 28 women; mean age 65.30 years (SD 12.63); mean time since stroke 45.65 months (SD 57.69) Inclusion criteria: physical and occupational therapy practices: treating adults with upper limb dysfunction after stroke unless they already offered CIMT, with 1 therapist with a professional qualification or at least 2 years of experience in treatment of chronic impairment caused by stroke; patients: >6 months after stroke, mild-to-moderate impairment of arm function and minimal residual hand function (minimum 10° active wrist extension, 10° active thumb abduction or extension, and 10° extension of 2 additional fingers), had a referral for physical or occupational therapy, >18 years, had a caregiver who was prepared to be a non-professional coach (e.g. family member). Exclusion criteria: severely impaired verbal communication, inability to give consent, severe neurocognitive deficits (score <23 in the Mini-Mental State Examination), terminal illness, or life-threatening comorbidities, or previously received CIMT.
Interventions	Intervention: home CIMT: patients were instructed to train in their home environment for 2 hours each day, accompanied by a coach. Additionally, patients were asked to wear a resting glove during exercises and ADL to immobilise their non-affected hand. The therapists guided the coach on how to document the time or repetitions per time for each exercise and to assist the patient in keeping a training diary. Therapists used the first of 5 home visits to instruct the patient and the coach in the principles of home CIMT, set individually tailored goals, and work through the first 2 to 3 exercises, focusing on everyday practice. During subsequent weekly home visits, therapists supervised the training, set up new exercises, and applied behavioural techniques. Professional therapy time was not used to practise exercises. Control: conventional physical or occupational therapy, but additional home training was not obligatory. Standard therapy could consist of various therapeutic techniques typical of stroke therapy. The standard therapy group therapists reported details of professional treatment delivery and any agreements (e.g. homework) made with patients via a standardised documentation sheet. Setting: intervention group - home; control group - therapy practice

Barzel 2015 – *Continued*

Outcomes	Included outcomes: Motor Activity Log - quality of movement, Wolf Motor Function test - performance time, Motor Activity Log - amount of use, Wolf Motor Function test - functional ability, Nine Hole Peg Test, SIS hand function, Barthel index, IADL Measurements: baseline assessment, post intervention assessment after 4 weeks, follow-up assessment at 6 months. Interim interview (Motor Activity Log) at 3-month follow-up
Notes	For mean changes of outcomes means and 95% confidence intervals were given. To calculate SDs, we used the Z-score (1.96).

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Practices were stratified and randomly allocated by an external biometrician using a computer-generated sequence.
Allocation concealment (selection bias)	Low risk	By computer-generated sequence. Furthermore, patients were included in the study before randomisation of practices to minimise differential self-selection.
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel cannot be blind for the intervention.
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors and the statistician were masked.
Incomplete outcome data (attrition bias)	Low risk	5 withdrawals in intervention group and 4 in the control group; well described and for similar same reasons. Missing data were imputed using correct methods; analyses were by ITT and in case of missing values, a last observation carried forward imputation was performed.
Selective reporting (reporting bias)	Low risk	The study protocol is available and preselected outcomes are in the review. There are some minor differences: EQ-5D, costs and SIS are not described in this paper.
Other bias	Low risk	

Dai 2013

Methods	Design: randomised trial of VR plus conventional rehabilitation vs conventional rehabilitation Study duration: 4 weeks Randomisation: the wards of the same hospital were randomly assigned to the intervention or control group Allocation concealment: not described Blinding: assessors blind for group allocation ITT: no
Participants	Randomised: 55 participants Withdrawals: 3 withdrawals in the intervention group because of depression, upper gastrointestinal bleeding, and transfer to another hospital, 4 withdrawals in the control group because of declination (2), asthma attack (1), and transfer to another hospital (1). Intervention: 24 participants; 16 men and 8 women; mean age 57.21 years (SD 12.23); time since stroke 56.88 days (SD 38.93) Control: 24 participants; 12 men and 12 women; mean age 65.54 years (SD 14,67); time since stroke 73.88 days (SD 37.86) Inclusion criteria: for the stroke patients: being diagnosed by physicians by CT or MRI scan of the brain as having experienced a right hemispheric stroke, including haemorrhagic or ischaemic strokes, and first-time stroke with a duration <6 months from the stroke onset; meeting the conditions for neglect on any of the 2 scales within the Behavioral Inattention Test Conventional subtest; capable of communicating in Mandarin Chinese or Taiwanese, and understanding instructions; for the primary caregivers: being defined as primary caregivers by patients during inpatient rehabilitation, including family members, friends, employed nursing aides, and foreign caregivers; willing to participate in supervising and guiding the patients' VR training; capable of communicating in Mandarin Chinese or Taiwanese. Exclusion criteria: recurrent stroke with duration > 6 months from stroke onset; <2 subtests of diagnosed neglect; incapability to communicate; lack of primary caregivers.
Interventions	Intervention: VR plus conventional rehabilitation (see control); VR: 1. with their eyes open, the patients moved their head up and down for 20 times or for 1 minute. They also moved their head from side to side for 20 times or for 1 minute, 2. with their eyes closed, the patients moved their head up and down for 20 times or for 1 minute. They also moved their head from side to side for 20 times or for 1 minute, 3. the polypropylene corrugated board was placed on the trainers' thighs. The target was at the same height as the patients' eyes. The patients gazed at the target while moving their head up and down and from side to side for 20 times, 4. the patients rested as necessary. The patients performed steps 1 to 3 repeatedly, and the entire process took approximately 30 minutes; patients were seated in their wheelchairs and their heads and bodies were in the middle position. The instructors verbally reminded the patients to maintain their heads and bodies in the middle position; first and second week a registered trained nurse trained the patients in VR; third and fourth week: patients were guided and supervised by their primary caregivers (the nurse taught the caregivers how to do this in sessions of 5 to 10 minutes, 2 to 4 in total); training once a day for 30 minutes; total of 10 sessions in 2 weeks. Control: conventional rehabilitation: the exercise training for the physiotherapy included passive exercises, active exercises, resistive exercises, ambulation training, and so on. The occupational therapy included maintaining or improving physiological functions such as endurance, balance, and training; to improve ADL, such as dressing, using the toilet, sanitation, home care, and others; 5 days/week for 2 hours. Setting: rehabilitation wards of 2 medical centres

Dai 2013 – *Continued*

Outcomes	Included outcomes: Rivermead Behavioral Inattention Test, Functional Independence Measure, Postural Assessment Scale for people with stroke, falls/person Measurements: baseline assessment, assessment at day 14, and assessment at day 28
Notes	"In the Taiwanese health care system, informal caregivers typically assist patients in their activities of daily living"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The wards were randomly assigned, but method not described.
Allocation concealment (selection bias)	Unclear risk	The wards were randomly assigned, but method not described.
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel cannot be blind for the intervention.
Blinding of outcome assessment (detection bias)	Low risk	Assessors were blinded.
Incomplete outcome data (attrition bias)	Low risk	7 withdrawals: 4 in control group and 3 in intervention group. Reasons were well described and about the same.
Selective reporting (reporting bias)	Unclear risk	No trial registry; nothing stated
Other bias	Unclear risk	No ITT analysis

Galvin 2011

Methods	Design: randomised trial of exercise therapy (FAME (Fitness And Mobility Exercise) programme) plus 'routine' physiotherapy vs 'routine' physiotherapy Study duration: 5 months (8 weeks' intervention and 3 months' follow-up) Randomisation: computer-generated random numbers placed in sealed envelopes. The envelopes were opened by an independent person by enrolment of a participant. Allocation concealment: yes, by the sealed envelopes Blinding: assessor blind for group allocation ITT: yes
Participants	Randomised: 40 participants Withdrawals: 2 participants in the intervention group withdrew because of second stroke and myocardial infarction. 1 participant in the control group withdrew because of medically unwell Intervention: 20 participants; 13 men and 7 women; mean age 63.15 years (SD 13.3); time since stroke 18.9 days (SD 2.9)

Galvin 2011 – *Continued*

	Control: 20 participants; 7 men and 13 women; mean age 69.95 years (SD 11.69); time since stroke 19.7 days (SD 3) Inclusion criteria: for the people with stroke: first unilateral stroke (MRI or CT); no impairment of cognition (>23 of 30 on the Mini-Mental State Examination); aged ≥18 years; participating in a physiotherapy programme; a family member willing to participate in the programme; 3.2 to 5.2 on the Orpington Prognostic Scale (to control for heterogeneity); for the caregivers: willing to participate in the programme; nominated by the person with stroke as the person that he or she would most like to assist him or her in the performance of the exercises; medically stable and physically able to assist in the delivery of exercises Exclusion criteria (only described in protocol): hemiplegia of a non-vascular origin; discharge <2 weeks following stroke; pre-existing neurological disorder resulting in a motor deficit in addition to that resulting from the stroke; present with any lower extremity orthopaedic condition such as recent fractured femur or amputation; have receptive/expressive dysphasia Suitability was determined after consultation with the individual, their family, and the physiotherapist in charge of the patient's routine care.
Interventions	Intervention: FAME programme plus 'routine' physiotherapy (see control); FAME programme: doing exercises together with a nominated family member; daily, 35 minutes, inpatient or at home; weekly were treatment goals set and instructions given by a treating therapist; individual treatment protocol except for the time component; emphasis of the programme was on achieving stability and improving gait velocity and lower limb strength based on patterns derived from findings reported in a systematic review of 151 intervention studies on stroke rehabilitation; a second family member could be involved; compliance was documented with an exercise diary. Control: 'routine' physiotherapy: inpatient or outpatient in either hospital or rehabilitation unit; duration was not recorded; given by staff not linked to the project. Setting: 6 (acute) hospital stroke units or rehabilitation units, or both, in the same hospital or linked to the hospital; inpatient and (if possible) outpatient
Outcomes	Included outcomes: lower limb section of the Fugl-Meyer Assessment, Motor Assessment scale, Berg Balance Scale, Six-Minute Walk Test, 100-point original Barthel Index, Reintegration to Normal Living Index, Nottingham Extended Activities of Daily Living Index, Caregiver Strain Index Measurements: baseline, post intervention (8 weeks) and follow-up 3 months after postintervention assessment
Notes	No SDs were available for Caregiver Strain Index, Nottingham Extended Activities of Daily Living Index and Reintegration to Normal Living Index at post intervention. Contact with authors was unsuccessful.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers in sealed envelopes, which were opened by an independent person.
Allocation concealment (selection bias)	Low risk	Random numbers in sealed envelopes
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel cannot be blind for the intervention.
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor was not involved in care and unaware of group allocation.
Incomplete outcome data (attrition bias)	Low risk	2 withdrawals in intervention group and 1 in the control group; well described and for similar reasons. Missing data were imputed using correct methods; analyses were by ITT and a last measurement carried forward method was used to account for attrition.
Selective reporting (reporting bias)	Low risk	Study protocol was available and all the preselected outcomes were in the review.
Other bias	Unclear risk	No SDs were available for Caregiver Strain Index, Nottingham Extended Activities of Daily Living Index and Reintegration to Normal Living Index at post intervention. SDs from follow-up were imputed.

Gómez 2014

Methods	Design: randomised trial of CIMT in addition to usual care with help of a caregiver vs usual care Study duration: 14 days Randomisation: simple alternating randomisation Allocation concealment: no Blinding: no information about the assessor of the measurements ITT: not clear: withdrawals were not described. Different numbers were given in the outcome tables.
Participants	Randomised: 60 participants Withdrawals: not described Intervention: 30 participants; 20 men and 10 women; mean age 68.03 years (SD 12.43); time since stroke not described Control: 30 participants; 20 men and 10 women; mean age 68.33 years (SD 12.78); time since stroke not described Inclusion criteria: 20 grades extension in the wrist and 10 grades extension in metacarpal joints, subacute phase after stroke, people in wheelchairs or with severe balance problems, people with mild cognitive impairment, people with family support Exclusion criteria: excessive spasticity, behavioural problems

Gómez 2014 – *Continued*

Interventions	Intervention: CIMT therapy with a restriction of 75% of the non-affected arm with a mitt (4 hours free), forced use of the affected arm: daily 1.5 hours with an occupational therapist, 2 hours and ADL monitored by personnel and family and 2 hours of manual activities proposed by the occupational therapist and supervised by family (for 14 days every day?) Patients wore the sling for 14 days. Before the start there was a meeting with the family in which the exercises were explained and a log sheet with activities to be completed every day during the 14 days of the therapy was given. Control: usual care: traditional occupational therapy Setting: a chronic care and long-stay facility in Spain, inpatient rehabilitation setting
Outcomes	Included outcomes: Barthel Index, Index of Lawton and Brody (version 8), Purdue Pegboard, Dynamometer Test, Cognitive Mini Mental Examination of Lobo, modified scale of Socio-family Gijon; outcomes that needed clarification: cancellation, Nlesulam Measurements: baseline and post intervention (14 days?)
Notes	Article in Spanish. No means and SDs for outcome measures were given, included outcomes were not all clear, intervention and timing of measurements needed some clarification. However, contact with the authors was unsuccessful.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation by simply alternating. However, it was not described which method was used.
Allocation concealment (selection bias)	Unclear risk	It was not described which randomisation method was used. Therefore, allocation concealment was unknown.
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel cannot be blind for the intervention.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Unclear risk	Withdrawals were not described.
Selective reporting (reporting bias)	Unclear risk	No trial registry, nothing stated
Other bias	Unclear risk	No means and SDs were described.

Souza 2015

Methods	Design: randomised trial of CIMT partly supervised by a caregiver vs CIMT supervised by a therapist Study duration: 6 months (22 days' intervention and 6 months' follow-up) Randomisation: patients were randomised by a staff member not involved in the study. Randomisation information was stored in sealed envelopes that were kept in a cabinet accessible solely to the principal investigator. Allocation concealment: yes, by the sealed envelopes Blinding: assessor blinded for group allocation ITT: no
Participants	Randomised: 24 participants Withdrawals: 3 participants in the intervention group withdrew because of fatal recurrent stroke, moving away, and financial limitations; 2 participants in the control group withdrew because of returning to work and finding the exercises too difficult. Intervention: 9 participants; 6 men and 3 women; mean age 61.7 years (SD 12.7); time since stroke 27.6 months (20.9) Control: 10 participants; 9 men and 1 women; mean age 59.5 years (SD 9.1); time since stroke 35.3 months (SD 33.8) Inclusion criteria: aged >18 years; history of ischaemic or haemorrhagic stroke leading to upper limb paresis in the previous 24 months; minimal active range of motion of 10° for wrist extension, 10° for abduction/extension of the thumb and at least 2 additional digits, 90° for shoulder flexion and abduction, 45° for shoulder external rotation, 30° for elbow extension, 45° for forearm supination and pronation (from neutral position), wrist extension (from neutral), and finger extension of all digits; amount-of-use score on the Motor Activity Log >2.5; balance and stability to move using a glove in the unaffected hand; safe and independent transfer to toilet; ability to stand for 2 minutes with and without the glove (with support of upper limbs, if necessary); availability of a family member to supervise home exercises Exclusion criteria: medical problems or cognitive deficit (Mini-Mental State Examination score <24) that could interfere with study completion; aphasia or hemi-neglect; intended or actual participation in any other study; significant pain (≥4 on a visual analogue scale) in any joint; upper limb treatment with antispasticity drugs in the previous 6 months; and severe upper limb spasticity (≥3 in the Modified Ashworth Scale)
Interventions	Intervention: in the CIMT1.5h_direct group, patients performed exercises with the paretic upper limb for 1.5 hours at an outpatient facility and home exercises, supervised by a caregiver or family member, for additional 1.5 hours. 2 days before treatment started, the caregiver was trained for 1 hour by the researcher providing CIMT on how to supervise the prescribed exercises performed by the patient at home. Each caregiver was instructed to make notes in a log book about the exercises performed, the number of repetitions, and difficulties experienced by the patient. At the beginning of each session, the homework was discussed and when necessary, the level of difficulty was increased or new tasks were prescribed. The CIMT1.5h_direct group received written assignment of practice at home. Control: in the CIMT3h_direct group, patients performed exercises under direct supervision of a therapist, at the outpatient facility,

Souza 2015 – *Continued*

	In both groups , training was provided in an individual basis and consisted of shaping principles and task-specific practice. Shaping exercises comprised a battery of tasks including grasping and releasing objects of different shapes, playing cards and board games, clay activities, drawing, and painting. Tasks were tailored to needs of each patient. Task-specific practice for both groups involved preparing a snack (sandwiches and juice), including arranging dishes and cutlery on a table, washing and drying them, and putting them in a cupboard. Treatment regimens were designed to ensure that both groups received the same amount of task practice and shaping. Furthermore, in both groups, patients were required to use a padded mitt in the unaffected hand at home, as much as possible during waking hours. The mitt prevented use of the unaffected hand to perform fine motor activities and was used during ADL and household activities. All patients were instructed to record the use time of the mitt and any difficulties perceived at home, in log books. At the beginning of each outpatient session the notes were discussed and, if necessary, problem-solving strategies were applied. Setting: at home and an outpatient clinic
Outcomes	Included outcomes: Motor Activity Log - quality of movement, Fugl-Meyer Assessment upper extremity scale, Stroke Specific Quality of Life Scale Measurements: baseline, post intervention 2 days after stop of the intervention, and follow-up 6 months after post intervention assessment
Notes	No means and SDs were published of post intervention or follow-up scores, but effectiveness indexes were. However, contact with the authors was unsuccessful. Stroke leading to upper limb paresis in the previous 24 months was named as an inclusion criterion. However, mean time after stroke was 27 months in the intervention group and 35 months in the control group.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised by a staff member not involved in the study". But not described how
Allocation concealment (selection bias)	Low risk	Used sealed envelopes
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel cannot be blind for the intervention.
Blinding of outcome assessment (detection bias)	Low risk	Assessor blinded for group allocation
Incomplete outcome data (attrition bias)	Low risk	5 withdrawals: 2 in control group and 3 in intervention group. Reasons were well described and similar
Selective reporting (reporting bias)	Unclear risk	No trial registry; nothing stated
Other bias	Unclear risk	No ITT No means and SDs were described

Wall 1987

Methods	Design: randomised trial about exercise therapy; 4 groups: home exercise programme alone, outpatient physiotherapy alone, home exercises + physiotherapy, no intervention Study duration: 9 months (6 months' intervention, 3 months' follow-up) Randomisation: 'randomly assigned' is stated in article. No further information Allocation concealment: not described Blinding: not described ITT: yes, no withdrawals
Participants	Randomised: 20 participants Withdrawals: 0 Intervention and control: 4 interventions; 5 participants per intervention; no information about participants per intervention; in general: aged 45 to 70 years; men and women; time since stroke between 18 months and 10 years Inclusion criteria: not clearly stated (capable of walking with or without a walking stick) Exclusion criteria: negative prognosticators such as serious or unstable medical conditions, major central sensory disorders, homonymous hemianopia, marked cognitive disturbances, intractable pain, motivation defects, incontinence of bowel or bladder
Interventions	Intervention: Group B: home exercise programme: 10 exercises over 1 hour. They were designed hierarchically in terms of complexion. Each exercise lasted 5 minutes with the same distribution of exercise and rest. After the fifth and the eighth exercise there was a 5-minute rest. After 1 month, the most basic exercise was dropped and an additional, more demanding, exercise was added. The exercises were done twice a week. A booklet describing the exercises, duration, and sequence was provided. The programme was undertaken in the person's home with supervision of their spouse or companion. Twice a week for 1 hour. The physiotherapist monitored the programme. Instructional videotapes were available to demonstrate the correct way to do the exercise. These were shown to patients and caregivers when they came for assessment. Group C: outpatient physiotherapy + home exercise programme: exercise programme (as Group B); once a week for 1 hour outpatient physiotherapy and once a week for 1 hour home exercise programme. Control: Group A: outpatient physiotherapy alone; the exercises were taught by a physiotherapist. Feedback and correction was given by this therapist. Twice a week for 1 hour. Group D: control group: no therapy Setting: outpatient
Outcomes	Included outcomes: walking speed Other outcomes: measurements of duration of the single support phase of the affected side, measures of the degree of temporal symmetry; asymmetry ratio Measurements: baseline assessment, 1 month interval during treatment, after treatment, and follow-up after 3 months
Notes	Inclusion criteria were not clearly stated. There was information about the participants: all participants had residual hemiplegia due to stroke experienced between 18 months and 10 years previously. They all had undergone rehabilitation and were discharged from this. All participants were capable of walking and showed (subjectively) a reduced support phased time of the affected limb.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned", but not stated how.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel cannot be blind for the intervention.
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	No withdrawals
Selective reporting (reporting bias)	Unclear risk	No trial registry; nothing stated
Other bias	Low risk	

Wang 2015

Methods	Design: randomised trial of a caregiver-mediated home-based intervention vs usual care Study duration: 12 weeks Randomisation: with computer-generated numbers, each approved patient drew a folded piece of paper with 1 of these numbers from a bag. Allocation concealment: yes, folded pieces of paper in a bag Blinding: assessor blind for group allocation ITT: yes, no withdrawals
Participants	Randomised: 51 participants Withdrawals: 0 Intervention: 25 participants; 13 men and 12 women; mean age 62.0 years (SD 9.5); time since stroke 18.0 months (SD 15.2) Control: 26 participants; 17 men and 9 women; mean age 65.4 years (SD 10.6); time since stroke 18.5 months (SD 17.1) Inclusion criteria: single ischaemic or haemorrhagic stroke in the cerebral hemisphere, as determined through CT or MRI; >6 months post onset; mild-to-moderate disability (Brunstrom 3 to 5); undergoing rehabilitation activities ≤2 times a week; home dwelling; had family members, friends, or paid workers as caregivers; still required assistance to accomplish everyday activities Definition caregiver: a person who was most responsible for person's daily care and who lived with the person. Exclusion criteria: patient: required use of nasogastric feeding, urine tube, tracheal tube; exhibit 1 of the following conditions: recurring stroke, dementia, global or receptive aphasia, severe orthopaedic disability, unstable medical condition; caregiver: poor physical health; mental or behavioural disorders; unable to provide the person at least 2 x 60- to 90-minute sessions of rehabilitation training per week

Wang 2015 – *Continued*

Interventions	Intervention: caregiver-mediated home-based intervention (CHI): CHI programme consisted of 3 phases: phase 1 (weeks 1 to 4) to improve person's body functions and structural components; phase 2 (weeks 5 to 8) to improve person's ability to undertake everyday activities within their living environments using task-specific restorative and compensatory training methods; and phase 3 (weeks 9 to 12) to help the person reintegrate into the society by participating in restorative outdoor leisure activities; a physiotherapist outlined a personalised weekly training schedule according to the CHI programme; weekly visit of the physiotherapist of about 90 minutes: tasks were explained, demonstrated, practiced, and evaluated; individualised training guidelines or illustrations were written; frequency of training and tasks completed was recorded; caregiver was asked to encourage and help if necessary the patient to perform the planned activities twice weekly and if possible every day. Control: usual care: patients maintained their everyday routines; received weekly visits or telephone calls by the therapist to talk about rehabilitation progress, daily activities, and general health; no specific instructions or guidance related to rehabilitation skills. Setting: rehabilitation and neurology departments of teaching hospitals
Outcomes	Included outcomes: Barthel Index, Caregiver Burden Scale, Berg Balance Scale, Six-Minute Walk Test, walking speed, SIS Measurements: baseline assessment, post intervention assessment (12 weeks)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated numbers on folded pieces of paper in a bag: each approved patient draw a folded paper".
Allocation concealment (selection bias)	Low risk	"Folded pieces of paper in a bag"
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel cannot be blind for the intervention.
Blinding of outcome assessment (detection bias)	Low risk	"All outcome measurements were evaluated by an independent physical therapist".
Incomplete outcome data (attrition bias)	Low risk	No withdrawals, no missing outcomes
Selective reporting (reporting bias)	Unclear risk	No trial registry; nothing stated
Other bias	Low risk	

Characteristics of excluded studies

Footnotes: CME = caregiver-mediated exercise; RCT = randomised controlled trial

Study	Reason for exclusion
Adie 2014	No CME intervention. Caregivers were involved in the intervention, but were not obliged.
Araujo 2015	No CME intervention, but skill training and a bit educational intervention.
Barzel 2009	CME, not RCT
Baskett 1999	No CME intervention. Family and caregivers were encouraged to participate during therapy.
Bertilsson 2014	No CME intervention. Caregivers were asked to be involved in the intervention, but were not obliged.
Cameron 2015	No CME intervention. Intervention about how and at which moment to support caregivers.
Chang 2015	No CME intervention. Part of the intervention was skill training. Another part was an intervention for the patient. The 2 interventions could not be separated.
Chinchai 2010	No CME intervention. Educational intervention for the caregiver, with a small part consisting of skill training.
El-Senousey 2012	No CME intervention but skill training and educational intervention for the caregivers.
Evans 1984	No CME intervention. Educational intervention for patient and caregiver.
Forster 2013	No CME intervention but skill training and educational intervention for the caregivers.
Goldberg 1997	No CME intervention. Intervention consists of a support programme for patient and caregivers at home.
Grasel 2005	Not an RCT, no CME but skill training for the caregivers.
Harrington 2010	No CME intervention. Group community education programme where caregivers were invited to also participate.
Harris 2009	No CME intervention. Family and caregivers were encouraged to participate during therapy. 1 article reported specifically about the role of caregiver involvement in this treatment.
Hebel 2014	No CME intervention, but skill training intervention
Hirano 2012	CME, not RCT
Jones 2015	No CME intervention. "Optional caregiver inclusion"
Kalra 2004	No CME intervention but skill training and educational intervention for the caregivers
Koh 2015	No CME intervention. Caregivers were included to provide safety, but the exercises were done by the patient him- or herself.

Study	Reason for exclusion
Larson 2005	No CME intervention. Educational intervention by nurse for caregiver
Lin 2004	No CME intervention. Family and caregivers were encouraged to participate during therapy.
Maeshima 2003	CME, not RCT
Marsden 2010	No CME intervention. Exercises for patient, educational intervention for both patient and caregiver
McClellan 2004	No CME intervention. Family and caregivers were encouraged to participate during therapy.
Mudzi 2012	No CME intervention but skill training and educational intervention for the caregivers
NCT00908479	No CME intervention. Family and caregivers were encouraged to participate during therapy. Only trial information was found.
Osawa 2010	CME, not RCT
Parker 2012	No CME intervention. Educational intervention for the caregiver, with a small part consisting of skill training
Redzuan 2012	Comparison of 2 caregiver-mediated interventions. Studied intervention was video therapy, not CME.
Schure 2006	No CME intervention. Educational intervention for the caregiver, with a small part consisting of skill training
Shyu 2010	No CME intervention. Educational intervention for the caregiver, with a small part consisting of skill training
Smith 2004b	No CME intervention. Educational intervention for patient and caregiver
Van de Port 2012	No CME intervention. Family and caregivers were encouraged to participate during therapy.
Walker 1996	No CME intervention. Intervention aimed at dressing. Family and caregivers were encouraged to participate during therapy.

Characteristics of ongoing studies

Footnotes: CME = caregiver-mediated exercise; RCT = randomised controlled trial

ATTEND trial 2013

Study name	ATTEND trial
Methods	RCT
Participants	People with stroke, recent ischaemia (<1 month), residual disability, aged 18 to 99 years, able to identify a nominated caregiver
Interventions	Intervention: trained family-led caregiver-delivered, home-based rehabilitation programme: patient is advised to undergo therapy twice a day for 6 months. Caregiver training is given for approximately 60 minutes/day for up to 3 days. Components: information, joint goal setting, task-orientated training, discharge planning, exercises. Detailed instructions for exercises will be used from www.physiotherapyexercises.com/ Control: usual care
Outcomes	Primary outcome: modified Rankin Scale Secondary outcomes: Barthel Index, Caregiver Burden Scale, health-related quality of life: WHO Quality of Life - BREF and EuroQoL, patient and caregiver mood: Hospital Anxiety and Depression Scale, Nottingham Extended Activities of Daily Living Index, costs. On 3 and 6 months
Starting date	1 August 2013 Study duration: 4.5 years Sample size: "1200" Information authors: first results are expected in 2016
Contact information	r.lindley@sydney.edu.au jeyarajpandian@hotmail.com
Notes	CTRI/2013/04/003557

Care4Stroke trial 2014

Study name	Care4Stroke program: caregiver mediated exercises with e-health support for early supported discharge after stroke
Methods	RCT
Participants	People with stroke, aged >18 years, in the early rehabilitation phase (24 hours to 3 months), knowing and able to appoint a caregiver who he/she wants to participate in the programme, living independently before the stroke, planned to be discharged home, being able to follow instructions (a Mini-Mental State Examination score >23 points), Functional Ambulation Score <5, score of <11 on Hospital Anxiety and Depression Scale, motivated for CME, no serious comorbidity Caregivers: aged >18 years, sufficiently motivated for CME, score of <11 on the Hospital Anxiety and Depression Scale, medically stable and physically able to perform the exercises with the patient, no significant caregiver strain (<4 points on Caregiver Strain Index), no serious comorbidity

Care4Stroke trial 2014 – *Continued*

	To determine suitability of both patient and partner, an intake exercise session together with a trained therapist will be scheduled prior to inclusion. The therapist will check the inclusion/exclusion criteria and judge if the exercises can be done adequately and safely.
Interventions	Intervention: the Care4Stroke programme consists of 8 weeks of complementary exercise therapy done with a caregiver, alongside usual therapy. 31 standardised exercises are available that can be customised per individual situation. The exercises are presented in a smart phone/ tablet app with videos and voiceover. The patient and their caregiver are asked to do the exercises minimally 5 times/week for 30 minutes on at least both weekend days or the equivalent dosage with an adopted schedule. Patients and their caregiver will have a weekly session with a trained therapist. In this session, the participating couple will be instructed as to which exercises should be performed safely during the next week and evaluate the exercises done last week. All patients and caregivers will be supported by a handbook with instructions. The programme starts when the patient is admitted. When the discharge date of the patient is earlier than the finishing of the programme, the programme continues at home with monitoring from the treating therapist. Control: patients will receive usual care according to the Dutch guidelines for people with stroke and the Royal Dutch Guidelines of Physical Therapy.
Outcomes	Primary outcomes: length of stay and the mobility part of the Stroke Impact Scale 3.0 Secondary outcomes: other domains of Stroke Impact Scale 3.0, Fugl-Meyer Assessment lower extremity Scale, Motricity Index Lower Extremity, Six-Minute Walk Test, walking speed, Timed-Up-and-Go Test, Berg Balance Scale, Rivermead Mobility Index, Barthel Index, Nottingham Extended Activities of Daily Living Index, modified Rankin Scale, personal opinion questionnaire for empowerment, EuroQol, amount of daily activity For the caregiver: Expanded Caregiver Strain Index, Carer Quality of Life Scale For both patient and caregiver: Hospital Anxiety and Depression Scale, General Self-efficacy Scale, Fatigue Severity Scale, and (cost) diaries Measurements at baseline, post intervention (8 weeks after randomisation), and follow-up (12 weeks after randomisation)
Starting date	1 April 2014 Study duration: 2 years Sample size: "66"
Contact information	g.kwakkel@vumc.nl r.nijland@reade.nl e.vanwegen@vumc.nl
Notes	www.trialregister.nl/trialreg/admin/rctview.asp?TC=4300 In Australia, a study with the same objective, inclusion and exclusion criteria has been done. Analyses are currently been done. This study is part of the Care4Stroke trial.

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Chapter 3

Description of the CARE4STROKE program: a caregiver-mediated exercises intervention with e-health support for stroke patients

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Abstract

Background:

Intensity of practice and task- and context-specificity are key factors for improving functional outcome in stroke survivors. Novel methods are needed to augment intensity of practice with minimal use of resources and costs. Caregiver-mediated exercises (CME) focused on mobility, in which a caregiver acts as an exercise coach, can increase the intensity of practice. There is preliminary evidence that CME can improve functional outcome, reduce length of stay (LOS), and allow early supported discharge (ESD), without an increase in caregiver burden. In the CARE4STROKE program (C4S), CME therapy and e-health support are combined to promote a smoother transition from the inpatient setting to the home environment, with active rehabilitation continuing in the community. The objective of this paper is to describe the content of the C4S intervention in detail and explain implementation of this intervention in practice using the Template for Intervention Description and Replication (TIDieR) checklist.

Methods:

Content, timing and intensity of the program, participant screening and selection and intervention procedures were described using the TIDieR checklist. Mobility exercises and use of a video application on tablet/smartphone are explained. The role of the caregiver as provider of the intervention is illustrated.

Discussion:

C4S prescribes an additional exercise dose of 1200 minutes, and may be a promising novel and effective method to augment the pallet of therapeutic options for stroke rehabilitation. Important aspects for successful implementation are availability and suitability of a caregiver. Suggestions for additional use of e-health technology are described.

Implications for physiotherapy practice:

The presented description of C4S gives physical therapists practical guidelines to facilitate implementation of the CME intervention.

INTRODUCTION

Intensity of practice and task- and context-specificity are key factors of post stroke rehabilitation, since it can improve outcome in terms of mobility and activities of daily living (ADL),[1-8] and thereby facilitate Early Supported Discharge (ESD).[1, 9] Caregiver- or family-mediated exercises (CME)[10-13] in which caregivers, such as partners, family-members or friends are actively involved in rehabilitation training, may be a promising and cost-effective way to augment intensity of daily practice during inpatient stay. CME can continue after discharge to a patient's own home situation and thereby facilitate ESD. A systematic review of nine trials found very low to moderate quality evidence that CME can improve standing balance, walking distance and quality of life, without increasing caregiver burden, suggesting that CME may augment the pallet of therapeutic options for rehabilitation after stroke.[13] However, none of these trials included e-health technology such as tele-rehabilitation services to support treatment adherence or included exercise Apps to support CME. The combination of CME and supported self-management by using e-health technology may be a novel way to improve self-efficacy and empower stroke patients and their families, and reduce caregiver burden.[14]

The CARE4STROKE program (C4S) combines CME with e-health support after stroke, and is hypothesized to augment intensity of practice, increase functional outcome and facilitate ESD. One recent phase II proof-of-concept trial tested a similar approach to C4S in Adelaide (Australia).[11] A significant reduced level of caregiver fatigue with increased feelings of self-efficacy was found at follow up. Per protocol analysis showed a reduced length of inpatient stay (LOS) and fewer re-admissions, whereas patients reported a significant improvement of their extended activities of daily living. Using the same design and primary and secondary outcomes, an observer-blinded multicentre randomised controlled CARE4STROKE trial is currently in the analysis stage in Amsterdam to investigate the (cost) effectiveness of CME combined with e-health tools to improve self-reported mobility and to reduce length of inpatient stay, caregiver burden, and costs when compared to usual care.[12]

C4S is a complex rehabilitation intervention.[1, 15] The description of complex rehabilitation interventions in stroke rehabilitation is typically incomplete.[16] As a result of the lack of transparency, it is difficult to replicate interventions, properly interpret the effects and implement promising interventions in clinical practice. The aim of the present paper is, therefore, to describe in detail the essential elements of the C4S intervention using the Template for Intervention Description and Replication (TIDieR) checklist.

METHODS

The CARE4STROKE program (C4S) is an 8-week exercise intervention, investigated in the multicentre randomized controlled CARE4STROKE trial. A detailed description of trial design, in- and exclusion criteria, primary and secondary outcomes and applied statistics is published elsewhere.[12] The Medical Ethics Review Committee of the Slotervaart Hospital and Reade approved the study (NL34618.048.12). The trial is registered in the Dutch trial register as NTR4300.

The CARE4STROKE program (C4S), description of the intervention according to TIDieR guidelines

Item 1. Brief name of the intervention

CARE4STROKE (C4S)

Item 2. Why – Rationale of the essential elements of C4S

C4S is a complex rehabilitation intervention, containing several interrelated components.[15] A comprehensive treatment package is tailored to the individual patient.[1] A detailed description of the rationale behind C4S has been described earlier.[12] The main components of C4S are 1) the exercises, which are caregiver mediated and do not replace, but are in addition to usual care, and 2) the use of e-health tools. The caregiver can for example be a partner, family member or friend of the stroke patient.[12] The CME are aimed to increase intensity of practice, by being an addition to usual care, and thereby facilitate ESD. They are task-specific and specifically focused on general mobility, because independence in transfers and gait is an important component for ESD after stroke.[1, 7, 9]

The exercises are presented in videos with voiceover in an e-health application ('the CARE app') (Figure 3.1). We hypothesize that this app can support adherence to the program by patient and caregiver and promote self-management.[20, 21] Safety of both patient and caregiver is a fundamental consideration during CME. New exercises and exercise modifications are practiced with therapist supervision to identify any safety concerns or questions prior to practicing independently. In addition, safety precautions are included in the voiceover accompanying each exercise video.

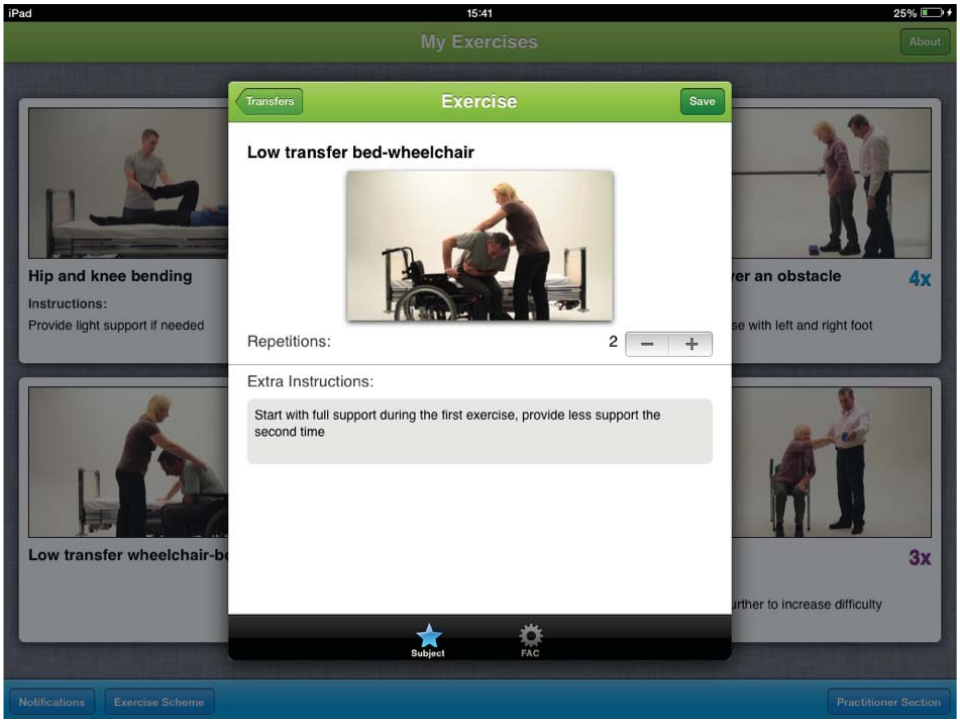

Figure 3.1 Screenshot of the CARE4STROKE app.

Item 3. What – Materials used in the intervention

Exercises

A total of 37 task-specific exercises were developed for the purpose of C4S, an overview of these exercises are provided in Table 3.1 and an example in Figure 3.2. The exercises, performed 5 times a week for 30 minutes, are aimed at improving general mobility, including transfers, standing balance and gait. In addition, there are exercises available such as sitting or standing balance, range-of-motion and strength exercises for the lower extremity. Subsequently, exercises such as walking outside, stair climbing, walking on uneven ground and cycling can be trained. The exercises were developed by experienced physical therapists and rehabilitation physicians, with the help of patient–caregiver couples, and proved feasible in a pilot study (unpublished data).

E-health support

The exercises in C4S are presented in an app on a smartphone or tablet computer with touch screen interface allowing independent use by the patient–caregiver couple (Figure 3.1).

Table 3.1 Exercises categorized by domain and by Functional Ambulation Category scale (FAC)

Domain	Name of exercise	FAC:
Lying	Rolling to the affected side	0-1-2-3-4-5
	Rolling to the unaffected side	0-1-2-3-4-5
	Hip and knee flexion	0-1-2-3-4-5
	Ankle towards face and back	0-1-2-3-4-5
	Trunk rotation	0-1-2-3-4-5
	Bridging	0-1-2-3-4-5
	Leg raise	0-1-2-3-4-5
	Side line exercise	0-1-2-3-4-5
Sitting	Reaching exercise	0-1-2-3-4-5
	Look behind you	0-1-2-3-4-5
	Buttocks raise	0-1-2-3-4-5
	Knee extension	0-1-2-3-4-5
	Hip flexion	0-1-2-3-4-5
	Practice to stand up	1-2-3-4-5
Transfers	Transfer from lying to sitting	0-1-2-3-4-5
	Transfer from sitting to lying	0-1-2-3-4-5
	Low transfer from bed to wheelchair	1-2-3-4-5
	High transfer from bed to wheelchair	1-2-3-4-5
	Transfer sit to stand and back	2-3-4-5
	High transfer from bed to wheelchair	2-3-4-5
	High transfer from wheelchair to bed	2-3-4-5
Standing	Standing supported / unsupported	1-2-3-4-5
	Static balance	2-3-4-5
	Dynamic balance	3-4-5
	Squatting	3-4-5
	Picking up exercise	3-4-5
Walking	Walking with support	1-2-3-4-5
	Oriented walking	2-3-4-5
	Step exercise	3-4-5
	Stair climbing	4-5
	Different plain walking	4-5
Other	Cycling on a hometrainer	3-4-5
	Cycling on a MOTOmed	0-1-2-3-4-5

The exercises of C4S are all demonstrated as instructional videos in the app with a voiceover. The voice instruction leads the patient and caregiver systematically through the exercise. The app contains a practitioner and a patient section. In the practitioner section, a tailored exercise program can be compiled and locked by the therapist. Exercises can be chosen by domain or by FAC score (Table 3.1). The number of repetitions can be specified. The order

Figure 3.2 An example of an exercise.

Transfers: Low transfer from bed to wheelchair
Aim: Improve sliding transfer from bed to wheelchair.
Task description for the patient: The patient sits on the edge of bed. The wheelchair has to stand on the unaffected side. The wheelchair should be at the same level as the bed at a 45° angle to the bed. Armrest and footrest of the wheelchair near the bed should be removed. The break of the wheelchair has to be on. The patient sits up straight with feet supported on ground. The legs are looking away from wheelchair. The feet are placed under knee. The patient leans forward, shoulders directly over knees. The patient reaches and holds with unaffected arm the armrest of the wheelchair. The patient pushes with feet and lift his/her buttock off the bed. Then slides from bed to the wheelchair. The patient puts the armrest and footrest back into place.
Task description for the caregiver: If needed, the caregiver places the palms flat on patients back and gives support during movement.

of the exercises can be adapted and additional instructions can be entered. The therapist can select the affected side of the patient, to match the orientation of video exercises. In the patient section, the selected videos and number of repetitions are displayed, exercise reminders can be set with an alarm and there is an exercise diary in which the patient can record exercise adherence. In addition, tele-rehabilitation tools like video-conferencing and email are used to keep contact between the physical therapist and patient–caregiver couple.

Diary

The patient–caregiver couples are provided with a diary to 1) record daily exercise time, 2) keep notes about the exercises, and 3) record questions for the physical therapist. The format of the diary can be obtained from the authors.

Availability

After the RCT is finished, the e-health application, diary and guidelines will be made available to the public through an implementation project. Knowledge and experiences to implement the intervention in other settings will be shared. A short introduction film about the exercises can be found at: https://youtu.be/pNcmbU9R-A4.

Item 4. What – Procedures

Patient and caregiver selection

Both patient and caregiver should be: 1) motivated for CME 2) able to understand the Dutch or English language. Additional criteria for the patient are: 1) a functional mobility limitation (FAC <5), 2) willing and able to appoint a caregiver (with a maximum of two caregivers), and 3) being able to understand and follow instructions. Patients and caregivers with a serious comorbidity that interferes with proper and safe execution of mobility training or with symptoms of depression should not participate.

After informed consent, patients will be asked to appoint one or two preferred caregivers to perform CME with. These caregiver(s) can be asked by the patient, or in consultation with the patient by the treating therapist. It is crucial that both patient and caregiver agree on participation. Thereafter, suitability of the caregiver(s) has to be checked.

Screening session

The screening session is an initial exercise session in which a trained physical therapist evaluates the physical capacities of patient and caregiver, by judging if the couple can perform the exercises safely and adequately and whether the caregiver can physically support the patient. The therapist observes if the patient–caregiver couple can work together and if the caregiver can adequately coach the patient during the exercises. A short checklist, evaluating these criteria, is used by the physical therapist. In case of doubt, the treating physician, the physical therapist in charge and/or the rehabilitation team can be consulted.

Instruction and evaluation sessions

After enrolment, a one-hour session with the patient–caregiver couple and the supervising physical therapist is scheduled to explain the use of the app. In addition, the exercises for the upcoming week are selected by the physical therapist, taking the rehabilitation goals of the patient into consideration, and in consultation with the patient–caregiver couple. The exercises are practiced, the amount of repetitions is set and the therapist can give additional instructions. The physical therapist hands out the tablet and the exercise diary. Thereafter,

a weekly 30-minute session with the treating physical therapist and the patient–caregiver couple takes place. Exercises of the previous week are evaluated in terms of experienced difficulty and fatigue, and a new or modified exercise program for the upcoming week can be selected and practiced.

Evaluation of the CARE4STROKE program

After 8 weeks, the effects of participation in the CARE4STROKE program can be measured using validated mobility assessments.[12]

Item 5. Who – Provider of the intervention

The caregiver

The caregiver acts as an exercise coach by actively supporting and assisting the patient during the task-specific mobility exercises. This involves both mental as well as physical support during the exercises. In the sessions with the physical therapist, the caregiver is instructed and trained to give this support. It should be emphasized that the caregiver is not the trainer or therapist.

Caregiver strain is measured before the start of the intervention. During the intervention, the physical therapists closely monitors and discusses caregiver strain. When deemed necessary, based on the professional opinion of the therapist, extra attention is given to the caregiver by the physical therapist or another member of the rehabilitation team.

If desired or more practical, two caregivers can be involved with one participant to divide the time investment of the CME. We set the maximum at two caregivers to ensure optimal practical feasibility and safety, without loosing quality of intervention.

The physical therapist

The patient–caregiver couple is supported during the intervention by a physical therapist experienced in treating stroke patients and trained to deliver C4S.

Item 6. How – Modes of delivery

The sessions with the physical therapist and the patient–caregiver couple are individual face-to-face sessions. In addition, and specifically after discharge home, the patient–caregiver couple is encouraged to contact the therapist whenever appropriate, using tele-consultation via telephone, or video-conferencing and email via the smartphone or tablet computer.

Item 7. Where – Location of the intervention

C4S can be executed in any rehabilitation setting, whether it is in a rehabilitation centre, hospital, nursing home or in the home environment. When patients are discharged during the intervention period, training can continue at home. Most exercises can be executed without any added materials. For some, simple materials like a ball or chair are needed. In addition, there are exercises in which a staircase, hometrainer or motor assisted stationary bicycle is needed.

Item 8. When and how much

Patient and caregiver are instructed to exercise together, five times a week for 30 minutes preferably including the weekend, during the 8-week intervention period. With this, a surplus of 150 minutes therapy each week, and a total of 1200 minutes (8 weeks x 150 minutes) augmented therapy time, is accomplished. This additional dose is in line with recommendations of evidence-based guidelines.[7] In addition, CME allows the patient to train in the weekends as well. Patient and caregiver themselves decide when they exercise, when necessary the physical therapist can help them plan the sessions.

Item 9. Tailoring the program

During C4S the physical therapist compiles a tailored exercise program for the patient–caregiver couple from 37 standardized exercises, choosing those exercises related to the patient goals. C4S is progressive in nature and is specifically aimed at offering an incremental training regimen.[7] The physical therapist, therefore, adapts the level of difficulty progressively during the intervention period to be commensurate with the patients' ability. This is achieved by, for example, increasing the number of repetitions or adding instructions for variations.

Item 10. Modifications during the course of the study

The C4S program is used in the CARE4STROKE trial. No modifications during the course of the trial were made.

Item 11. How well planned – Intervention adherence and fidelity

To measure if participants actually exercised an additional 150 minutes a week, patients and caregivers fill in a diary. In addition, during the weekly evaluation session the therapist explicitly inquires about adherence and completing the diary.

For uniform delivery of the intervention, therapists will be trained in a training course with the following content: 1) the in- and exclusion criteria, 2) the standardized exercises and the possibilities to customize the CME, 3) therapists role in the screening session, intake exercise

session and weekly exercise sessions, 4) how to fill in the diaries, 5) the use of the app. In addition, regular retraining sessions will be organized for these participating therapists.

Item 12. How well the intervention was actually delivered

The randomized controlled trial is finished. Patients in the intervention group reported a median of 1190 minutes (interquartile range 870.0–1530.0) of exercise time with a caregiver. This approaches the intended 1200 minutes of CME time.

DISCUSSION

In this paper we used the TIDieR checklist to systematically describe in detail all key elements of the C4S intervention.[16-19] Recently, developing, monitoring and reporting interventions by using TIDieR was suggested as an important step for improving the quality and transparency of recovery trials after stroke.[22] The C4S intervention combines CME with e-health support and aims to augment intensity of daily practice during inpatient stay, continuing after discharge to patient's own living environment and as such improve functional outcome and facilitate ESD.

A crucial prerequisite for any CME program is the availability of a suitable caregiver willing to deliver and coach practice. This mutual agreement of patient and caregiver willing to participate is an essential part of C4S and a limiting factor for recruiting potential couples. A strict procedure is described in which the patient appoints the caregiver(s), a caregiver has to meet suitability criteria and a physical therapist gives his accord after the screening session. Only thereafter, the patient–caregiver couple can start with CME. As it is important to know more about the availability of caregivers to participate in CME for future recommendations and implementation of the program, details about the characteristics of available and suitable caregivers, as well as their perceived strain will be reported in the CARE4STROKE trial. C4S could be construed as an extra task for a caregiver in already stressful times.[23] However, it has been shown that CME could also decrease caregiver burden and fatigue and increase feelings of self-efficacy by providing patients and caregivers with more knowledge and education.[10, 11, 24, 25] When in doubt about the strain on the caregiver, either before or during the intervention, the treating physician and rehabilitation team should be consulted. Important aspects to study concerning the availability of a caregiver and the willingness to participate in a CME intervention are cultural, ethnic, and societal differences. For example, the availability of rehabilitation services, travel distances or the role of the caregiver in society can play an important role. When implementing a CME intervention, these aspects need to be taken into account.

In C4S, CME are combined with e-health technology, by using a mobile application with videos and tele-rehabilitation services. Despite a lack of trials in this area,[26] e-health technology seems promising and is increasingly used.[20, 21] The functionality and content of the current app and tele-rehabilitation services in C4S can be expanded. It would be interesting to implement incentives after practice, for example using text-messages or social media to give feedback and a type of reward for patients and caregivers.[27-29] Evaluation and monitoring with built-in questionnaires or rating scales could be used to monitor difficulty of the exercises, fatigue of the patient or strain of the caregiver using experience sampling methods.[30] In addition, the paper and pencil diary could be included electronically in the app. This might be more accurate to measure adherence with the program, especially when combined with wearables.

We are currently analysing the results of the CARE4STROKE trial. Our obtained knowledge about the intervention will be communicated through scientific as well as laymen publications. In addition, a teaching course for health care professionals will be developed in due time in an implementation project.

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Chapter 4

Caregiver-mediated exercises with e-health support for early supported discharge after stroke (CARE4STROKE): study protocol for a randomized controlled trial

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Abstract

Background:

Several systematic reviews have shown that additional exercise therapy has a positive effect on functional outcome after stroke. However, there is an urgent need for resource-efficient methods to augment rehabilitation services without increasing health care costs. Asking informal caregivers to do exercises with their loved ones, combined with e-health services may be a cost-effective method to promote early supported discharge with increased functional outcome. The primary aim of the CARE4STROKE study is to evaluate the effects and cost- effectiveness of a caregiver-mediated exercises program combined with e-health services after stroke in terms of self-reported mobility and length of stay.

Methods:

An observer-blinded randomized controlled trial, in which 66 stroke-patients admitted to a hospital stroke unit, rehabilitation center or nursing home are randomly assigned to either eight weeks of the CARE4STROKE program in addition to usual care (i.e., experimental group) or eight weeks of usual care alone (i.e., control group). The CARE4STROKE program is compiled in consultation with a trained physical therapist. A tablet computer is used to present video-based exercises for gait and gait-related activities in which a caregiver acts as an exercise coach. Primary outcomes are the mobility domain of the Stroke Impact Scale and length of stay. Secondary outcomes are the other domains of the Stroke Impact Scale, motor impairment, strength, walking ability, balance, mobility, (Extended) Activities of Daily Living, psychosocial functioning, self-efficacy, fatigue, health-related quality of life of the patient as well as the experienced strain, psychosocial functioning and quality of life of the caregiver. An economic evaluation will be conducted from the societal and health care perspective.

Discussion:

The main aspects of the CARE4STROKE program are 1) increasing intensity of training by doing exercises with a caregiver in addition to usual care and 2) e-health support. We hypothesize this program leads to better functional outcome and early supported discharge, resulting in reduced costs.

Trial registration:

The study is registered in the Dutch trial register as NTR4300, registered 2 December 2013.

BACKGROUND

Stroke poses major social and healthcare problems worldwide. The prevalence of stroke is increasing.[1] In 2010, the absolute numbers worldwide of people with first stroke (169 million), stroke survivors (33 million), stroke-related deaths (59 million), and DALYs lost (102 million) were high and had significantly increased since 1990. About 28 % of stroke patients remain dependent in basic activities of daily living (ADL) such as dressing, toileting and/or indoor mobility at twelve months after stroke.[2] Although the main target of stroke rehabilitation is to reduce long term dependency and allow patients to return to their own community,[3] only 60% of the stroke patients can ultimately walk independently with or without assistive devices in the community.[4]

In the 27 EU countries, total annual cost of stroke is estimated at €27 billion: €18.5 billion (68.5%) for direct and €8.5 billion (31.5%) for indirect costs. A further sum of €11.1 billion is calculated for the value of informal care.[5] The already overstretched health resources worldwide emphasize the need for early supported discharge (ESD) of stroke patients,[3, 6] because a large part of the stroke care costs are spent on inpatient rehabilitation services.[7, 8] A large number of stroke patients are using inpatient services because they are not safe and independent in their mobility. ESD is enabled as soon as these patients are safe and independent in their transfers and gait, suggesting that ESD heavily depends on improvement of standing balance and motor control of the lower limbs.[3, 9]

A number of meta-analyses show that intensity of training and repetitive task training are crucial aspects of stroke rehabilitation, concluding that more exercise therapy improves outcomes.[3, 10-16] Guidelines recommend that patients admitted to a rehabilitation facility should have the opportunity to receive a daily dose of 45 minutes of exercise therapy in the first three months after stroke.[15, 17-20] However, most patients admitted to hospital stroke units, rehabilitation centers or nursing homes are physically inactive or involved in activities that contribute little to their recovery.[21-23] A recent survey in the Netherlands of 91 hospital stroke units showed that patients receive on average about 24 minutes of exercise therapy each working day.[24]

Acknowledging that the resources (mostly staff) in rehabilitation settings are limited, novel methods to increase the intensity of exercise therapy with minimal use of resources are needed.[3, 24] One such novel method could be to actively involve caregivers in mediating exercises. In particular if caregiver mediated exercises (CME) are combined with e-health/tele-rehabilitation services, easy contact with, and monitoring by the rehabilitation team is promoted.[25] This way, CME enhances ESD by providing a smoother transition from inpatient setting to the home situation. And CME can continue in the community setting.

Recently, Galvin et al found favorable effects of CME on functional outcome in stroke patients and on perceived strain by caregivers.[26] In addition, we hypothesize, CME might contribute to improved feelings of quality of life (QOL) and empowerment for both patient and caregiver by providing them with more knowledge about the capabilities of the stroke patient.

Few randomized controlled trials (RCTs) have investigated CME and their quality is heterogeneous.[26-31] In addition, CME has not been combined with e-health facilities to promote self-management and empowerment of patient and caregiver, whereas studies investigating cost-effectiveness of CME after stroke are still lacking.

The aim of the current paper is to describe the CARE4STROKE study design. The CARE4STROKE study aims to evaluate the effects and cost-effectiveness of a CME program combined with e-health, added to usual care in hospital stroke units, rehabilitation centers and nursing homes. We hypothesize that the CARE4STROKE program will lead to better self-reported mobility and reduced length of inpatient stay (LOS) in stroke patients compared to usual care, resulting in reduced costs.

METHODS

Design

This study is an observer-blinded, multicenter randomized controlled trial with an economic evaluation alongside. The trial will be conducted by trained therapists of the participating centers. Within each type of setting, patients will be randomly allocated to either CME combined with e-health services (CARE4STROKE) in addition to usual care or to usual care alone. The study is registered in the Dutch trial register as NTR4300, registered 2 December 2013.

Setting

The study will take place in hospitals (stroke unit and outpatient clinic), rehabilitation centers and rehabilitation departments of nursing homes in the Netherlands. A trained researcher, blinded to group allocation, will visit the participants in the center of admission for obtaining informed consent and conducting measurements during the study. Reade Rehabilitation Center and VU University Medical Center are the initiators of this study. The study protocol is approved by the Medical Ethics Review Committee of the Slotervaart Hospital and Reade and is registered with the trial number: NL34618.048.12.

Participants

Sixty-six patients with a first-ever or recurrent stroke, who are admitted to one of the participating centers and their caregivers, will be recruited for this study. Stroke is defined by the World Health Organization as "a clinical syndrome typified by rapidly developing signs of focal or global disturbance of cerebral functions, lasting more than 24 hours or leading to death, with no apparent causes other than of vascular origin".[32] A caregiver is defined as someone close to the patient, who is willing and able to do exercises together with the patient, for example a partner, family member or friend. This caregiver is not a professional and is not paid for his/her efforts.

Inclusion criteria for both patient and caregiver are: 1) 18 years or older, 2) written informed consent, 3) able to understand the Dutch or English language (on a sufficient level to understand instructions on CME and e-health application), 4) motivated for CME, 5) a score of <11 on the domain 'depression' on the Hospital Anxiety and Depression Scale (HADS).[33, 34] Additional inclusion criteria for the patient are: 1) willing and able to appoint a caregiver who wants to participate in the program (with a maximum of two caregivers), 2) living independently before the stroke, 3) planned to be discharged home, 4) being able to follow instructions (MMSE score >18 points),[35] 5) Functional Ambulation Score (FAC) <5.[36] Additional inclusion criteria for the caregiver are: 1) being medically stable and 2) physically able to perform the exercises together with the patient.

Exclusion criterion for both patient and caregiver will be serious comorbidity, which interferes with mobility training. Patients will be excluded when they, for example, have another neurological disease like Multiple Sclerosis or Parkinson disease, fractures or congestive heart failure. Caregivers will be excluded when they are not able to walk 100 metres, stand and/or keep their balance.

To determine suitability in terms of safety, cognition and communication skills of both patient and partner, an intake exercise session with one of the trained physical therapists is scheduled prior to inclusion. This therapist checks the inclusion/exclusion criteria and judges if the exercises can be done adequately and safely. Reasons of exclusion will be recorded.

Baseline characteristics

Patient characteristics at baseline will be recorded from the medical status. These include demographics (age, gender), type of stroke, time post stroke, hemiplegic side, somato-sensory deficits (yes/no), homonymous hemianopia (yes/no), visuo-spatial neglect (yes/no), aphasia (yes/no) and comorbidity following Cumulative Illness Rating Scale (CIRS).[37] Characteristics

of the caregiver that will be recorded are: demographics (age, gender), relation to patient, work and existing comorbidities following CIRS.

Study procedures

Patients will be stratified by type of participating center (hospital stroke unit, rehabilitation center or nursing home) and subsequently randomized, by an independent researcher blinded for patient characteristics, to the control or the experimental group. An online randomization procedure with a minimization algorithm is used to prevent unequal group sizes.[38] Patients will start immediately after admission, continue for eight weeks irrespective of time of discharge and will be followed-up until twelve weeks after randomization. Outcomes will be measured at baseline, eight and twelve weeks. (See Figure 4.1: Study design) Outcomes are either self-reported by patients and caregivers (not blinded) or measured by an independent observer who is blinded for treatment allocation. A self-reported (cost) diary will be kept during the intervention period to monitor compliance and to collect relevant cost-data.

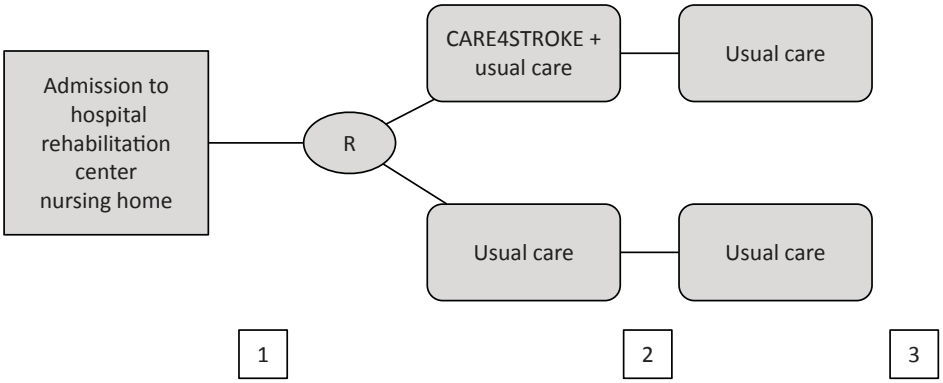

Figure 4.1 Study design.
R = Randomization; 1 = Measurement 1, baseline, before start of the intervention; 2 = Measurement 2, end of intervention (8 weeks post randomization); 3 = Measurement 3, follow up (12 weeks post randomization).

CARE4STROKE intervention

The CARE4STROKE program consists of eight weeks of exercise therapy executed with a caregiver, in addition to usual care. A total of 37 standardized exercises were developed that are aimed at improving mobility skills related to walking like, standing, turning and making transfers, or are supporting exercises to improve mobility, strength and (sitting) balance. Subsequently, exercises can be combined into a patient-tailored, weekly progressive

and incremental training regimen. All exercises were developed in collaboration with rehabilitation specialists (movement scientists, physical therapists and physicians) and have been shown feasible in a pilot study.

The exercises are presented as instructional videos in an e-health application ('app') on a tablet computer. All exercises are explained by a voice over. Regular reminders to exercise can be set in the app. The patients and their caregivers are asked to perform the selected set of exercises minimally five times per whole week for 30 minutes. Patients and caregivers are in particular advised to do the exercises during the weekends, acknowledging that patients are often physically inactive during the weekend. When the intervention is correctly performed patients will thus have a surplus of 150 minutes of caregiver-mediated exercise training during a whole week.

During the intervention period patients and their caregivers will have a weekly session with one of the trained physical therapists. In these sessions, the set of exercises performed in the previous week is evaluated and adapted in a progressive manner. The participating couple is subsequently instructed as to which set of exercises should be performed during the next week. To make sure exercises are correctly performed, the therapist will give instructions about the new exercises and the patient-caregiver couple will be asked to do these exercises in the presence of the therapist during this session. The therapist will register all planned exercises and also if any adverse event happened during the last week. Furthermore, patient – caregiver couples are encouraged to contact the coordinating therapist through telephone, skype or email when appropriate.

The CARE4STROKE program starts when the patient is admitted to one of the participating centers. When the discharge date of the patient is earlier than the anticipated end date of the CME program, the CME program continues at home with the continuity of the use of the app, the weekly sessions with the therapist and the possibility to contact the therapist through tele-rehabilitation services when appropriate.

Usual care

The participants in the control group will receive usual care according to the Guidelines of Physical Therapy for patients with stroke of the Royal Dutch Physical Therapy Association KNFG.[15]

Compliance

In order to conduct this trial uniformly in the different centers, all participating therapists will be thoroughly trained in a training course before they start delivering the program.

Each therapist will be informed about 1) the aims, design and measurements of the CARE4STROKE study, 2) the in- and exclusion criteria, 3) the CARE4STROKE program: the standardized program and the possibilities to customize the CME, 4) their role in the intake exercise session and following exercise sessions, 5) how to fill in the diaries, 6) the use of the app. Regular retraining sessions will be organized for the participating therapists. A researcher (RN) will monitor if the intervention is implemented appropriately in the participating centers. A self-reported diary will measure compliance of patient and caregiver with the CME program.

Outcome measures

Primary outcome measures are the mobility domain of the Stroke Impact Scale (SIS 3.0) and LOS.

Stroke Impact Scale (SIS) version 3.0, Mobility domain

The SIS is a self-reported, stroke specific measure that includes 59 items and assesses eight domains related to activities and participation. The mobility domain of the SIS includes questions about patients' perceived competence to walk, keep balance, and move around in their own community. Each item is scored from 'not difficult at all' to 'cannot do at all' on a 5-point scale. The SIS has shown excellent clinimetric properties in English, as well as in the Dutch translation.[39-43]

Length of Stay (LOS)

LOS will be defined as the number of days of inpatient stay in a rehabilitation facility and/or hospital setting, from the day of admittance until the day of discharge. Mean length of stay for each setting will be determined. Possible reasons for an extended inpatient stay, like medical complications or time needed for the realisation of facilities at home, will be recorded.

Secondary outcomes

**** Patient***

Stroke Impact Scale, other seven domains

The other self-reported domains of the SIS will be assessed as secondary outcome measures.

Fugl Meyer (FM) motor score of lower extremity

The FM will be used to assess motor impairment. It is a reliable and valid motor performance test and evaluates the ability to make movements outside the synergistic movement pattern.[44]

Motricity Index (MI), lower extremity

The MI is a valid and reliable measure of the strength of the lower extremity. Scores range from 0 (no activity) to 33 (maximum muscle force) for each dimension.[45]

Six minute walking test

Gait performance and endurance will be assessed by the six minute walking test.[46, 47] The walking distance covered in six minutes will be recorded.

Ten meter walking test

Gait speed will be measured by the ten-meter walking test. Comfortable walking speed will be assessed. The mean of three repeated walking speed measurements will be calculated.[46, 47]

Timed up and go test (TUG)

The TUG is a test of basic functional mobility. The participant is asked to rise from an armchair, walk three metres as fast as possible, cross a line, turn, walk back and sit down again. The time to complete this test will be recorded.[46, 47]

Berg Balance Scale (BBS)

Balance will be evaluated by the BBS. BBS is a widely used clinical test of a person's static and dynamic abilities. There are 14 items scored from 0–4 (maximum), with a total score of 56. The BBS is a valid and reliable measure.[48, 49]

Rivermead Mobility Index (RMI)

The RMI is a test to evaluate functional mobility. It consists of 14 questions and one observation (of balance) covering aspects from turning in bed to running. The questions are scored dichotomously. The RMI is valid, reliable and responsive.[50-52]

Barthel Index (BI)

The BI is an ordinal scale to measure performance in activities of daily living (ADL). It uses ten variables describing ADL and mobility. A higher score indicates higher independence in ADL. It has excellent clinimetric properties and can also be filled out by an experienced nurse or relative.[53]

Nottingham Extended ADL scale (NEADL)

The NEADL is a self reported questionnaire on activities actually performed. It consists of 22 items in four domains (mobility, kitchen, domestic, leisure). Each item is rated by one of

four responses (able, able with difficulty, able with help, unable). The NEADL has proved to be a reliable and valid outcome measure in patients with stroke.[54]

Modified Rankin Scale (MRS)

The MRS is a measure for the degree of disability or dependence in the daily activities. The score runs from 0-6, ranging from perfect health without symptoms to death. The score will be dichotomised to good outcome (0–2) or poor outcome (3–6). It is a valid scale and frequently used in stroke outcome studies.[55]

EuroQol (EQ-5D)

The EQ-5D measures health related quality of life. It consists of a self-assessment questionnaire about current health in five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/ depression) and a VAS score in which a person is asked to rate their own health status. It is a widely used generic questionnaire, which is validated for people with stroke. By combining the questionnaire and VAS score a health state is described, and each health state combined with population estimates can be transformed to a utility. A utility is an expression of the Quality Adjusted Life Years (QALY) and can be used in economic evaluations.[56-59]

**** Caregiver***

Expanded Caregiver Strain Index (CSI+)

The CSI+ evaluates experienced strain of the caregiver. There are 18 items answered with 'yes' or 'no' and scored dichotomously. The CSI+ is an expansion of the Caregiver Strain Index and also rates positive aspects of caring. The CSI+ is proven valid and responsive.[60-62]

Carer Quality of Life Scale (CarerQOL)

The CarerQOL is a valid instrument to evaluate care-related quality of life in informal caregivers. The instrument consists of a burden instrument (encompassing seven important burden dimensions) and a valuation component (a VAS scale for happiness). It consists of seven questions with each three-answer options (no, some, a lot) and a VAS scale ('how happy are you at this moment?').[63-65]

**** Patient and caregiver***

Hospital Anxiety and Depression Scale (HADS)

The HADS is a measure to evaluate mood: anxiety and depression. The HADS consists of 14 items (seven anxiety and seven depression), each with a 4-point rating scale (0–3). It is a brief, reliable, responsive, valid and widely used measure.[33, 34]

Fatigue Severity Scale (FSS)

The FSS measures the impact of fatigue. It consists of nine items, and scores for each item range from 1 to 7. The total FSS score is the mean of the nine item scores. The FSS was validated and demonstrated to be a simple and reliable instrument to assess and quantify fatigue for clinical and research purposes.[66]

General Self-efficacy Scale

The General Self-Efficacy Scale is a valid 10-item psychometric scale that is designed to assess optimistic self-beliefs to cope with a variety of difficult demands in life. It has a 4-point rating scale ('not at all true'. 'barely true', 'moderately true' and 'exactly true'). The scale has been originally developed in German and has been used in many studies with hundred thousands of participants. General self-efficacy appears to be a universal construct that yields meaningful relations with other psychological constructs.[67, 68]

(Cost) Diaries

Each patient-caregiver couple will be asked to keep a weekly cost diary during twelve weeks. Direct and indirect cost data will be collected. The diary will comprise questions for the patient on medical consumption (for example questions about consultation with doctors, therapists, re-admission, home care), missing hours at work, household, sports or hobbies and time invested by the caregiver in the caregiver-mediated training.[69] In addition, the patient will be asked to record the exercises done each day during the eight-week intervention period (in therapy, by themselves, with nurses or with a caregiver). Thereby we can evaluate the total time spent on (additional) exercises done by the couples in the intervention and control group. Problems and adverse events like for example falls, fractures, and concurrent illness will also be recorded.

Process analysis

At the end of the intervention, semi-structured interviews will be conducted with a subgroup of patients and caregivers to collect qualitative data regarding the experience of CME to evaluate facilitators and barriers for implementation.

Power analysis

We expect a significant reduction of five points (11%) on the SIS mobility domain in favor of the experimental training group, with an estimated standard deviation for this population at a maximum of 14 points,[70] requiring inclusion of minimally 30 patients per arm of the trial. Including 10% dropouts, a minimum of 66 stroke patients, (i.e. 22 per type of center), is needed to achieve a sufficient statistical power of 80% using a significance level alpha of $P<0.05$.

Data analyses

Baseline characteristics will be presented and between group differences will be studied to determine whether groups are comparable at baseline. Normality of data distributions will be judged by visual plot. When data are not normally distributed, non-parametric Wilcoxon signed rank sum tests will be used. When the data are normally distributed student t-tests for independent samples will be used. The two-tailed α-level will be set at 0.05.

The main outcomes will be compared between the intervention and control group at the different time points using multilevel regression analysis. Depending on the number of settings of participating centers we will use random coefficient analysis (SPSS GLM). Time since stroke, group, location and baseline values will be added to the model. Intention-to-treat analysis will be done and missing data will be imputed using multiple imputation techniques. All hypotheses will be tested two sided, with a critical value of <0.05.

Economic evaluation

The economic evaluation will be performed from a societal perspective and a health care perspective with a time horizon of twelve weeks. For the measurement and valuation of the costs the Dutch costing guidelines will be used.[71] All relevant costs will be measured and valued, including cost of production loss where applicable. The analysis will be done according to the intention-to-treat principle. Missing cost and effect data will be imputed using multiple imputations according to the MICE (Multiple Imputation by Chained Equations) algorithm.[72] Bias-corrected and accelerated bootstrapping with 5000 replications will be used to calculate 95% confidence intervals around the mean difference in total costs between the two groups. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in mean total costs by the difference in mean effects on the primary outcomes (SIS mobility and LOS) between the treatment groups. A cost-utility analysis will be performed estimating the incremental costs per QALYs gained. In the costs utility-analysis the outcome measure will be QALYs based on the Dutch tariff for the EuroQol.[56] Bootstrapping will be used to estimate the uncertainty surrounding the ICERs, which will

be graphically presented on cost-effectiveness planes. Cost-effectiveness acceptability curves and net monetary benefits will also be calculated. To estimate indirect costs of production loss the human capital approach will be used. Sensitivity analyses will be performed on the most important and uncertain cost parameters.

DISCUSSION

The CARE4STROKE trial is the first observer-blinded randomized clinical trial aimed to investigate the effectiveness of a CME program combined with e-health, added to usual care, in terms of self-reported outcome of mobility (SIS 3.0) and LOS in patients with stroke admitted to hospital stroke unit, rehabilitation center or nursing home. The main aspects of the CARE4STROKE program are 1) increasing intensity of training by doing exercises with a caregiver in addition to usual care and 2) e-health support.

A higher intensity of training improves functional outcome after stroke.[3, 10-16] However only few studies have been done in which a higher intensity of training is achieved by CME.[26, 29-31] Moreover, none of these existing studies investigated the cost-benefits of CME and none combined CME with e-Health services. We assume that e-health can support adherence to the program for patient and caregiver and promote self-management.[25, 73] In this intervention e-health consists of the CARE4STROKE tablet application, which clearly explains the exercises through video instructions and is simple and attractive to use. And, in addition to this, tele-rehabilitation services are available such as telephone, skype or email to contact the coordinating therapist when appropriate. We hypothesize that the combination of a weekly progressive, incremental training regimen done with a caregiver together with continuing support of a therapist through additional e-health services may enhance ESD and increase feelings of QoL, perceived empowerment and self-management of the patient – caregiver couple. As a consequence, we expect that CARE4STROKE will lead to a reduced LOS and will thereby reduce care costs.

Defining LOS should be done carefully, since it may be influenced by non-medical factors that are not directly related to the functional ability of the patient. Data on additional factors which could also influence LOS will be collected, like discharge destination, comorbidity, the need for facilities at home, etc.[74] We will also record the planned discharge date and the real discharge date. We will describe these data and, when necessary, do subgroup analyses.

The optimal dose for caregiver-mediated exercises is not yet known, while few studies have been done.[26-31] We asked patients and caregivers to perform the selected set of exercises minimally five times a week for 30 minutes. This dose was chosen because it leads to a

surplus of 150 minutes of exercise a week, which is in line with recommendations of most guidelines[15, 17-20] and proved to be feasible in our pilot study.

Caregivers are more intensively involved in CME than during usual care. At first glance, this could influence caregiver strain. Other studies show no significant negative influence or even a decrease in caregiver strain in the CME intervention group.[26, 30] It is suggested that the latter effect arises due to more knowledge and experience of the caregiver about what the patient can and cannot do. We will not only assess caregiver strain, but also anxiety, depression, quality of life, fatigue and self-efficacy of the caregiver, to closely monitor the effects of our intervention on the caregiver.

CME will be implemented in three different rehabilitation settings, i.e. hospital stroke units, rehabilitation centers and nursing homes, to study its applicability and effectiveness in different care settings. The inclusion criteria are liberally defined, in order to get more insight in the type of patients and caregivers that are eligible for CME and facilitators and barriers for implementation. For example we will include patients with MMSE >18[35] and patients and caregivers with a HADS score on the domain 'depression' <11,[33, 34] acknowledging that patients with some cognitive decline and patients and caregivers with some depression may benefit from our CARE4STROKE program. Probably a major factor for successful implementation is that the patient and caregiver are physically and emotionally able and willing to perform the exercises together. Therefore, an intake exercise session with the physical therapist is incorporated to judge whether patient and caregiver can adequately perform the exercises together.

Interestingly, in a small-scale pilot study, about 25% of the eligible participants with stroke, did not have a willing and/or able caregiver. We will keep track of inclusion-rates and reasons for exclusion and will record how many possible participants cannot continue because of a lack of caregivers. This is relevant data in light of a trend worldwide in transferring care from professional to informal caregivers with focus on self-management and has not been addressed in previous RCTs on CME.[26-31]

A limitation of our current design is that participants in the control group continue with usual care but do not receive any (new) intervention. With that the trial is not dose- matched. In addition, the adherence of the participants included in the control group to fill in the diaries could be low. Furthermore, in some centers, participants in control and intervention groups are admitted to the same wards. This could lead to contamination in the control group, when patients and/ or caregivers see how others exercise together. Finally, our selection criteria are liberally defined, this could be a limitation of external validity. During the training course, participating therapists are instructed to pay specific attention to the

diaries and dangers for contamination to minimize these effects. A number of outcome measures, including one of the primary outcome measures (mobility domain of SIS 3.0), are self-reported. It is impossible to blind the patient-caregiver couple, and therefore these outcome measures are not blinded. However, a blinded outcome assessor assesses the other objective outcome measures.

In conclusion: The CARE4STROKE study will be the first clinical trial in which the effects and cost-effectiveness of CME combined with e-health services to enhance ESD is investigated. The first results are expected early 2018.

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Chapter 5

Caregiver-mediated exercises with e-health support for early supported discharge after stroke (CARE4STROKE): A randomized controlled trial

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Abstract

Background and purpose:

We designed an 8-week caregiver-mediated exercise program with e-health support after stroke (CARE4STROKE) in addition to usual care with the aim to improve functional outcome and to facilitate early supported discharge by increasing the intensity of task specific training.

Methods:

An observer-blinded randomized controlled trial in which 66 stroke patient-caregiver couples were included during inpatient rehabilitation. Patients allocated to the CARE4STROKE program trained an additional amount of 150 minutes a week with a caregiver and were compared to a control group that received usual care alone. Primary outcomes: self-reported mobility domain of the Stroke Impact Scale 3.0 (SIS) and length of stay (LOS). Secondary outcomes: motor impairment, strength, walking ability, balance, mobility and (Extended) Activities of Daily Living of patients, caregiver strain of caregivers, and mood, self-efficacy, fatigue and quality of life of both patients and caregivers. Outcomes were assessed at baseline, 8 and 12 weeks after randomization.

Results:

No significant between-group differences were found regarding SIS-mobility after 8 (β 6.21, SD 5.16; *P*=0.229) and 12 weeks (β 0.14, SD 2.87; *P*=0.961), and LOS (*P*=0.818). Significant effects in favor of the intervention group were found for patient's anxiety (β 2.01, SD 0.88; *P*=0.023) and caregiver's depression (β 2.33, SD 0.77; *P*=0.003) post intervention. Decreased anxiety in patients remained significant at the 12-week follow-up (β 1.01, SD 0.40; *P*=0.009).

Conclusions:

This proof-of concept trial did not find significant effects on both primary outcomes mobility and LOS as well as the secondary functional outcomes. Treatment contrast in terms of total exercise time may have been insufficient to achieve these effects. However, caregiver-mediated exercises showed a favorable impact on secondary outcome measures of mood for both patient and caregiver.

Clinical trial registration:

NTR4300, URL – http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4300.

INTRODUCTION

Stroke rehabilitation aims to reduce long-term dependency and to allow patients to return to the community.[1] Meta-analyses have shown that increased intensity of training leads to better functional outcome in stroke patients.[2,3] However, resources for rehabilitation services after stroke (mostly staff) are becoming increasingly scarce and it proves to be difficult to offer a sufficient dose of exercise therapy.[4] Therefore, alternative treatment strategies are needed to increase the amount of exercise therapy without increasing healthcare costs.[5,6] Caregiver-mediated exercises, in which stroke patients perform exercises with a caregiver, may be a promising approach. In addition, caregiver-mediated exercises have the potential to facilitate early supported discharge (ESD)[7-9] by smoothing the transition from inpatient care to the home setting and providing opportunities to continue exercise therapy in the community. Since independence in transfers and/or gait is an important factor in enabling discharge to the community,[10] focus of caregiver-mediated exercises on patients' independence in terms of regaining mobility and gait-related activities is useful.

A recent Cochrane review, in which 333 patient-caregiver couples were included for meta-analysis, found very low to moderate quality evidence in favor of caregiver-mediated exercises for standing balance, walking distance, and quality of life. However, the included nine studies were heterogeneous in terms of quality, methodology, content, timing and duration of the intervention, warranting further investigation.[11] A recent phase IV trial in 14 hospitals in India failed to show positive effects of a family-led rehabilitation program on the modified Rankin Scale (mRS) when compared to usual care. In this program, rehabilitation professionals were educated to train nominated family members. The nominated family member practiced upper limb function, mood management, positioning, transfers and mobility with the patient.[12] This broad-spectrum program may have been too diluted and too weak, and the dose of augmented exercise therapy insufficient, to introduce significant shifts in mRS scores. In addition, no strict procedure for caregiver selection was described, and the number of caregiver training sessions seems too small to provide progressive and high-quality exercise training for the patient.[13]

To increase adherence and self-efficacy of the patient-caregiver couple, and to facilitate remote coaching and monitoring by the rehabilitation team,[14] the present proof-of-concept trial supported caregiver-mediated exercises with e-health methods and combined it with tele-rehabilitation services.[15]

We hypothesized that the CARE4STROKE program would lead to better self-reported mobility, with a clinically important difference of 5 points on the mobility domain of the Stroke Impact Scale (SIS, version 3.0)[16] and a reduced length of stay (LOS) for stroke patients

compared to usual care, without increasing caregiver burden. In addition, we hypothesized that psychosocial functioning and mobility related functional outcomes, such as balance and lower limb function, would significantly improve by the CARE4STROKE program.

METHODS

Design

The CARE4STROKE trial was an observer-blinded multicenter randomized controlled trial in which a caregiver-mediated exercises program with e-health support, combined with tele-rehabilitation, in addition to usual care, was compared with a control group that received usual care alone. Participants were recruited from hospital stroke units, rehabilitation centers and nursing homes in the Netherlands. Design, inclusion and exclusion criteria, outcome measures and data analysis have been described in detail elsewhere and are summarized here.[15] Methods and results are reported in accordance with the CONSORT statements.[17]

Patients were randomly allocated (1:1) to either the intervention or the control group. An online randomization procedure, using a computerized minimization algorithm with 'type of setting' as only covariate, was applied by an independent researcher who was not involved in the treatment program. Subsequently, the independent researcher informed the treating physical therapists about the treatment allocation of the patient (and caregiver). The allocation schedule was only visible for the coordinating researchers who were not involved in inclusion or assessment of participants.

All assessments were performed at baseline and 8 and 12 weeks post randomization by 2 observers (MM and QG), who were trained in standardized outcome assessment. Observers were blinded for treatment allocation (Figure 5.1). Participants and physical therapists could not be masked for group allocation.

The study protocol was approved by the Medical Ethics Review Committee of the Slotervaart Hospital and Reade (number NL34618.048.12) and was registered in the Dutch trial register as NTR4300, registered 2 December 2013 (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4300). All participants provided written informed consent. There were no changes in trial design[15] during the study period, except the removal of the Caregiver Strain Index as an exclusion criterion (>4 points), since caregiver-mediated exercises might actually reduce caregiver strain and it would therefore be unfortunate to deny caregivers to participate in the intervention.

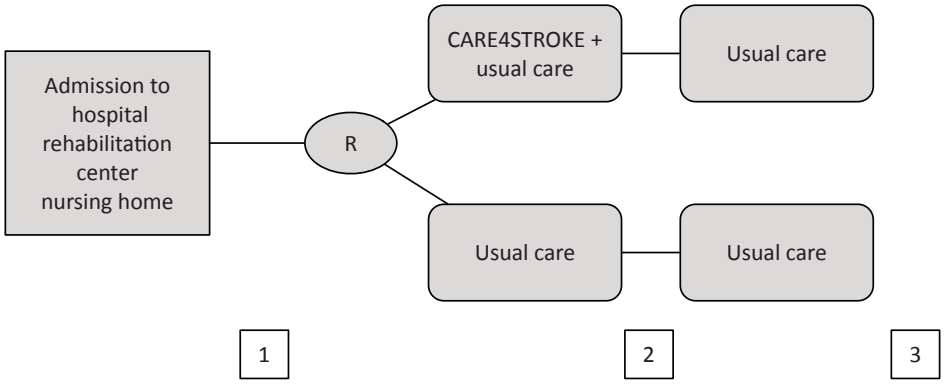

Figure 5.1 Study design.
R = Randomization; 1 = Measurement 1, baseline, before start of the intervention; 2 = Measurement 2, end of intervention (8 weeks post randomization); 3 = Measurement 3, follow up (12 weeks post randomization).

Participants and setting

Patients were recruited in the participating hospitals (N=4), rehabilitation centers (N=2) and geriatric rehabilitation departments of nursing homes (N=7). All patients admitted were screened by participating physiotherapists and physicians. When patient and caregiver seemed to be eligible, they received a participant information letter explaining the study and the consequences of participating. During a subsequent session with one of the research assistants (MM and QG), the research assistant checked the following in- and exclusion criteria and obtained informed consent.

Patients were eligible if they (1) had a stroke according the WHO definition[18]; (2) had lived independently before the stroke; (3) were planned to be discharged home; (4) were able to follow instructions (MMSE score >18 points) (5) had a Functional Ambulation Score (FAC) <5 and (6) were willing and able to appoint a caregiver who wanted to participate in the program (with a maximum of two caregivers). A caregiver was defined as someone close to the patient who was willing and able to do exercises together with the patient, for example a partner, family member or friend. This caregiver was not a professional and was not paid for his/her efforts. Patients were asked to appoint one or two preferred caregivers, thereafter inclusion criteria for the caregivers were checked. These inclusion criteria for the caregiver were: (1) being medically stable and (2) being physically able to perform the exercises together with the patient. Inclusion criteria for both patients and caregivers were (1) aged 18 years or older; (2) written informed consent; (3) ability to understand Dutch or English (at a sufficient level to understand instructions); (4) sufficiently motivated to participate in

the caregiver-mediated exercise program; and (5) a score of <11 on the 'depression' domain of the Hospital Anxiety and Depression Scale (HADS).

An exclusion criterion for both patients and caregivers was a serious comorbidity that interfered with mobility training, for example a severe cardiopulmonary illness or a disabling orthopedic comorbidity of the lower extremity. To finally determine the suitability of patients and caregivers, an intake exercise session with a trained physical therapist was scheduled prior to inclusion. During this session the therapist judged if the patient-caregiver couple was able to exercise adequately and safely together. A short checklist, evaluating these criteria, was used by the physical therapist (S5.1 checklist physiotherapist intake exercise session).

Intervention

The content of the CARE4STROKE program is reported in accordance with the TIDieR guidelines[19, 20] and has been published elsewhere in more detail.[21] Briefly, the program consisted of 8 weeks of exercise therapy, executed with a caregiver, in addition to usual care following the current guidelines in the Netherlands.[2] The exercise program was composed by a trained physical therapist during weekly sessions. The therapist could choose from 37 standardized exercises aimed at improving mobility, presented in an e-health application ('app').

For each patient, exercises were combined into a patient-tailored, progressive training regimen, related to the patient goals. Patient-caregiver couples were encouraged to contact the coordinating therapist using tele-rehabilitation services like telephone, video conferencing or email when appropriate in between the weekly exercise sessions. The patients and their caregivers were instructed to perform the selected set of exercises at least five times a week for 30 minutes. This meant that patients received 20 hours of caregiver-mediated exercises in addition to usual care during the 8-week intervention period. When the patient's discharge date fell before the anticipated end date of the CARE4STROKE intervention, the program was continued at home. All physical therapists were thoroughly trained in a training course, prior to delivering the CARE4STROKE program.

The participants in the control group received usual care according to the guidelines for physical therapy for patients with stroke of the Royal Dutch Society for Physical Therapy (KNGF).[2] Therapy sessions are designed according to patient goals. Therefore, there were no restrictions with respect to content, time or duration of the physical therapy. Task and context specificity are important aspects of physical therapy after stroke. With that, in current guidelines, exercises are recommended to improve functional outcomes such as standing balance, physical condition, and walking competence.

Outcome measures

Primary outcome measures were the mobility domain of the SIS 3.0[22, 23] and LOS. LOS was defined as the time from stroke onset to the moment of discharge from the rehabilitation facility.

Secondary outcome measures were all other domains of the SIS; Fugl-Meyer motor score of the lower extremity; Motricity Index of the lower extremity leg; Six-minute walking test; Ten-meter walking test; Timed Up and Go test; Berg Balance Scale; Rivermead Mobility Index; Barthel Index; Nottingham Extended ADL scale and mRS, for the patient. Secondary outcome measures for caregivers included the Caregiver Strain Index and Carer Quality of Life Scale. The HADS, Fatigue Severity Scale and General Self-Efficacy Scale were included for both patients and caregivers. In addition, patients and caregivers kept a diary recording exercise times and relevant cost data (e.g. visits to specialists, missed work time). An economic evaluation carried out alongside the randomized controlled trial will be reported on in a separate publication. During the trial, we excluded the personal opinion questionnaire for empowerment from the outcome measures, to reduce the time load of the assessments. Since evidence suggests that adding the five positively phrased items in the Expanded Caregiver Strain Index does not improve the psychometric properties of the Caregiver Strain Index,[24] we decided to report the Caregiver Strain Index.

Statistical analysis

Sample size calculation showed that 66 patients were needed to achieve sufficient statistical power (80%) to detect a significant difference with a two-tailed alpha level of $P<0.05$. [15] We powered the study for a significant reduction of five points (11%) on the SIS mobility domain measured post intervention, with an estimated standard deviation for this population at a maximum of 14 points.[25]

We tested the successful blinding of the assessors for treatment allocation by comparing assessors' guesses with actual treatment assignment, using a Cohen's κ statistic.

Data were analyzed according to the intention-to-treat principle and the statistician was kept blinded for group allocation. Missing items were imputed using serial means. Missing values were not imputed if entire questionnaires or scales were missing.

Between-group differences at baseline were studied using Mann-Whitney U tests. Subsequently, main outcomes were compared between the intervention and control groups at 8 and 12 weeks after randomization, using a Generalized Estimating Equations (GEE) model with an exchangeable covariance structure. Time, group, baseline value of the dependent

variable, covariates that showed significant differences at baseline and the interaction between group and time were included in the regression model. We calculated β-values and standard errors for the group × time interaction effects and applied a Wald statistic to obtain corresponding *P*-values. All hypotheses were tested two-sided, with an $\alpha<0.05$. To test if the model was appropriate, we repeated the analysis with other covariance structures. Differences in LOS were analyzed using a Mann-Whitney U test.

RESULTS

After screening 1082 patients admitted on the neurological wards of the participating centers, we recruited 66 participants between April 2014 and July 2016. Most patients were excluded because they did not suffer a stroke (Figure 5.2). Follow-up measurements were completed in October 2016. Recruitment of patients and numbers of dropouts are presented in the flow chart (Figure 5.2). Fifty-six of the 66 patients were recruited from rehabilitation centers, whereas 10 patients were recruited from nursing homes and no patients were recruited from participating hospitals. As a result, we did not carry out separate analyses for type of participating center. We found a Cohen's κ coefficient of 0.3 when comparing observers' guesses about treatment allocation and actual allocation.

Baseline characteristics of the participants are presented in Table 5.1. Mean age of the included patients with stroke was 59.9 years (Standard deviation (SD) 14.8). Median time after stroke was 37 days (Interquartile range (IQR) 28–56). There was a significant difference in favor of the control group at baseline regarding SIS communication, and a significant baseline difference in favor of the control group regarding depression (HADS) of the caregivers. Both factors were used as covariates in the main regression analysis.

Patients in the intervention group reported a median of 1190 minutes of additional exercise therapy with a caregiver (*P*=0.002). However, when the total amount of self-reported exercise time was calculated (i.e. time during therapy + independent + with a nurse + with a caregiver), there was no significant difference between the intervention and control groups (median 4060 minutes versus 3735 minutes; *P*=0.098). Table S5.2 in the supporting information shows that these findings did not change when using different imputation methods.

Absolute values, Beta (SE) scores and *P*-values for the time x group interaction effect after 8 and 12 weeks are presented in Table S5.3 in the supporting information. No significant time x group interaction effect was found for the primary outcome measure of SIS mobility at week 8 (β 6.21, SD 5.16; *P*=0.229) or week 12 (β 0.14, SD 2.87; *P*=0.961), nor was a significant difference found in LOS (*P*=0.818). Patients in the control group were admitted

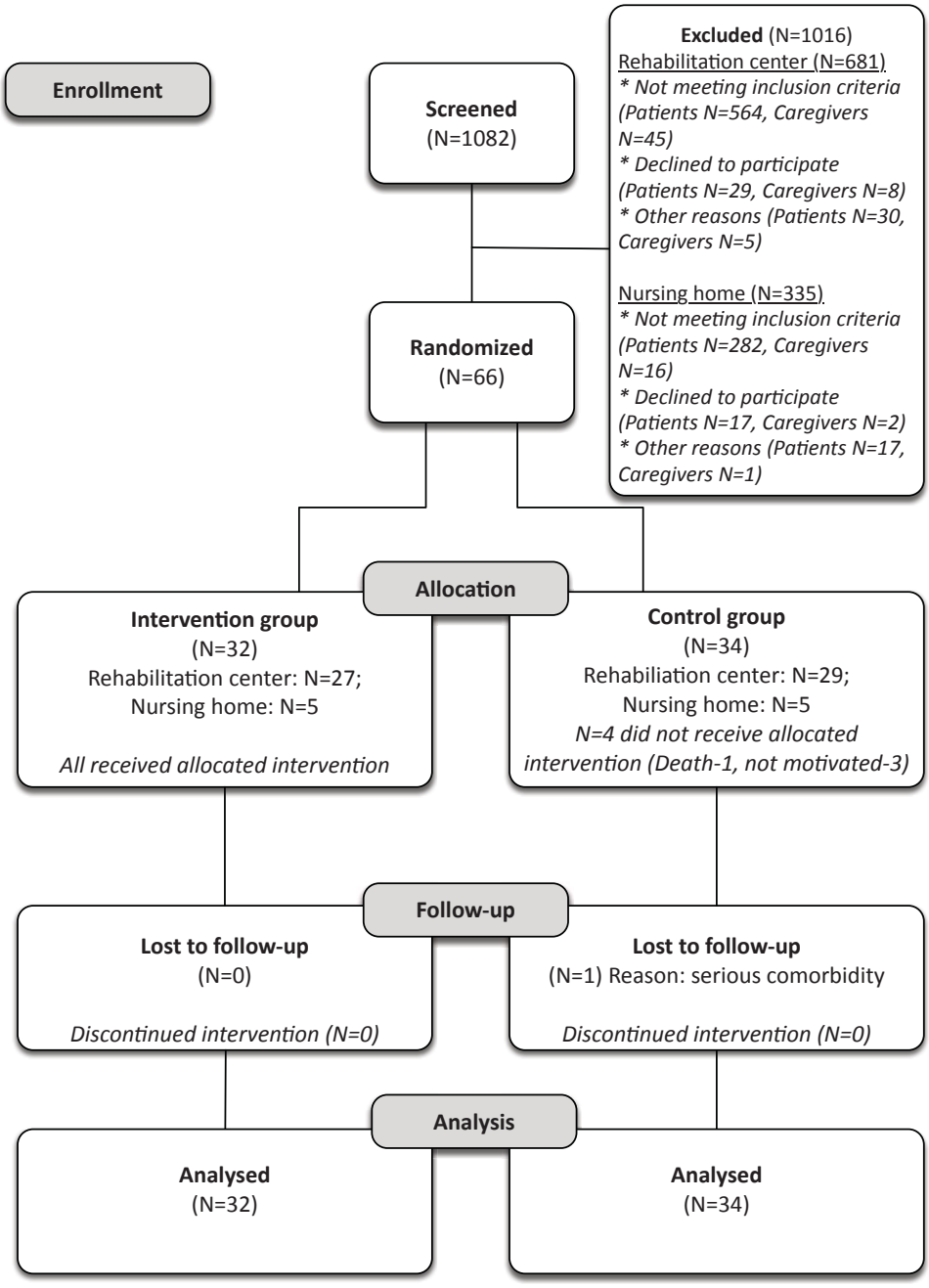

Figure 5.2 Consort flow diagram.

to inpatient stay for a mean of 117 (SD 54) days, versus a mean of 117 (SD 50) days for the intervention group. Significant interaction effects in favor of the intervention group were found regarding mood, viz. for HADS anxiety of the patient after 8 weeks (β 2.01, SD 0.88;

Table 5.1 Baseline characteristics of participants

	Control (N=34)	Intervention (N=32)
Patient		
Sex, female / male	14 / 20	11 / 21
Mean age (SD), years	59.26 (15.01)	60.53 (14.82)
Education, low / high [1] [mv]	20 / 13	21 / 10
Living arrangement, alone / together	10 / 24	10 / 22
Working before stroke, yes / no [mv]	21 / 12 [1 mv]	19 / 13
Time after stroke onset in days, median (IQR)	37 (26–55)	36 (28–57)
Stroke type, hemorrhagic / ischemic / SAH	4 / 28 / 2	10 / 22 / 0
Side of stroke, right / left / brainstem	21 / 12 / 1	16 / 16 / 0
Recurrent stroke, yes / no	3 / 31	2 / 30
Aphasia, yes / no	6 / 28	8 / 24
Hemianopia, yes / no	5 / 29	5 / 27
Visual spatial neglect, yes / no [mv]	9 / 23	10 / 22
MMSE (0–30), median (IQR)	28 (25–29)	27 (24–29)
FAC (0–5), median (IQR)	1.5 (0–3)	2 (0–3)
SIS mobility (0–100), mean (SD)	41.42 (20.45)	49.91 (24.17)
SIS communication (0–100), mean (SD)	87.92 (18.11)	78.57 (23.11)*
Caregiver		
Sex, female / male	21 / 13	23 / 9
Mean age (SD), years	54.00 (12.26)	53.91 (14.90)
Education, low / high [1] [mv]	13 / 18	14 / 18
Relation to the patient, N (%)		
Partner	19 (55.9)	20 (62.5)
Child	7 (20.6)	7 (21.9)
Friend	1 (2.9)	1 (3.1)
Parent	2 (5.9)	1 (3.1)
Sibling	4 (11.8)	2 (6.3)
Volunteer	1 (2.9)	-
Other family member	-	1 (3.1)
Currently working, yes / no [mv]	19 / 12	23 / 9
HADS depression (0–21), mean (SD)	2.88 (2.54)	4.28 (2.99)*
HADS anxiety (0–21), mean (SD)	4.44 (3.40)	5.68 (2.99)
CSI (0–13), mean (SD)	4.53 (2.11)	5.42 (2.66)

SD = standard deviation; IQR = interquartile range; mv = missing values; IQR = interquartile range; SAH = subarachnoid hemorrhage; MMSE = mini mental state examination; FAC = functional ambulation categories; SIS = Stroke Impact Scale; HADS = hospital anxiety and depression scale; CSI = Caregiver Strain Index.

[1] Education low: none/primary school/secondary school/ intermediate vocational education. Education high: higher vocational education, college, university.

* $P<0.05$.

P=0.023) and 12 weeks (β 1.01, SD 0.40; *P*=0.009), and for HADS depression of the caregiver after 8 weeks (β 2.33, SD 0.77; *P*=0.003). No significant interaction effects were found for any of the other secondary outcome measures. Findings did not differ when using a GEE model with a different covariance structure. No adverse events were reported.

DISCUSSION

In this observer-blinded randomized proof-of-concept trial comparing a caregiver-mediated exercises program with e-health support combined with tele-rehabilitation (CARE4STROKE) to usual care alone, we found no differential effect with respect to the primary outcome measures of self-perceived mobility (SIS-mobility) and LOS. In addition, we did find that the CARE4STROKE intervention was feasible and safe.

Insufficient treatment contrast in terms of total exercise time might explain the lack of effects found on functional outcome measures. However, a significant difference in favor of the intervention group was observed, in terms of decreased patient anxiety and caregiver depression. These significant treatment effects might be explained by the significant difference in exercise time with a caregiver. In contrast to exercise therapy supported by health professionals or exercising alone, practicing together with a partner, family member or friend seems to have a positive effect on psychosocial functioning of both patients and caregivers. The incidence of anxiety in stroke patients[26] and depression in their caregivers[27] is significantly higher than in healthy age-matched controls. In addition, depressive as well as anxiety symptoms are predictors of lower quality of life of patients,[28, 29] and of long-term burden and emotional problems of caregivers.[30] So, interventions that target anxiety and depression symptoms are important. The observed HADS values in our participants were in the low range (lower values correspond to less depression or anxiety), which might be caused by our inclusion criteria of <11 points on the HADS depression subscale. However, the found effects of caregiver-mediated exercises on the HADS values exceed minimal clinically important differences[31] and are therefore worth further exploring. Future trials may even consider including patients and caregivers who are mildly depressed or anxious, because caregiver-mediated exercises might help to decrease these symptoms. Of course, only with very strict monitoring during the caregiver-mediated exercises program.

These positive effects of CARE4STROKE on mood are also in line with previously reported positive effects of caregiver-mediated exercises on caregiver strain[32] and the quality of life of patients.[11] The present findings are also in line with a trial using the same protocol and running parallel in Adelaide, Australia (N=63).[33] They found a significant reduction of caregiver

fatigue and improved self-efficacy in the caregiver-mediated exercises group. In a qualitative study using semi-structured interviews we performed alongside the CARE4STROKE trial, participants reported that caregiver-mediated exercises made them feel more actively involved in the rehabilitation process, and prepared them for the home situation.[34] This might, at least in part, explain the reduced anxiety and depression we found in the present trial and so caregiver-mediated exercises may smooth the transition from the rehabilitation center to the home situation, which patients and caregivers report as a significant hurdle.[35, 36]

In this trial we did not find an effect on LOS and thus on facilitation of ESD. However, in view of the impact on mood, we argue that caregiver-mediated exercises might be an important component in future more protocolized ESD programs. First, to prepare patients and caregivers for discharge to their own home situation. Second, to continue exercising at home. The latter could probably well be supported by e-health tools and tele-rehabilitation services. It would be interesting to further expand this and study its effects.

The CARE4STROKE intervention has now been studied in two different parts of the world (i.e. Australia and Western Europe). In addition, caregiver-mediated exercises interventions have been studied in countries like India[12] and Ireland[32]. All these countries have quite different (socio-geographical) circumstances and health care systems. Future studies should investigate cross-cultural differences with respect to effectiveness of caregiver-mediated exercise programs in different health care systems.[13]

This study has several limitations. First, our hypothesis is based on 1200 minutes of additional exercise time by the patient-caregiver couples. Although the intervention group approached the intended dose of caregiver-mediated exercises (1190 minutes), there was no significant difference in the total amount of exercise time between the intervention and control group. Patients in the control group reported more exercise time with a therapist or nurse and also performed exercises with a caregiver. Therefore, there might have been insufficient treatment contrast to improve mobility and other functional outcomes. This type of contamination is often seen in stroke rehabilitation trials that require a long recruitment period of several years to finalize.[37, 38] Second, our sample size calculation was based on the assumption of a standard deviation of 14 points for the SIS mobility.[25] In the current study the standard deviation was approximately 20 points. Our study may therefore be under powered. Third, although independent mobility is an important factor in enabling discharge to the community, length of inpatient stay is also determined by other, including non-clinical, factors.[39] Interesting however is, that while we did not find differences in LOS, the parallel Australian trial found a 9-day reduction of LOS in a per-protocol analysis of 20 patients who received tele-rehabilitation at home.[33] Finally, our patients were not included

at fixed times after stroke, resulting in variable timings after stroke onset,[40] which increased the likelihood of not finding between-group differences.[41-43]

Future full-scale trials should focus on gaining a better understanding of the effects of caregiver-mediated exercises on psychosocial outcome measures and their value for ESD. Outcome measures might be aimed at constructs such as depression, anxiety, empowerment, quality of life and smoothness of transfer to the home situation. Sample size should be larger and to prevent contamination a cluster randomized trial is recommended.[44, 45] In order to advance precision one might consider a repeated measurement design with a longer follow up period. Finally, inclusion and assessments should preferably be done at fixed times post-stroke.[41]

Conclusions

This proof-of-concept randomized controlled trial showed that the CARE4STROKE program is a feasible approach to exercise with a caregiver. Although no significant differences were found on self-perceived mobility, LOS and functional outcomes, which may be caused by insufficient treatment contrast, CARE4STROKE did have a favorable impact on secondary outcome measures of mood for both patients and caregivers.

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SUPPORTING INFORMATION

S5.1 Checklist physiotherapist intake exercise session

- Is the caregiver able to sufficiently support the patient (physically and mentally)?
- Are the exercises performed safely together by patient and caregiver?
- Is the collaboration going well between patient and caregiver?
- Is the patient sufficiently instructable?
- Do both patient and caregiver know what is expected from them regarding the exercises?
- Do both patient and caregiver know what is expected from them regarding the diary?

Table S5.2 Self-reported exercise time over 8 weeks (in minutes) reported as medians and interquartile ranges (IQR)

	Without imputation			With imputation[1]			With imputation[2]		
	Control (N=25^{mv})	Intervention (N=25^{mv})	*P*-value	Control (N=28^{mv})	Intervention (N=30^{mv})	*P*-value	Control (N=29^{mv})	Intervention (N=31^{mv})	*P*-value
During therapy	2152.5 (1300.0–2846.25)	2010.0 (1395.0–2920.0)	0.793	2295.0 (1340.00–2842.50)	2040.0 (1430.0–2940.0)	0.767	2152.5 (1252.5–2838.8)	2010 (1394.0–2920.0)	0.688
Independent	570.0 (275.0–475.0)	400.0 (105.0–1292.5)	0.462	560.0 (272.5–1002.5)	510.0 (105.0–1200.0)	0.607	550.0 (275.0–985.0)	550.0 (110.0–1200.0)	0.773
With nurse	130.0 (0–475.0)	20.0 (0–120.0)	0.119	85.0 (0.0–420.0)	20.0 (0.0–142.5)	0.200	80.0 (0.0–380.0)	20.0 (0.0–140.0)	0.145
With caregiver(s)	350.0 (95.0–1065.0)	1150.0 (850.0–1500.0)	0.004*	595.0 (152.5–1117.5)	1195.0 (885.0–1533.3)	0.002*	480.0 (115.0–1105.0)	1190.0 (870.0–1530.0)	0.002*
Total	3860.0 (3153.5–4522.5)	4060.0 (3472.5–5275)	0.237	3742.5 (3184.0–4477.5)	4150.0 (3498.75–4915.0)	0.141	3735.0 (3153.5–4475.0)	4060.0 (3525.0–4850.0)	0.098

* $P<0.05$.

mv = missing values.

[1] Missing items were only imputed when a minimum of 5 weeks of the diary had been filled out.

[2] All missing items were imputed, except when the entire diary had not been filled out.

Table S5.3 Absolute values of outcomes reported as means and standard deviations (SD), Beta (SE = Standard error) and *P*-values of outcome measures

	Control group (N=34)							Intervention group (N=32)							Generalized Estimating Equations: beta (SE), *P* Group x Time					
	Baseline[N=34]		8 weeks[N=29]			12 weeks[N=29]		Baseline[N=32]			8 weeks[N=32]			12 weeks[N=32]			Baseline to 8 weeks			Baseline to 12 weeks		
Primary outcome measure																						
SIS mobility (0–100)	41.42	(20.45)	73.37	(19.65)		69.35	(20.81)	49.91	(24.17)		74.91	(19.39)	N=31	77.95	(21.44)		-6.21	(5.16)	*P*=0.229	-0.14	(2.87)	*P*=0.961
Secondary outcome measures - Patient																						
HADS depression (0–21)	4.65	(3.41)	5.70	(4.47)	N=27	4.52	(3.66)	N=27	4.22	(2.67)		4.19	(3.09)	N=31	3.69	(3.70)		-1.12	(0.88)	*P*=0.202	-0.34	(0.43)	*P*=0.434
HADS anxiety (0–21)	5.35	(3.57)	5.26	(4.56)	N=27	5.07	(4.70)	N=27	5.38	(3.60)		3.68	(2.63)	N=31	3.22	(3.05)		-2.01	(0.88)	*P*=0.023	-1.01	(0.40)	*P*=0.009
SIS strength (0–100)	39.34	(20.73)	51.94	(27.50)		49.35	(25.08)	39.06	(22.00)		51.21	(27.31)	N=31	50.00	(26.28)		-0.04	(5.05)	*P*=0.994	-0.28	(2.78)	*P*=0.921
SIS memory (0–100)	83.93	(14.90)	88.79	(12.36)		87.44	(11.83)	76.90	(19.83)		80.76	(17.39)	N=31	83.37	(16.24)		-2.39	(3.50)	*P*=0.495	1.14	(1.61)	*P*=0.479
SIS emotion (0–100)	74.02	(16.11)	73.18	(16.70)		75.19	(18.81)	79.95	(12.07)		81.45	(11.55)	N=31	83.96	(13.60)	N=31	1.61	(3.58)	*P*=0.652	1.62	(2.02)	*P*=0.423
SIS communication (0–100)	87.92	(18.11)	90.27	(14.09)		89.04	(15.51)	78.57	(23.11)		80.18	(20.58)	N=31	83.26	(19.15)		-2.30	(2.92)	*P*=0.431	1.52	(1.53)	*P*=0.322
SIS IADL (0–100)	54.12	(17.79)	69.22	(20.60)		69.66	(20.99)	55.39	(15.83)		66.13	(19.23)	N=31	67.34	(18.19)		-4.76	(4.22)	*P*=0.260	-2.12	(1.99)	*P*=0.285
SIS hand function (0–100)	25.74	(34.23)	41.90	(40.37)		40.34	(39.69)	23.91	(27.70)		36.61	(37.05)	N=31	37.97	(37.48)		-2.71	(6.71)	*P*=0.686	-0.71	(3.17)	*P*=0.822
SIS participation (0–100)	46.78	(22.71)	58.94	(22.23)		57.97	(19.09)	44.92	(25.39)		57.16	(20.32)	N=31	60.25	(24.05)		-2.10	(6.40)	*P*=0.743	1.19	(3.12)	*P*=0.703
SIS 9 (0–100)	42.35	(20.16)	58.79	(22.27)		60.86	(23.03)	41.41	(21.56)		57.90	(17.60)	N=31	59.06	(16.92)		-0.81	(6.09)	*P*=0.894	-0.80	(3.18)	*P*=0.801
SIS 16 (0–100)	48.41	(10.81)	63.21	(22.22)		56.62	(10.61)	51.72	(11.14)		61.55	(19.73)	N=31	59.34	(9.86)		-2.85	(1.85)	*P*=0.123	-0.29	(0.91)	*P*=0.748
SIS composite physical scale (0–100)	42.86	(17.57)	58.14	(10.21)		61.42	(20.82)	45.68	(15.28)		58.32	(10.48)	N=31	63.03	(19.28)		-4.04	(3.52)	*P*=0.252	-0.94	(1.76)	*P*=0.591
NEADL Mobility (0–18)	2.26	(3.55)	9.50	(6.05)	N=28	9.24	(6.25)	3.19	(4.22)		10.16	(5.26)		10.84	(5.03)	N=31	0.03	(1.36)	*P*=0.983	0.31	(0.68)	*P*=0.652
NEADL Kitchen (0–15)	6.15	(3.52)	11.04	(3.61)	N=28	11.45	(3.26)	5.87	(2.59)	N=31	10.47	(4.18)		11.29	(3.89)	N=31	-0.25	(1.14)	*P*=0.824	0.08	(0.53)	*P*=0.886

Table S5.3 continues on next page.

Table S5.3 ***Continued***

	Control group (N=34)									Intervention group (N=32)									Generalized Estimating Equations: beta (SE), *P* Group x Time					
	Baseline[N=34]			8 weeks[N=29]			12 weeks[N=29]			Baseline[N=32]			8 weeks[N=32]			12 weeks[N=32]			Baseline to 8 weeks			Baseline to 12 weeks		
NEADL Household (0–15)	1.91	(2.42)		5.93	(5.18)	N=28	6.93	(5.20)		0.66	(1.72)		5.88	(4.65)		7.00	(4.95)	N=31	1.39	(1.10)	*P*=0.207	0.71	(0.58)	*P*=0.219
NEADL Leisure (0–18)	7.06	(2.57)		10.21	(2.67)	N=28	9.79	(3.25)		5.84	(3.25)		8.47	(2.99)		8.29	(4.18)	N=31	-0.25	(0.65)	*P*=0.704	-0.17	(0.33)	*P*=0.606
Barthel Index (0–20)	13.18	(3.96)		16.75	(3.69)	N=28	16.89	(3.47)	N=28	13.22	(3.97)		17.63	(3.49)		17.87	(3.30)	N=31	0.94	(0.82)	*P*=0.251	0.41	(0.42)	*P*=0.320
Modified Rankin Scale (0–5)	3.68	(0.77)		2.50	(1.26)	N=28	2.44	(1.28)	N=27	3.78	(0.61)		2.41	(1.07)		2.23	(1.02)	N=31	-0.29	(0.26)	*P*=0.270	-0.19	(0.13)	*P*=0.141
Fatigue Severity Scale mean (1–7)	4.36	(1.37)	N=31	4.00	(1.69)	N=26	4.07	(1.79)	N=25	4.16	(1.49)	N=30	4.15	(1.51)	N=27	3.77	(1.74)	N=30	0.26	(0.33)	*P*=0.433	-0.05	(0.20)	*P*=0.821
General Self-Efficacy Scale (10–40)	32.74	(4.13)	N=31	32.81	(5.11)	N=26	33.24	(5.61)	N=25	33.97	(4.78)	N=29	33.30	(7.23)	N=27	34.63	(6.08)	N=30	-1.48	(1.70)	*P*=0.383	0.12	(0.67)	*P*=0.858
Rivermead mobility Index (0–15)	6.29	(2.93)		10.54	(3.88)	N=28	10.83	(3.61)		6.50	(3.31)		11.09	(3.16)		11.66	(3.26)		0.68	(0.72)	*P*=0.344	0.34	(0.37)	*P*=0.356
Motricity Index (0–100)	51.24	(25.84)	N=33	63.76	(25.87)		61.10	(27.87)		49.19	(25.95)		63.84	(27.20)		65.58	(25.23)	N=31	3.52	(4.15)	*P*=0.396	2.81	(1.98)	*P*=0.156
Fugl Meyer, leg section (0–66)	17.78	(7.65)	N=32	22.33	(7.84)	N=27	22.44	(8.53)	N=27	16.90	(8.05)	N=30	22.53	(8.22)	N=30	23.72	(8.55)		1.48	(1.28)	*P*=0.251	0.82	(0.65)	*P*=0.208
Berg Balance Scale (0–56)	30.72	(16.79)	N=32	44.07	(13.97)		44.79	(14.21)		31.91	(16.07)		46.03	(12.02)	N=31	47.03	(11.18)		2.47	(2.61)	*P*=0.344	0.84	(1.39)	*P*=0.545
Timed up and Go test (Seconds)	32.65	(20.00)	N=13	21.74	(14.04)	N=23	29.91	(35.73)	N=23	30.93	(20.40)	N=14	19.28	(11.61)	N=26	27.96	(33.87)	N=30	-3.88	(5.54)	*P*=0.484	-1.86	(3.14)	*P*=0.552
10 metre walking test (m/s)	0.46	(0.34)	N=14	0.85	(0.63)	N=23	0.90	(0.66)	N=21	0.55	(0.34)	N=15	0.85	(0.48)	N=25	0.90	(0.55)	N=29	-0.04	(0.15)	*P*=0.780	-0.17	(0.08)	*P*=0.836
6-minute walking test (total distance in meters)	159.96	(122.65)	N=12	266.70	(154.66)	N=20	279.43	(179.82)	N=21	185.46	(83.94)	N=13	259.00	(141.53)	N=25	258.61	(163.83)	N=28	2.49	(36.42)	*P*=0.946	-12.45	(21.07)	*P*=0.555

Secondary outcome measures - Caregiver																							
HADS depression (0–21)	2.88	(2.54)		4.85	(4.19)	N=26	3.50	(3.24)	N=24	4.28	(2.99)		3.58	(3.05)	N=31	3.21	(2.71)	N=28	-2.33	(0.77)	*P*=0.003	-0.72	(0.37)	*P*=0.053
HADS anxiety (0–21)	4.44	(3.40)		4.85	(3.89)	N=26	4.63	(3.50)	N=24	5.68	(2.99)	N=31	5.13	(3.28)	N=31	4.96	(4.08)	N=28	-0.45	(0.88)	*P*=0.607	-0.10	(0.55)	*P*=0.854
Caregiver Strain Index (0–13)	4.53	(2.11)	N=32	5.81	(3.23)	N=26	5.35	(2.95)	N=23	5.42	(2.66)	N=31	6.30	(3.03)	N=30	5.72	(3.14)	N=29	-0.54	(0.63)	*P*=0.393	-0.11	(0.29)	*P*=0.693
Fatigue Severity Scale mean (1–7)	2.54	(1.05)	N=33	2.85	(1.29)	N=26	2.98	(1.33)	N=23	2.78	(1.61)		2.98	(1.48)	N=29	2.99	(1.55)	N=29	-0.21	(0.32)	*P*=0.499	-0.17	(0.17)	*P*=0.314
General Self-Efficacy Scale (10–40)	34.76	(5.04)	N=33	33.42	(4.34)	N=26	34.74	(4.61)	N=23	34.25	(4.09)		34.29	(4.97)	N=31	34.93	(3.67)	N=29	1.03	(1.02)	*P*=0.311	0.06	(0.55)	*P*=0.908
Carer Quality of Life (0–14)	12.00	(1.87)	N=32	5.19	(1.83)	N=26	10.96	(2.16)	N=23	11.69	(1.75)		5.55	(1.52)	N=31	10.52	(2.03)	N=29	0.62	(0.69)	*P*=0.368	0.14	(0.28)	*P*=0.615

Chapter 6

Experiences of patients with stroke and their caregivers with caregiver-mediated exercises during the CARE4STROKE trial

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Abstract

Purpose:

Caregiver-mediated exercises are a novel way of delivering augmented exercise therapy for patients with stroke, in which patients do additional therapeutic exercises together with a caregiver. This explorative qualitative study is part of the CARE4STROKE trial and focussed on how participants manage these exercises together. The research questions were: 1) How do the patient-caregiver couples exercise together? And 2) what does exercising together bring about, besides more hours of practice?

Methods:

Semi-structured interviews were conducted with patients and caregivers who participated in the CARE4STROKE intervention. Inductive thematic data analysis was applied.

Results:

Seven patients and seven caregivers were interviewed. Three different role-dynamics were found during caregiver-mediated exercises: 1) patient in control, 2) in concert, and 3) the caregiver as informal carer. In addition, three themes were identified about what exercising together brings about: a) tailor made exercises through active involvement, b) preparation for the home situation, and c) opportunity to be involved.

Conclusion:

Different role-dynamics are at play in caregiver-mediated exercises and it is important for participating staff to be aware of their possible effects on strain of patient or caregiver. Caregiver-mediated exercises were found to enhance individualization of the treatment plan and preparation for home discharge.

Registration:

The trial is registered in the Dutch trial register as NTR4300.

INTRODUCTION

Several systematic reviews have shown that additional exercise therapy enhances functional outcome after stroke[1-8] and can thereby facilitate early supported discharge.[5, 9] However, there is an urgent need for resource-efficient methods to augment rehabilitation services without increasing health care costs.[5, 10] One such method could be to actively involve informal caregivers in physical rehabilitation exercises with their loved ones.[11]

In order to augment rehabilitation services, we developed the CARE4STROKE intervention program, in which caregiver-mediated exercises (CME) are combined with e-health tools.[12] Currently, a multicentre randomized controlled trial investigates the (cost) effectiveness of this approach.[13] The hypotheses are that CARE4STROKE leads to an increase in functional outcome of the patient as well as psychosocial functioning of patient and caregiver, including empowerment, health-related quality of life, and strain of the caregiver. In addition, CARE4STROKE is expected to facilitate early supported discharge and reduce costs. A similar approach is recently tested in a proof-of-concept trial in Australia, resulting in reduced levels of caregiver fatigue with increased feelings of self-efficacy. A per-protocol analysis showed a reduced length of inpatient stay and improved extended activities of daily living.[14]

The CME intervention is relatively new in stroke rehabilitation. A Cochrane review showed very low to moderate evidence that CME can improve standing balance, walking distance and quality of life, without increasing caregiver burden.[11] A recent phase IV neutral trial conducted in India did not show benefits of family-led rehabilitation program in terms of the modified Rankin Scale when compared to usual care.[15] However, the treatment contrast might have been too low, the focus of the program too diluted and the training of caregivers insufficient. Generalizability of the results is therefore burdensome.[16]

Little is known about the subjective experiences of patients and their caregivers with CME. To our knowledge, only Galvin and colleagues reported about these experiences.[17] They mainly aimed to examine how it was to be involved in a CME program from the perspective of the participants and whether the program influenced participants' perceptions of exercise and exercise delivery after stroke. They did not examine the interaction between patient and caregiver or additional effects for participants of CME.

To further explore the perspectives and experiences of the participants of CME we aimed to elucidate how patients and caregivers managed to do the exercises together. Therefore, we defined two research questions in this explorative qualitative study: 1) How do the patient-caregiver couples exercise together? And 2) what does exercising together bring about, besides more hours of practice? The results have the potential to promote better understanding of

contextual factors related with compliance and outcomes of the intervention and the results of the randomized controlled trial, in order to further improve the intervention and support future implementation.

METHODS

Design

To gain insight into the perspectives of patients and caregivers about CME, semi structured interviews were conducted with both patients and caregivers who participated in the CARE4STROKE intervention. The CARE4STROKE intervention is summarized in Textbox 6.1,[12] the design of the CARE4STROKE trial is described elsewhere.[13] The study protocol was approved by the Medical Ethics Review Committee of the Slotervaart Hospital and Reade (trial number: NL34618.048.12/NTR4300). Subsequently, local review boards of all participating centres approved the protocol. All participants gave written informed consent before data collection began, and all statements and comments from patients and caregivers are reported anonymously.

To be complete and transparent in our reporting we used the Consolidated criteria for reporting qualitative research (COREQ) checklist to describe our methods and results.[18] (Supplementary Material – COREQ checklist)

Participants

In- and exclusion criteria for participants in the CARE4STROKE trial are described in Textbox 6.1. Caregivers are asked by the patient with stroke to participate in the CARE4STROKE intervention. To achieve a broad perspective about the topic, the interviewed patients and caregivers, were not part of the same patient-caregiver couple. With each interview another story was told. To further maximize variation in the patient and the caregiver sample, participants were recruited with varying age, gender, relation to the caregiver or patient, and degree of disability of the patient as measured by the modified Rankin Scale.[19] In addition, we also included patients and caregivers who dropped out, who participated for a substantial part of the program in the outpatient setting, and patients who exercised with two different caregivers. The only exclusion criterion for recruitment was severe aphasia hindering understanding and collecting correct information. For practical reasons, participants were asked at different time points after completion of the intervention period. We asked patients and caregivers by letter to participate in a semi-structured interview. Informed consent was already obtained for the randomized controlled trial. Participants were included until data saturation was achieved.

Textbox 6.1 The CARE4STROKE intervention

The CARE4STROKE program consists of eight weeks of exercise therapy executed together with a caregiver, in addition to usual care. 37 standardized mobility exercises were developed, which can be combined into a patient-tailored, weekly progressive and incremental training regimen. The exercises are presented as instructional videos in an e-health application ('app') on a tablet computer (iPad). A short introduction film about the exercises can be found at: https://youtu.be/pNcmbU9R-A4. The patient-specific content of the CME program is compiled in consultation with a trained physical therapist. The patients and their caregivers are asked to perform the selected set of exercises minimally five times a week for 30 minutes. The exercises can be performed in any setting, whether it is a rehabilitation setting or the home environment. During the intervention period patients and their caregivers have a weekly session with a trained physical therapist. Furthermore, patient – caregiver couples are encouraged to contact the coordinating therapist through telephone, skype or email whenever appropriate (as needed). In addition, patients and caregivers are asked to keep a diary to record daily exercise time, keep notes and record questions for the physical therapist. In the CARE4STROKE trial the intervention started as soon as possible after stroke in an inpatient setting. However, the program can also be conducted in an outpatient setting. Inclusion criteria for both patient and caregiver in the CARE4STROKE trial were: (1) motivation for CME, (2) able to understand the Dutch or English language, (3) 18 years or older, (4) written informed consent, (5) a score of <11 on the domain depression of the Hospital Anxiety and Depression Scale. Additional criteria for the patient were: (1) a functional mobility limitation (FAC <5), (2) willing and able to appoint a caregiver (with a maximum of two caregivers), (3) being able to understand and follow instructions (MMSE score >18 points), (4) living independently before the stroke, (5) planned to be discharged home. Patients and caregivers with a serious comorbidity that interferes with proper and safe execution of mobility training or with symptoms of depression should not participate.

After in- and exclusion criteria are checked an initial screening exercise session with a trained physical therapist is planned. In this exercise session the physical therapist evaluates if the patient – caregiver couple can safely and adequately perform the exercises together, allowing to start the start the CARE4STROKE program.

A detailed description of the content of the CARE4STROKE program can be found elsewhere.[12]

Data collection

The semi-structured interviews were undertaken in the setting of best convenience for the participants, either the current setting of rehabilitation of the patient or at their home, and were conducted by the first author (JV). JV is a rehabilitation physician and researcher and not the treating physician of the patients. She was trained in interview techniques before the start of the study by the second author (MD), experienced in qualitative research. The duration of each interview was approximately 1 hour, and the interviews were conducted in Dutch or English. All interviews were audio-recorded on a password-protected smartphone. In addition, the interviewer recorded field notes about the environmental setting, and, where applicable, interruptions or other relevant contextual matters.

The interviewer used a topic guide that was slightly different for patient and caregiver (Supplementary Material – Topic guide for patient and caregiver) and focused on training experiences, and feelings and attitudes about exercising with a caregiver.

After a brief explanation of the purpose of the interview, the researcher encouraged the participants to speak open and freely. The topics were flexibly adjusted according to the participants' perspectives. The researcher used techniques as summarizing, reflecting and comparing to assess the accuracy of her understanding and impressions. The researcher took communication problems, like aphasia and cognitive communication disorders, into account when interviewing the patients, and adjusted interview techniques when necessary. For example, when patients had a right hemisphere communication disorder, the researcher did not use metaphors. Participants knew that the interviewer was a rehabilitation physician and that she was involved in the CARE4STROKE study.

Data analysis

All of the recordings were verbatim transcribed by a paid, independent medical student. The transcripts were crosschecked by the interviewer. Inductive thematic analysis was used to interpret the data, which means themes were derived from the data and no a priori hypotheses were made.[20] We, therefore, also decided to analyse the interviews with patients and caregivers as a single data set. The interview transcripts were analysed independently by the researchers (JV, MD). Transcribed data at the manifest level was coded line by line and recurring themes were identified and listed, using citations from the interviews. During the process of analysing the researchers had multiple meetings in which themes were identified and compared for similarities and differences. Any data that did not fit the emerging themes was discussed and new (sub)themes were added when necessary. In addition, throughout this analysing process the researchers discussed data saturation. Concerning data saturation, the researchers discussed if there could be any new themes or further coding.[21] Interviewing participants continued until both researchers agreed data saturation was reached. In a final consensus meeting the two researchers determined the final themes. Themes were illustrated by citations of participants; no interpreter was used translating or interpreting the citations from Dutch into English.

RESULTS

Eight patients and nine caregivers were approached to be interviewed. One approached patient had new medical problems and with two approached caregivers an appointment could not be scheduled. The other seven patients and seven caregivers were interviewed. After these 14 interviews both researchers agreed data saturation was achieved. The age of the participants ranged between 44–79 years for the caregivers and between 27–76 years for the

patients. The modified Rankin Scale ranged from 2–5. Participants were interviewed between 4–22 months after their participation in the intervention. Even though it was intended to interview participants alone, in two patient-interviews the caregiver wanted to be present and in one caregiver-interview the patient wanted to be present allowing to add information. Characteristics of patients and caregivers can be found in Table 6.1 and 6.2.

Related to our first research question, how patient-caregiver couples exercise together, we identified one overarching theme about the distribution of roles between the patient and caregiver, with three different role-dynamics (1).

Related to our second research question, what brings exercising together about, we identified three themes: 2a) tailor made exercises through active involvement, 2b) preparation for the home situation, and 2c) opportunity to be involved. For neither of our research questions we found themes only for patients or only for caregivers.

1. The distribution of roles between patient and caregiver

Patient and caregiver are instructed to work together as a couple in CME. However, how the roles are distributed in terms of who is in charge, was found to be different per couple. We identified three role-dynamics: the patient in control, in concert, and the caregiver as informal carer.

The patient in control

In this role-dynamic the patient was in control in doing the exercises. He/she initiates the appointments to exercise together and initiates the start of the practicing: "*When my brother or niece (i.e. caregivers) were visiting, in the end I always said: oh yeah, we have to practice a bit.*" (Patient 6 (P6)) The tablet computer is owned and controlled by the patient and can for example be used by the patient, to instruct a second caregiver who did not attend the physiotherapy instruction session. The protocol dictates that after the patient agrees to participate, he/she carefully considers which person to ask to act as co-therapist. Patients 'in control' identified clear arguments about whom they chose. One patient (P6) told he asked his brother because "*he was a regular visitor*". Another patient (P4) specifically did not ask his wife to participate because "*the time investment would be too much for her. In addition, she would be too impatient*".

The patient realizes the caregiver is doing him/her a favour. One patient (P1) mentioned that he did not mind asking his relatives, however it "*was rather difficult of course, you take someone else's time*". He therefore chose to ask two relatives. In addition, the patients in this

Table 6.1 Characteristics patient participants

	Male/ Female	Age	Type of stroke	mRS	Characteristics caregiver(s) (relation – sex – age – working)	Months after intervention finished	Setting of interview	Remarks
P1	M	57	HCVA right	4	Sister – F – 56 – working Friend – M	13	Patients' home	
P2	M	72	ICVA left	3	Partner – F – 72 – retired	9	Patients' home	Partner was involved during interview
P3	F	27	ICVA right	3	Partner – M – 39 – working	10	Rehabilitation center	
P4	M	54	ICVA left	2	Friend – M – 41 – working	11	Rehabilitation center	
P5	M	50	ICVA right	4	Partner – F – 48 – working	4	Rehabilitation center	Drop out Partner was involved during interview
P6	M	43	ICVA right	4	Brother – M – 48 – working Cousin – F	8	Rehabilitation center	Mother (not the caregiver) was present during interview
P7	F	76	ICVA left	4	Daughter – F – 46 – working	4	Patients' home	

HCVA = haemorrhagic cerebrovascular accident (left or right hemisphere); ICVA = ischaemic cerebrovascular accident (left or right hemisphere); M = Male; F = Female; mRS = modified Rankin Scale:

1. No symptoms.
2. No significant disability. Able to carry out all usual activities, despite some symptoms.
3. Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
4. Moderate disability. Requires some help, but able to walk unassisted.
5. Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
6. Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
7. Dead.

Table 6.2 Characteristics caregiver participants

Number	Sort caregiver (male/female)	Age	Working?	Total number of caregivers involved	Characteristics patient (sexe – age – mRS Type of stroke)	Months after intervention finished	Setting of interview	Remarks
C1	Partner (F)	44	Working	1	M – 44 – 4 ICVA left	22	Patients' home	Patient with severe aphasia; Patient was present during the interview
C2	Partner (F)	57	Working	1	M – 48 – 4 ICVA left	18	Rehabilitation center	Patient with severe aphasia
C3	Daughter (F)	54	Working	2	M – 80 – 4 ICVA right	4	Patients' home	
C4	Partner (M)	79	Retired	2	F – 76 – 4 HCVA right	8	Rehabilitation center	
C5	Partner (F)	67	Retired	1	M – 73 – 4 ICVA left	6	Patients' home	
C6	Partner (F)	54	Not working	2	M – 59 – 5 HCVA right	7	Rehabilitation center	
C7	Partner (M)	77	Retired	1	F – 70 – 4 ICVA right	5	Patients' home	

HCVA = haemorrhagic cerebrovascular accident (left or right hemisphere); ICVA =- ischaemic cerebrovascular accident (left or right hemisphere); M = Male; F = Female; mRS = modified Rankin Scale:
1. No symptoms.
2. No significant disability. Able to carry out all usual activities, despite some symptoms.
3. Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
4. Moderate disability. Requires some help, but able to walk unassisted.
5. Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
6. Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
7. Dead.

role-dynamic could be worrying about the motivation of the caregivers. Patient P6 describes how he had to convince one of his relatives. He tells: "*Well, it was difficult to explain to her if doing exercises together would be really helpful for me*".

In concert

Patients and caregivers in this role-dynamic are in a close relationship and find it logical to practice together: "*We did everything together our whole life and still do.*" (Caregiver 2 (C2)) These caregivers spend a lot of time in the rehabilitation centre and are often asked together to participate in the study.

In this role dynamic, deciding at which time and place to practice is explicitly done in concert. In addition, doing the exercises often becomes a standard part of the visits in the rehabilitation centre or home routine. One patient (P7) tells that when her daughter came every day after work, "*we first exercised, then dined and finished with a cup of coffee*". Fatigue was often a consideration about whether to practice or not, as well as how much time the caregiver had.

The patient and caregiver have a shared goal: the best recovery of the patient as possible. One patient (P7) explains how her recovery was as important to her daughter as it was to her: "*She was so upset when my husband died. For her I was her only lifebuoy and nothing should happen to that. So she did everything she could*". When exercising, patient and caregiver often both perform the exercises. They for example walk together or do the exercises concurrently. The advantage for patients is that it is fun to do and that they can feel comfortable while doing the exercises: "*So when it was him by my side he would distract me and we would forget I had a stroke and just walk and talk about life. I wouldn't do that with a nurse or with a therapist. Because with him I have a real conversation, it's different.*" (P3)

The caregiver as informal carer

In this role-dynamic, the caregiver is the person who decides whether or not to participate and whether or not to practice. He/she mainly decides the moment of practice: "*it is just when you have the time in your own life to go … So every day I picked a time slot, but that was another one every day.*" (C1) The caregiver not only takes the initiative, he/she also sometimes has to stimulate the patient for practice: "*he (patient) did not feel like doing the exercises because they were a little bit painful and they cost him enormous effort, so yes, sometimes we (i.e. two caregivers: partner and daughter) had to stimulate him a bit.*" (C6) He/she is often the keeper of the tablet computer and uses it as a means to instruct and stimulate the patient regarding exercising. Doing the exercises seems more important to the caregiver than to the patient.

In this role-dynamic the patients are often the most severely disabled and have for example severe aphasia or a high modified Rankin Scale of 5 (= Severe disability. Requires constant nursing care and attention, bedridden, incontinent). The patient is not (yet) independent, and the caregiver has to take care of the patient. So, doing exercises together seems to be part of the standard care-tasks of this informal caregiver. One patient-caregiver couple stopped exercising but remained in the study. In their role-dynamic the caregiver was the informal carer. For her, doing exercises together was too time consuming and yet another task. She told (caregiver of P5): "*So, you are juggling a lot of plates, and then CARE4STROKE came and I thought: of course we do that. And then everything started and after 3 weeks I found out it this was all too much*".

2.a. Tailor-made exercises through active involvement

Doing exercises together, without a physical therapist, seems to make patients and their caregivers more actively involved in the rehabilitation treatment. Together they find out what works and what not. They ask for more and more specific exercises ("*I asked for exercises*" P6/C1) or take initiative on their own: "*Sometimes I did another exercise because I thought it was more useful*" (P1), and "*we made adjustments when we thought they made the exercises more effective*" (P7).

Patient and caregiver partner up with the physical therapist in compiling the treatment plan, allowing treatment to become more targeted to the individual patient. One patient (P4) noticed he could move his feet again during CME and tells: "*I immediately went downstairs and asked my physical therapist: I did this, don't you have an exercise so I can practice that (i.e. moving my feet)?*" Another caregiver (C1) mentioned asking the therapist for help with getting in and out of the car: "*for example in the car… we practiced that and he could do it. They showed me how and it gave so much freedom*".

Most participants describe that they watched the advised videos once or twice, and thereafter only sporadically. For some of the participants most exercises in the app were too easy or not applicable. Here also they partner up with the physical therapist, for example the patient (P4) who tells "*… later, I have done more challenging exercises than those on the iPad, in consultation with the physical therapist*".

2.b. Preparation for the home situation

Several partners indicated that doing exercises together gave them more insight in the patient's condition, which helped them later on in the home situation. One partner (C5)

for example explained: "*… participating gave me insight in what he could do and what he could not do. And what we need to work on and yes, what I need to watch out for…*". Another partner (C1) tells: "*I found it very nice to get a better sense of how to deal with someone who cannot do certain things, physically*". And later on in the interview she explains: "*It was in part because you get a kind of confidence on how to interact with each other*". In addition, patients also indicated that practicing together gave them and their caregivers more insight. Patient P6 for example mentions: "*To be able to learn or do things, which I did not even know I could do*". And "*… practicing with your caregiver, gives you more insight in your recovery*". About his caregivers he told: "*Caregivers also gain insight in your recovery*". Practicing together seems to lead to more understanding and patience, also when couples were at home. One patient (P2) noticed: "*I think it best to participate in CARE4STROKE as a couple, because it must be done together later on too*".

Furthermore, caregivers learn skills to help when necessary. One patient fell and needed to be lifted up, her partner (C4) explains: "*I used the grip they (the therapist, red) taught me to pick her up*". Another partner (C7) mentioned how he learned to support his wife during stair climbing. A third partner (C1) tells about how she learned to exercise the transfer from wheelchair to normal chair and climbing the stairs. Of the latter she mentions: "*That also opened many doors*".

2.c. Opportunity to be involved

CME provided caregivers an opportunity to show they are involved and want to actively contribute to the recovery of the patient. One caregiver (C5) found having influence on recovery agreeable: "*I think it is very good, when you can have a role, as partner, in the recovery of your partner*". A daughter (C3) described a positive effect on the relationship with her father: During the walking exercises, she had quite different conversations than when sitting during visiting hours, and she found this pleasant. Another partner (C6) tells about how the patient was very sick in the beginning. She and her family could not talk much with him. Doing exercises together gave them something concrete to do and be involved instead of feeling helpless and passive.

The opportunity to be involved is not only a need of the caregiver, patients also highly appreciate the involvement of the caregiver in their treatment. It allows them to show their improvements. A young female patient (P3) told: "*because if the person sees you're getting better, he won't think of the negative things, but he will try to be positive I guess. That's important*". Another patient (P6) describes how his caregivers "*saw real progress*" and got enthusiastic, which helped him and motivated him to perform the exercises.

DISCUSSION

The aim of this qualitative study was to gain insight in how the CARE4STROKE program, a CME e-health intervention, is executed and experienced by patients and caregivers. Our first research question was directed at how patient-caregiver couples exercise together and we identified an overarching theme about who is in control during CME. We found three different role-dynamics: the patient in control, in concert and the caregiver as informal carer. Our second research question concerned what does exercising together bring about, besides more hours of practice. We found three themes: tailor-made exercises through active involvement, preparation for the home situation, and opportunity to be involved.

The three types of role-dynamics that we identified, imply that there is no single type of 'caregiver exercise coach' during CME. When the patient is in control the task of coordinating CME is in hands of the patient, the patient has to motivate and persuade the caregiver and has to be thankful. This suggests that this role can become a burden for the patient and caution is needed for his wellbeing. On the other hand, when the caregiver is in control, caregiver burden needs to be monitored. In this role the caregiver does not only help with the exercises, but also finds him- or herself to be responsible for logistics/coordination, motivation and monitoring progress. When patient and caregiver work 'in concert' as a team, CME seems to empower them the most.[22] A recent review suggests that strain on the caregiver does not increase during CME.[11] Others have suggested that strain can even decrease because a CME program can prepare caregivers for their future role, by teaching them the appropriate coping skills.[23, 24] Providing care can then be a positive experience, especially when caregivers have higher levels of mastery.[25] Our findings suggest that strain during a CME program may be related to who is in control. This implies that in clinical practice, staff need to be aware and educated about these differences in role-dynamics. Wellbeing of patient and caregiver need to be monitored and possible unfavourable patient-caregiver interactions need to be re-directed. In addition, an open discussion between staff and the patient-caregiver couple about these aspects of CME seems important.[26, 27] It might be helpful to develop an instrument to screen for role-dynamics to increase awareness for all involved in CME.

As Galvin et al., we found that active involvement of patient and caregiver seems to lead to more tailor-made exercises and rehabilitation becomes more individualized.[17] These individualized specific exercises and skills help participants to be prepared for the home situation. Lutz and colleagues note that patients and caregivers are often not ready for the transition from rehabilitation to home.[28] Beunder et al. describe going home after a stroke as: 'that's when it really begins'.[29] Caregivers of stroke patients often report stress and burden,[30, 31] several studies indicate this is associated with the time required of the caregiver.[31] Caregivers

pinpoint skills training required to implement physical care and information provision, especially about cognitive and emotional changes, as the most important to prepare them.[29, 32, 33] CME might be effective and useful in preparation for return to home by being more 'hands on'[17] and being a combination of learning skills and getting insight in patients' functioning (physical, cognitive and emotional) outside the more controlled rehabilitation setting. In addition, this all could facilitate early supported discharge.[5, 9]

In addition, CME seems to bring and keep patients and caregivers closer together and more concerned with each other. This in line with previous results where family members also reported that the program gave them a sense of involvement in the recovery process. Importantly, this involvement was perceived as a positive experience in the program.[17]

A strength of this study is the use of the COREQ checklist, with which we aim to be complete and transparent in our reporting.[18] In addition, this qualitative study is complementary to the randomized controlled trial by providing more context about the experiences of the participants with the intervention, which has the potential to promote better understanding of the results of the randomized controlled trial.

To achieve a broad perspective about the topic and identify as much exercise situations as possible in the available time we interviewed patients and caregivers from different couples, not from the same couple. Future studies could further explore the factors that explain differences with respect to role-dynamics within couples. To prevent mutual contamination of responses, we aimed to interview participants without patient or partner being present. In three interviews, however, not only the interviewee was present, but also the partner (patient or caregiver). Persons might have given different answers without the presence of the partner. However, because in all the other instances participants were able to speak freely, we feel we adequately covered the spectrum of topics. In addition, regarding some themes we have more input from the patient and about other themes more from the caregiver. To maximize variation in the sample, we included participants with varying characteristics. However, we were limited by the available sample included in the randomized controlled trial and could for example include fewer male caregivers than females. Lastly, another limitation is that participants were included between 4 and 22 months after participating in the CARE4STROKE intervention. Although subjects did not mention difficulty recalling aspects of their participation during the interviews, presence of some recall bias cannot completely ruled-out.

CARE4STROKE is a CME program combined with e-health tools. During the interviews we asked about experiences, likes and dislikes of participants when using the tablet computer and app to stimulate recall and provide some context for the results of the intervention

study. We did not specifically report about these aspects because they are outside the scope of our research questions.

CME programs are studied and implemented worldwide, for example Australia,[14] Ireland[23] and India.[15] The CME programs differ, and different effects are found. The recently performed ATTEND trial with 1250 participants in India, for example, showed no positive trends to favour family-delivered rehabilitation services at home in terms of the modified Rankin Scale.[15] However, the content of this intervention and caregiver selection was more diluted when compared to CARE4STROKE. In addition, one might question the generalisability of this intervention that is designed for a low-middle-income country, cross-cultural differences might exist.[16] It is likely that how participants manage to do the exercises together will also differ between cultures. Future research should study these cross-cultural differences to support optimal implementation of CME in different countries.

In the present qualitative study, we identified information that is relevant for further improvement and implementation of CME, in clinical practice or future studies. We found three different role-dynamics. When the patient is in control or the caregiver has the role of the informal carer, CME can become a burden for them. We advise to educate the participating staff about the different role-dynamics during CME and carefully monitor strain of caregiver and patient. In all role-dynamics, in addition to having more exercise time, additional effects of CME were found. Treating therapists could utilize CME in individualization of the treatment plan and preparation for home discharge.

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Implications for rehabilitation

- Caregiver-mediated exercises, in which a caregiver does exercises with a patient, are currently under investigation as a new form of augmented exercise delivery after stroke.
- Doing exercises together seems to make patient and caregivers actively involved in rehabilitation, which they appreciate, and which seems to help them prepare for the home situation.
- Caregiver selection and monitoring role-dynamics during exercising is an important task of the rehabilitation team.

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SUPPLEMENTARY MATERIAL – COREQ CHECKLIST

No	Item	Description
Domain 1: Research team and reflexivity		
Personal characteristics		
1	Interviewer	First author (JV) conducted the interviews
2	Credentials	JV is a medical doctor
3	Occupation	JV is a rehabilitation physician and researcher
4	Gender	JV is a female
5	Experience and training	JV conducted some test interviews before start of the study to get experience with interviewing participants and discussed them with MD, an experienced qualitative researcher
Relationship with participants		
6	Relationship established	JV was not treating physician of the patients. In one interview with a caregiver she was the treating physician of the corresponding patient.
7	Participant knowledge of the interviewer	Participants knew that the interviewer was a rehabilitation physician and that she was involved in the CARE4STROKE study
8	Interviewer characteristics	JV is co-iniator of the CARE4STROKE study
Domain 2: Study design		
Theoretical framework		
9	Methodological orientation and theory	Inductive thematic analysis was used
Participant selection		
10	Sampling	Participants were purposively selected
11	Method of approach	Participants were approached by letter, and a week later called
12	Sample size	14 participants were in the study: 7 patients and 7 caregivers
13	Non-participation	2 approached caregivers did not participate because the making of an appointment did not work out. 1 approached patient did not participate because of other medical problems.
Setting		
14	Setting of data collection	Interviews were held at the location of participants' convenience. This was at their homes or in the rehabilitation center.
15	Presence of non-participants	In two patient interviews the caregiver was present and added information. In one caregiver interview the patient was present. In one patient interview another relative was present who did not act as caregiver during the study. (See also Table 6.1 and 6.2)
16	Description of sample	See Table 6.1 and 6.2
Data collection		
17	Interview guide	Topic guides were used
18	Repeat interviews	No repeat interviews were carried out
19	Audio/visual recording	All interviews were audio recorded with a password protected smartphone
20	Field notes	Some field notes were made after an interview was done about setting, sphere and, where applicable, interruptions
21	Duration	The duration of the interviews was about one hour

No	Item	Description
22	Data saturation	Data saturation was achieved after 14 interviews. Researchers determined data saturation in consensus meetings.
23	Transcripts returned	Transcripts were not returned to participants for comment and/or correction
Domain 3: analysis and findings		
Data analysis		
24	Number of data coders	Two researchers (JV and MD) coded the data
25	Description of the coding tree	Not applicable
26	Derivation of themes	Recurring themes were identified and listed. These were compared for similarities and differences and final themes were identified. Any data that did not fit the emerging themes was discussed in a consensus meeting (JV, MD) and new (sub) themes were added when necessary.
27	Software	No software was used
28	Participant checking	Participants did not provide feedback on the findings
Reporting		
29	Quotations presented	Quotations are presented and identified with a participant number
30	Data and findings consistent	They are consistent
31	Clarity of major themes	For research question one, one major theme is described. For research question two, three major themes were described.
32	Clarity of minor themes	In the description of the major themes diverse cases are discussed. No minor themes are described.

SUPPLEMENTARY MATERIAL – TOPIC GUIDE: PATIENT AND CAREGIVER

Topic guide patient

[General]

How are you doing now?

How do you look back on the rehabilitation?

You practiced together with a caregiver during the rehabilitation? How was this for you?

[Who, where, when, how]

With who did you practice? How was it to ask this person? Did you practice with one or two caregivers?

Where and when did you practice? How did you decide where and when you would practice? How often did you practice?

Can you describe how you practiced together?

[Physical therapist]

Did you do the exercises described by the physical therapist? Did you do other exercises? Who decided that?

How was it to exercise without a physical therapist?

What would you change in the involvement of the physical therapist?

[Tablet computer and e-health]

Did you use the tablet computer? How and how often?

What did you think of the CARE4STROKE app?

What would you change to the CARE4STROKE app or the videos in the app?

Did you ask the physical therapist for advice in between the exercise sessions? How, did you for example use email or phone?

[Diary]

You were asked to keep a diary, how was this?

Did your caregiver help with the diary?

[Through time]

How long did you continue to practice together? If you stopped, what were the reasons?

Did you have enough time to practice? Were you able to practice in addition to your regular schedule? Was your caregiver able to make time in addition to his or her regular schedule?

[Relation with your caregiver]

How do you think your caregiver found the program? Did he/she like to do it, or not?

Was doing exercises at the expense of other visits? Had you spend the time with your caregiver rather on a different way?

Did doing exercise influence your relationship? How?

[Evaluation]

Did you make progress? Do you think the program helped you?

Did the program change your confidence?

Did the program give you information for the future?

Would you recommend the program to others? Why?

What would you change in the program?

Topic guide caregiver

[General]

How are you doing now?

How do you look back on the rehabilitation of the patient with stroke you exercised with?

How was it for you, to practice together?

[Who, where, when, how]

What was your relationship with the patient with stroke? How was it to be asked to practice together? Were you the only one exercising with the patient, or were other caregivers also asked?

Where and when did you practice? How did you decide where and when you would practice? How often did you practice?

Can you describe how you practiced together?

[Physical therapist]

Did you do the exercises described by the physical therapist? Did you do other exercises? Who decided that?

How was it to exercise without a physical therapist?

What would you change in the involvement of the physical therapist?

[Tablet computer and e-health]

Did you use the tablet computer? How and how often?

What did you think of the CARE4STROKE app?

What would you change to the CARE4STROKE app or the videos in the app?

Did you ask the physical therapist for advice in between the exercise sessions? How, did you for example use email or phone?

[Diary]

Did you help to keep the diary?

[Through time]

How long did you continue to practice together? If you stopped, what were the reasons?

Did you have enough time to practice? Were you able to practice in addition to your regular activities? Was the patient with stroke able to make time in addition to his or her regular schedule?

[Relation]

How do you think the patient with stroke found the program? Did he/she like to exercise together, or not?

Was doing exercises at the expense of other visits? Had you spend the time with the patient with stroke rather on a different way?

Did doing exercise influence your relationship? How?

[Evaluation]

Do you think the program helped the patient with stroke?

Did the program change your confidence, and/or that of the patient with stroke?

Did the program give you information for the future?

Would you recommend the program to others? Why?

What would you change in the program?

Chapter 7

General discussion

This thesis is focused on investigating the effects and effectiveness of caregiver-mediated exercises (CME) in the context of stroke rehabilitation. With CME, the patient with stroke and a caregiver are trained to perform exercises together to increase intensity of exercise training for the patient after stroke. The caregiver can for example be a partner, family member, neighbour or friend. In this chapter we will summarize our main findings and critically appraise our results in light of the current focus of stroke services on Early Supported Discharge (ESD). From this perspective, we give recommendations on how to move forward with CME.

Main findings

First, we evaluated the current evidence for CME by summarizing and systematically reviewing the available evidence of published trials in this field using Cochrane methodology (**chapter 2**). Up to December 2015, nine trials investigating CME in stroke rehabilitation were found. Six trials, involving 333 patient-caregiver couples in total, could be included in quantitative (meta-)analysis. The included studies were small numbered, heterogeneous in methodological quality, type of intervention (e.g. in terms of content, timing and duration) and outcome measures which affected the internal validity as well as the generalizability of the observed results. The overall quality level of the evidence was rated as very low to moderate. No differential effects between CME and control group were found for the outcome measures basic and extended ADL, and caregiver burden. However, CME did significantly improve outcome measures of standing balance, quality of life and walking distance.

Subsequently, in **chapter 3**, we described the rationale and content of an innovative CME intervention program with the acronym 'CARE4STROKE' aimed at improving self-reported mobility and decreasing length of inpatient stay (LOS). In this program we combined CME with e-health, including tele-rehabilitation services. The CARE4STROKE program is an 8-week rehabilitation therapy program in which a patient with stroke performs exercises with his or her caregiver. The exercises focus on mobility and are done in addition to usual care, 5 times a week for 30 minutes per session. A trained physical therapist compiles an incremental training program from the 37 standardized exercises which are available in a custom-made app. Once a week, the patient-caregiver couple has a face to face session with the trained physical therapist in which exercises of the previous week are evaluated and a new or modified exercise program is selected and practiced. The TIDieR checklist was used to describe this complex rehabilitation intervention in detail to facilitate implementation and make future replication possible.

Thereafter, we presented the design (**chapter 4**) and results (**chapter 5**) of a proof-of-concept, observer-blinded, randomized controlled trial to reveal the effects and effectiveness of the CARE4STROKE program compared to usual care. We found no significant effect of CME on the primary outcome measures self-reported mobility, in terms of the Stroke Impact Scale 3.0 mobility domain, or LOS. Post-intervention, we did find a significant effect in favour of the intervention group for patients' anxiety and caregivers' depression, according to the Hospital Anxiety and Depression Scale. This significant reduced anxiety of patients sustained at follow up. Patients in the intervention group exercised significantly more together with caregivers, compared to the control group (1190 minutes versus 480 minutes). However, our aim to increase intensity of training in the intervention group beyond a treatment contrast of minimal 16 hours[1] was not fully reached. The total exercise time (i.e. the time combined the patient exercised in therapy, with a caregiver, with a nurse and independently) did not differ significantly between the intervention and control group.

Finally, we presented a qualitative study (**chapter 6**) which focused on how participants managed CME together. The results show that the distribution of roles during CME, in terms of who is in charge, varied per couple. Three different role-dynamics were found during CME: 1) patient in control, 2) in concert, 3) the caregiver as informal carer. Furthermore, three additional themes were identified. First, doing exercises together elicits a more active involvement from patient and caregivers in the rehabilitation treatment as they ask for more and more specific exercises. Second, CME provided caregivers and patients with more information about what the patient can and cannot do. Participants indicated this helped them to prepare for when the patient would come home, because they knew what to expect. Third, CME provided caregivers an opportunity to be involved and made it possible to actively contribute to the recovery of the patient. Overall, the involvement of the caregiver is also highly appreciated by the patients, since it gives them the opportunity to show their improvements to their loved ones.

REFLECTION ON OUR RESULTS

Pragmatic phase II trial

We deliberately chose for a randomized controlled trial design to support CME as a 'proof of concept', acknowledging that this design offers the lowest bias in identified results. While we found no significant differences concerning the primary outcome measures self-reported mobility and LOS, our results did show that the CARE4STROKE intervention is a neutral, but safe and feasible approach. In addition, a parallel trial conducted in Adelaide (Australia), using the same design, measurement and intervention protocol, found a 9-day reduction

of LOS in a per-protocol analysis examining 20 patients who were discharged home with tele-rehabilitation.[2] The fact that we did not fully reach the treatment contrast might be an explanation for not finding significant effects in our trial concerning the primary outcome measures. CARE4STROKE aimed to increase functional outcome and to facilitate ESD[3-5] by increasing the intensity of exercise training after stroke.[6, 7] In our trial as well as the trial conducted in Adelaide, patients with stroke did exercise significantly more with a caregiver in the intervention group compared to the control group. However, the contrast in total exercise time (i.e. the time combined the patient exercised in therapy, with a caregiver, with a nurse and independently) was not significantly different after the proof-of-concept trial. A possible reason might be contamination, e.g. the possibility that patients in the control group also did copy the applied caregiver exercises. The problem that the control group gradually adapts to the experimental group is often seen in stroke rehabilitation trials that take many years to finalize.[8, 9] However, the number of minutes that patients reported to exercise with a caregiver was significantly less in the control groups (our trial 8.6 minutes/day; Adelaide trial 5 minutes/day) versus the intervention groups (our trial 21.3 minutes/day; Adelaide trial 20 minutes/day) which suggests no major indications for contamination during both trials. According to therapists and nurses, another reason that may have affected total exercise time in our trial is, that their effort may have been directed more towards the support of patients in the control group, in order to compensate for having less exercise time during the trial. In addition, therapists mentioned that they may have considered the extra CARE4STROKE training as too strenuous, in light of (physical) possibilities of the patient and therefore cut back on other therapy time. One might conclude that rehabilitation professionals and organizations are still not permeated with the necessity to provide more therapy to patients with stroke.[10] In recent trials augmented intensities with 90 hours up to even 300 hours additional exercise therapy is studied and the results suggests that even more hours of therapy, compared to the number of hours found in previous trials,[6, 7] might be necessary to introduce clinical meaningful differences in stroke rehabilitation trials.[11-13] In that light, further changes to our organizational structures and mindsets are necessary, in order to provide patients with sufficiently intensive therapy after stroke.

An alternative explanation for not finding significant differences, might be that our primary outcome measures SIS mobility and LOS are not responsive enough for CME induced improvements. The Stroke Impact Scale Version 3.0 (SIS) is a self-reported questionnaire which is a subjective measure of mobility. It measures the patients' perception about mobility and response shift may occur.[14] However, the SIS has shown excellent clinimetric properties and is widely used in stroke rehabilitation.[15-20] Although no significant differences were found regarding SIS mobility, walking speed or other functional tests in our trial and the

trial in Adelaide, in both trials a trend towards significance for SIS mobility was found which justifies further investigation of the domain mobility in a cost-effectiveness, phase IV trial. In addition, it should be considered to investigate mobility in a more objective way in order to prevent response shift. A systematic review in 2010 and several subsequent studies showed that wearable activity monitors yield valid and reliable data about the physical activity of patients with stroke[21-23] and are for example, used to identify different movement behaviour patterns.[24] However, the literature concerning activity monitors in stroke research is still young, limiting the ability to draw firm conclusions.

A limitation of LOS as outcome measure is that it is not only influenced by patients' mobility and other functional outcomes, but by other non-clinical factors as well.[25] Due to randomization, these factors will be fairly balanced between the intervention and control group. However, during our trial, health care policy and financing changed by making LOS more pre-defined, standardized and less flexible. We therefore might have found less differential effect between the intervention and control groups. In general, in the Netherlands LOS in a rehabilitation centre is already gradually decreasing. In the year 2000, patients were admitted a mean LOS of 91.5 days, while in 2015 the mean LOS after stroke was 43 days.[26] The possibility to further reduce the duration of inpatient care in rehabilitation centres may therefore be limited and certainly not the same as for example in the Australian health care system. Acknowledging this restricted time window of inpatient stay, future programs should investigate if ESD combined with CME at home may be an alternative way to improve patient's activity and participation in the community.

In addition to LOS as outcome measure for costs an economic evaluation took place alongside our trial. This economic evaluation was performed from a health care perspective and a societal perspective. This means that on the one hand costs for, for example, days of admittance and doctor visits were included. On the other hand, costs for effort of the caregiver were included, such as loss of work production. No significant differences were found between intervention and control group (unpublished data). This latter finding suggests that CME can be added to usual care without extra costs.

Effects on mood

We did find a significant positive effect of CME on secondary outcomes of mood in terms of patients' anxiety and caregiver' depression in the CARE4STROKE trial. These results are further supported by the semi-structured interviews where participants indicated to feel more involved and informed. Other studies about CME, found a significant reduction of caregiver fatigue and improvement of self-efficacy,[2] improvement in quality of life (our

systematic review), CME as empowering experience[27] and sense of involvement.[28] There are two validity issues to consider regarding the positive effects found on mood, a statistical and a methodological issue. First, in our randomized controlled trial a multiple testing problem could have occurred. A number of outcome measures were tested, and we did not statistically correct for multiple testing. However, we have consciously opted for this, the trial being a proof-of-concept trial with the aim to determine whether CME is efficacious, and if so, in which outcome domains. Secondly, qualitative research is more subject to bias of the interviewer and it is not possible to prove statistical relationships. However, our study does give valuable insights in experiences with the intervention and direction for future studies. In addition, the fact that the positive effects on mood found in the randomized controlled trial were confirmed in the qualitative study strengthens the evidential value.

The beneficial effects on mood in terms of reduced anxiety of patients and reduced depression suggest that CME supports patients and caregivers in their perceived burden. One of the reasons might be that CME may help to bridge the gap between patients' and caregivers' expectations of recovery and residual disability.[29] This because patient and caregiver are more aware of patient's abilities and progress and are more involved in the process of rehabilitation. Another reason might be that CME can be seen as a sort of 'skill building' intervention, i.e. an intervention that equipped the caregiver with skills to provide care to the stroke survivor or skills to cope with the caregiver role. In a systematic review considering caregiver interventions, skill building seemed the most effective approach to reduce psychological distress and burden.[30]

Available evidence for CME in literature

In our systematic Cochrane review we summarized the evidence for CME. In this review we distinguished between trials in which CME was the intervention (defined as CME-core) and trials where caregivers provided another intervention, such as constraint induced movement therapy. In the latter trials, CME was more a mode of delivery rather than an intervention in itself. This distinction between CME-core trials and non-CME-core trials is debatable. One might also argue that CME is always a mode of delivery of a specific form of training, whether it is a modified version of constraint-induced movement therapy (mCIMT), neglect training or mobility training as in CARE4STROKE. However, the large differences in primary focus lead to heterogeneity between studies and make pooling less appropriate. This argues for making a distinction between CME-core and non-CME-core trials.

Our review included trials up to December 2015. Thereafter, more trials studying CME in stroke patients were published. These trials included outcome measures focused on

(extended) ADL[2, 31-33] and caregiver burden.[2, 31, 33] All these trials are neutral with respect to caregiver burden. This strengthens our finding that CME does not increase caregiver burden. Van den Berg et al even found reduced caregiver fatigue and increased caregiver self-efficacy.[2] Similarly, ESD interventions also have no adverse impact on mood or subjective health status of caregivers.[5] Results on (extended) ADL, concerning CME interventions, are not conclusive. Lee et al used basic ADL as a measurement of outcome, but did not adequately analyse the results by focusing on the within-group differences instead of between-group differences.[32] With respect to extended ADL, one study found a significant difference in favour of CME on the Nottingham Extended ADL questionnaire in a per-protocol analysis.[2] In contrast, the high-quality phase III trial 'ATTEND' with 1250 participants in India, showed no significant difference in ADL or any other outcome measure.[31] However, their CME program was quite broadly aimed at, among other things, upper limb function, mood management, positioning, transfers and mobility. The broad-spectrum program in ATTEND may therefore have been too diluted and by that too weak to cause significant differences. In addition, the dose of exercise therapy may have been insufficient as only about 30 minutes of therapy daily was reported by participants in the intervention group. In total, the ATTEND intervention seems not able to provide progressive high-quality exercise training for the patient. Finally, one might question the generalizability of these findings, since the intervention was designed for a low-middle income country, and cross-cultural differences might exist.[34]

In summary, we found the CARE4STROKE intervention to be safe and feasible, with no increase in costs. In addition, our proof-of-concept trial and qualitative study showed favourable effects on mood and quality of transition from inpatient care to the home situation. Finally, in literature we found improvements on quality of life, walking distance, standing balance, basic ADL and mood, without an increase in caregiver burden. We think these findings justify proceeding with the concept of CME in a larger phase III or phase IV cost-effectiveness trial targeting more the quality of transition from inpatient rehabilitation care to their own home situation.

ISSUES TO CONSIDER CONCERNING CME PROGRAMS

Involvement of the caregiver

CME are completely dependent on the availability of a caregiver. In an interim analysis, we found that 17% of our excluded patients (80 out of 508 screened patients) were eligible for participating in the CME program, however lacked an available, willing and/or suitable caregiver to support them during CME.[35] Within this group, more than 30% (N=25) could

not appoint a caregiver and about 15% (N=12) did not want to ask a caregiver. In the remaining part of the excluded group (N=43), caregivers indicated they were unwilling to participate, had insufficient time to provide the required dose of training, or caregivers were not medically stable, strained or depressed. The fact that our study took place in an urban area (Amsterdam) may be a potential explanation for this exclusion rate of 17%. However, the number of single households is quite similar compared to rural areas (1 in 2 households in urban areas, compared to 4 out of 10 in rural areas).[36] In addition, social networks seem only slightly larger in rural areas (contact with family members 52.2 versus 51.1%, neighbours 53.1 versus 42.7% and friends 51.1 versus 48.3%).[37] In other words, it remains questionable if CME might be easier to implement in a rural area. The CME trial conducted in Adelaide also reported information about excluding patients who were 'unable to appoint a caregiver'. This was about 10% of the eligible patients. However, they did not describe the reasons of exclusion in more detail.[2] Unfortunately, other trials do not report about the caregiver as reason for exclusion.

These numbers lead to two important considerations. First, patients are currently more and more asked to appeal to their social network when in need (in Dutch: 'participatie-maatschappij'). However, our findings highlight that not every patient is able to appoint a caregiver or does not want to appoint a caregiver. Policy makers and staff members should be aware of these numbers and provide alternative options for these patients. The help of volunteers, therapy assistants, paid caregivers[38] or other means (for example self-training, with robotic devices, or with a therapist) to provide more therapy should be considered. In addition, not every caregiver is willing and/or able to provide care when asked. Giving informal care is not as custom for native Dutch people as it is for immigrants with other cultural backgrounds.[39] However, the need for informal care increases in a society in which the aging population is growing and the resources in health care are declining. There might be alternative solutions to support caregivers. One such solution is to provide caregivers with a financial 'informal care contribution' ('mantelzorgbijdrage') given by an employer to an employee with informal care duties.[40] With this contribution, a caregiver can make his or her own decisions about how to provide informal care and can, for example, use this contribution to hire someone else to provide informal care.

Secondly, in rehabilitation practice it can be difficult to actively involve caregivers during the rehabilitation process for a number of reasons. Examples are (cultural) expectations from caregivers and health care professionals about care and involvement, and time restrictions of caregivers with respect to obligations such as work or other activities. In this context, we must also ask ourselves if we offer caregivers enough support during the rehabilitation of their loved one. Support is offered, but appointments are often during working hours and

benefits for the caregiver are not specified. While there is a need for further information about the unmet needs of the caregivers,[41] CME programs might already be helpful as a structured program defining clear goals and expectations.

Type of setting

Another important consideration is the setting of CME. In the CARE4STROKE trial patients were recruited in hospitals, rehabilitation centres and geriatric rehabilitation departments of nursing homes. In the trial design phase, separate analyses for these different settings were planned. However, during the inclusion period it became clear that almost none of the participants were included in hospitals and very few in geriatric rehabilitation departments. In the Netherlands, the average LOS in a hospital after ischemic stroke is 7 days for men and 8 days for women.[42] Of all stroke patients, admitted to a hospital, 60–70% are discharged directly to their own home in the first days post stroke, often with mild disabilities. Our randomized controlled trial showed that the hospital stay in the Netherlands is too short for our strict step-by-step recruitment procedures which takes several days. However, the continuum of stroke care starts in the hospital and future CME programs can have their start in the hospital to accelerate recruitment. For example, by giving information about the CME program and start with the screening for possible inclusion of patient and caregivers. CME can thereafter continue in a rehabilitation setting or at home.

In the CARE4STROKE trial only a few participants (N=10, 15%) were included in geriatric rehabilitation departments, where patients are older, may be more vulnerable physically and/or mentally, and co-morbidities are more often reported.[43, 44] Therefore, patients may be less able to practice independently. In addition, the social networks of older patients are probably different in size and composition. Partners and same aged friends might be less able to physically and mentally support patients. The possibility to use CME might therefore be more dependent on the availability and willingness of their children or other family members who may have a busy work and family life. Due to the limited inclusion in geriatric rehabilitation departments, we were unable to provide separate analyses for this type of health care setting. However, in order to support CME, Lawler and colleagues did show that CME in older adults (mean age 84.1 years) is safe and feasible.[45] They studied a CME program in 35 patients with multimorbidity (five with a stroke) transitioning from hospital to the community. They did not find significant between-group differences for their primary outcome measures falls-related self-efficacy and falls. Patients receiving CME did walk twice as many daily steps compared to the control group and had a significant reduction in activity limitation. However, the total minutes exercise therapy applied additionally was lower than in our study (56.3 minutes/week versus 148.8 minutes/week) and they did not

report about treatment contrast. Because of the large number of people with stroke admitted in geriatric rehabilitation wards, further investigation of CME in geriatric rehabilitation and the difference with other settings does seem useful. A qualitative study aimed at clarifying the barriers concerning CME might help to modify the CME program for better use in these settings. One might hypothesize that adjustments in the CME program for example regarding difficulty or quantity of the exercises are necessary, as also adjustments in mindsets of therapists and organizations, for example about increasing intensity of training in geriatric rehabilitation and what the role of a caregiver can be.

Is the Care4Stroke program generalizable?

A final consideration is for which diagnosis and symptoms CME might be applicable. The current CARE4STROKE program is specifically aimed at patients with stroke who experience mobility problems. Experiencing (severe) cognitive and communicative impairments are often a huge burden for patients as well as for caregivers[46] and a CME program for patients with cognitive impairments or aphasia might increase understanding about the abilities of the patient, as we found that our program did for awareness of the mobility problems. In addition, CME is already used to provide a modified version of constraint induced movement therapy.[47-50] However, it might also be very well applicable in other upper limb training programs, especially when a high number of training sessions a week must be provided and part of these sessions could be executed with CME. Another example is to use CME in fall prevention training.

The above reasoning might also be true for other diagnosis groups in rehabilitation medicine. Our research group has extended the CARE4STROKE program to a group of patients with acquired brain injury, within the CARE4BRAIN study, of which the results will follow. In addition, CME programs might also be useful in for example spinal cord injury rehabilitation or rehabilitation after amputation.

IMPLICATIONS

CME as a tool

The results presented in this thesis show that CME with e-health tools, including tele-rehabilitation services can be performed safely, are appreciated by patients and caregivers, has positive effects on mood, and can be implemented in rehabilitation practice with minimal use of staff members. No significant adverse effects compared to the control group were found in the CARE4STROKE trial or in our systematic review. We can therefore conclude

that CME can be used by therapists as one of the tools to provide rehabilitative exercise therapy. To assure that the patient-caregiver couple is able to exercise together in a safe way, we advise a strict procedure including a practice exercise session, such as designed in the CARE4STROKE program. All evidence until now shows that caregiver strain does not increase with CME, or even decreases. However, following the results of our qualitative study which suggested that caregiver strain may increase when the caregiver takes the role of the informal carer, we recommend to always monitor caregiver strain during a CME program.

Future CME programs

In current times rehabilitation is primarily aimed at learning basic skills and safe return home, however a large part of the recovery will take place in the home situation.[26] ESD, defined as 'an intervention for adults after stroke that allows their care to be transferred from an inpatient environment to a community setting'[51] is therefore becoming more and more important as an alternative for usual care. It can reduce long-term dependency, admission to institutional care and reduce length of hospital stay.[5] Currently, there is a shortage of ESD services in European countries. The stroke alliance for Europe (SAFE) defined as target for 2030 to provide ESD to at least 20% of stroke survivors in all countries.[52] 'ESD enables patients to continue their rehabilitation therapy at home, with the same intensity and expertise that they would receive in hospital'.[51] However, at this moment rehabilitation therapy rarely continues with the same level of intensity and expertise. CME programs might, in the future, fulfil a role in bridging this current gap of care and can be used as part of an ESD intervention. CME programs might than encourage patients to stay active and decrease sedentary behaviour.[24, 53]

In the design of future CME programs should the following three aspects be taken into account. First, CME programs could be used during the whole rehabilitation phase from inpatient rehabilitation, through discharge, and continue after discharge in the home situation. Because the transition from rehabilitation setting to the home situation is often reported as a significant hurdle leading to stress and burden[54-58] and our results suggests CME to be helpful in this transition, implementation around discharge should especially be encouraged.

Second, CME programs could be supported by more tailored e-health tools, including tele-rehabilitation services. Although evidence for using e-health tools or tele-rehabilitation alone remains limited,[59-63] these techniques may be well suited to support evidence-based interventions.[63] The latter is confirmed by our work which shows that the use of e-health to support CME is feasible. In the outpatient or community setting e-health tools are even

more important and could facilitate remote coaching and monitoring by therapists to ensure safety when performing the exercises at home. In future CME programs face-to-face sessions with a therapist may be replaced by tele-rehabilitation sessions, for example. The use of activity monitoring devices as a feedback instrument for patients in order to motivate them to increase their activity level[64] might be another example of an e-health tool that could be part of a CME program.

Third, CME programs could be developed in such a way that they promote independence in patients and progressively reduce the level of caregiver support over time, leading to better self-efficacy and quality of life, and reduced levels of anxiety and depression for both patients and caregivers. This could be effectuated, for example, by starting the program with only exercises for the patient-caregiver couple together and then continuing, over time, by introducing also exercises for the patient alone.

Implications for future research

To further confirm the usefulness of CME, future studies are warranted. There are a number of considerations concerning future trial design. First, to prevent contamination a cluster randomized trial design is worth to consider as a next step.[65, 66] Patients should, therefore, be included in a number of hospitals, rehabilitation centres and nursing homes. Second, a more extensive economic evaluation should be part of the study design, especially concerning the role CME can have in an ESD intervention. Alternative outcome measures should hereby be considered to quantify the effects of CME on psychosocial functioning and transition from rehabilitation setting to the home situation. For the latter, a tool quantifying how patient and caregiver experience the transition from inpatient rehabilitation to the home situation like the Care Transitions Measurement[67, 68] might be used although this measurement applies more to the transition from hospital to home. A better option can therefore be to measure how prepared caregiver and patient are for their roles at home in future CME trials. This could be measured with the preparedness for caregiving scale which is a valid and reliable outcome measure in caregivers of stroke survivors.[69-71] Both outcome measures have not yet been translated and validated in Dutch.

Finally, to determine in which setting CME is most effective, CME could be studied in patients with other impairments after stroke, and more specific in the outpatient rehabilitation setting, geriatric rehabilitation setting, and at home. A consideration could be to use broader inclusion criteria. This applies in particular to the inclusion criteria concerning mood. The effects found on mood for both patients and caregivers lead to the hypothesis that CME might also decrease symptoms of anxiety and depression in participants who are

already anxious or depressed. Of course, further validating the effects on mood and close monitoring these participants is necessary.

CME programs are already studied around the world, in for example Ireland,[72] Australia,[2, 45] and India.[31] However, the use of CME programs is not the same everywhere. CME is either used as a replacement for usual care with the aim of giving therapy even though there are few resources. This form is mostly used in low-income countries. Or CME is used as an addition to usual care with the aim to increase intensity of exercise training and thereby improve functional outcome. Hereby, the content of the current CME programs differs widely. Not all programs include patient-tailored practice with a progressive training program supported by e-health, as in CARE4STROKE. We believe these differences are also related with cross-cultural differences like the role of a caregiver when a loved one gets ill, travel distances to rehabilitation facilities or the (financial) possibilities within a health care system. For further development and implementation of CME, consensus about the concept, definitions, outcome and dosing is needed. Along that line it is useful to examine cross-cultural differences and to learn from these differences with respect to implementing CME. We made a start to examine cross-cultural differences by comparing the results of the studies in the Netherlands and Adelaide, Australia (Mulder et al., manuscript in preparation).

Our research group continues to investigate CME. Meanwhile, we developed an improved version of CME with a different timing, more attention for goal setting and emphasis on augmentation of internet-based tele-rehabilitation services to prevent inactivity at home. This intervention is studied in the recently started ARMED4STROKE (Allied Rehabilitation using caregiver MEDiated exercises for Stroke) trial financed by a KNGF-ZonMw grant. I am looking forward to continuing to study the concept of caregiver-mediated exercises, hopefully in a larger multicentre phase IV, cost-effectiveness trial, and find the optimal way of implementing CME in rehabilitation practice.

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List of abbreviations

ADL	Activities of Daily Living
ARAT	Action Research Arm Test
BBS	Berg Balance Scale
BI	Barthel Index
CI	Confidence Interval
CIMT	Constraint-Induced Movement Therapy
CME	Caregiver-mediated exercises
COREQ	Consolidated criteria for reporting qualitative research
CSI	Caregiver Strain Index
CSI+	(Expanded) Caregiver Strain Index
C4S	Care4Stroke
ESD	Early Supported Discharge
EQ-5D	EuroQoL
FAC	Functional Ambulation Categories
FAI	Frenchay Activities Index
FIM	Functional Indepence Measure
FM	Fugl Meyer
FMA	Fugl Meyer Assessment
FSS	Fatigue Severity Scale
GEE	Generalized Estimating Equations
ICER	Incremental cost-effectiveness ratio
ICT	Information and Communication Technologies
ICVA	Ischeamic Cerebrovascular Accident
HADS	Hospital Anxiety and Depression Scale
HCVA	Haemorrhagic Cerebrovascular Accident
KNGF	Koninklijk Nederlands Genootschap voor Fysiotherapie
LOS	Length of (inpatient) Stay
MD	Mean Difference
MI	Motricity Index
MICE	Multiple Imputation by Chained Equations
MMSE	Mini Mental State Evaluation
MRS	Modified Rankin Scale
NEADL	Nottingham Extended ADL Index
RCT	Randomized Controlled Trial
RMI	Rivermead Mobility Index
SAFE	Stroke Alliance for Europe
SD	Standard Deviation

SE	Standard Error
SIS	Stroke Impact Scale
SMD	Standardised Mean Difference
TIDieR	Template for Intervention Description and Replication
TUG	Timed Up and Go Test
QALY	Quality Adjusted Life Year
QOL	Quality of Life

Summary

Stroke is the third most common cause of disability in the world. Effects of stroke vary from minor neurological symptoms to severe deficits, that can have a major impact on daily functioning and quality of life. Exercise training is an important part of the rehabilitation process after stroke. Meta analyses show that increased intensity of exercise training after stroke leads to better functional outcome for patients in terms of mobility and activities of daily living (ADL). One such way to increase this intensity of training, especially in times where resources (mostly staff) become increasingly scarce, is to involve caregivers in the training of stroke patients. Therefore, in Reade centre for rehabilitation and rheumatology, together with Amsterdam UMC location VUmc, a so-called 'caregiver-mediated exercises' (CME) program, with the acronym CARE4STROKE was developed. In CARE4STROKE the person with stroke performs exercises together with a caregiver in addition to the regular therapy. The program is supported by weekly sessions with a trained therapist. A caregiver is defined as someone close to the patient, who is willing and able to do exercises together with the patient, for example a partner, family member or friend. CME can take place in the hospital, rehabilitation centre or geriatric rehabilitation department of a nursing home as well as in the home situation.

CME have the potential to facilitate early supported discharge (ESD) to patients own home setting. Early supported discharge includes the transfer from an inpatient environment to a community setting combined with the continuation of therapy and support. CME is hypothesized to improve functional outcome and to reduce length of inpatient stay (LOS) by increasing intensity of training. LOS is an important contributor to costs after stroke, CME might therefore be a way to reduce costs of inpatient stay and rehabilitation after stroke. In addition, CME may smoothen the transition to the home situation because patient and caregiver are more aware of what the patient can and cannot do in terms of mobility. Finally, CME can provide the opportunity to continue exercise therapy at home.

The overall aim of this thesis was to study the use and effects of CME after stroke. An overview of the evidence for earlier developed CME-interventions by using systematic review methods was therefore made as a start. Thereafter, the treatment protocol for the CARE4STROKE intervention was described in more detail. The CARE4STROKE program was then studied in a randomized controlled (cost-)effectiveness trial with the primary outcome measures self-reported mobility and LOS. Finally, patients and caregivers were interviewed about their experiences with participating in the CARE4STROKE program.

In **chapter 2** the available evidence about CME is summarized in a systematic review with meta-analysis. Available literature until October 2015 was searched for randomized controlled trials which compared CME to usual care, no intervention or another intervention

as long as it was not caregiver mediated. We found nine trials about CME, aimed at improving motor function in people who have had a stroke. Six trials, with 333 patient-caregiver couples, could be included in the meta-analysis. Due to the variety of outcome measures and low methodological quality, summarizing and combining of data was possible for a limited number of studies. When pooling available data, very low to moderate quality evidence in favour of CME on standing balance, walking distance and quality of life was found. For hand function, measured with the Wolf Motor function test, a significant effect in favour of the control group post intervention was found (2 studies, low quality of evidence). We did not find significant summary effect sizes on outcome measures of basic (for example bathing and dressing) and extended ADL (focused on activities in the kitchen, gardening) and caregiver burden. In contrast to the primary analysis, sensitivity analysis of CME-core trials did show a significant effect on basic ADL post intervention in favour of CME. CME-core refers to trials in which CME was the only intervention in contrast to non-CME-core trials in which caregivers were used to provide another existing intervention. We concluded that there is very low to moderate quality of evidence that CME may be a valuable intervention to augment the pallet of therapeutic options after stroke. Included studies were small and heterogenous and future high-quality research focused on effectiveness and cost-effectiveness is necessary.

Using the available evidence, the aforementioned CARE4STROKE program was developed: A caregiver-mediated exercise intervention supported by e-health using a tablet-app and tele-rehabilitation. We expected these innovative tools to be feasible and both motivating and supportive for the patient-caregiver couple. The practical content of the program was developed in collaboration with physical and occupational therapists, physicians, rehabilitation scientists and patient-caregiver couples.

As outlined in **chapter 3** the CARE4STROKE program is an 8-week program in which a patient with stroke exercises with his or her caregiver. The TIDieR (Template of Intervention Description and Replication) checklist was used to describe the program in detail concerning content, timing and intensity of the program, participant screening and selection, and intervention procedures. The exercises and use of the video application are explained and the role of the caregiver and trained therapist is described. The TIDieR checklist made it possible to describe this complex rehabilitation intervention in such detail that others can replicate it.

The CARE4STROKE program was studied in a proof-of-concept randomized controlled trial (RCT). The design of the trial is described in **chapter 4**. The primary aim of the RCT was to evaluate the effects and cost-effectiveness of the CARE4STROKE program. Patients with stroke admitted to a hospital stroke unit, rehabilitation center or nursing home were

randomly assigned to either 8 weeks of the CARE4STROKE program in addition to usual care or to 8 weeks of usual care. Primary outcome measures of the trial were self-reported mobility, measured on the mobility domain of the Stroke Impact Scale (SIS 3.0), and LOS in rehabilitation centre or nursing home calculated from stroke onset. Secondary outcomes for the patient were the other domains of the Stroke Impact Scale. In addition, measurements for motor impairment, strength, walking ability, balance, mobility, (Extended) ADL, psychosocial functioning, self-efficacy, fatigue, health-related quality of life as recommended by treatment guidelines were used. For caregivers, experienced strain, psychosocial functioning and quality of life were measured. Outcomes were assessed at baseline, 8 (directly post intervention) and 12 weeks after randomization. We expected a significant reduction of five points (11%) on the SIS mobility domain in favour of the CARE4STROKE-intervention group. Including 10% dropouts we calculated that 66 participants were needed in the CARE4STROKE trial to achieve a sufficient statistical power of 80% using a significant alpha of $P<0.05$.

In **chapter 5** we described the results of the proof-of-concept randomized controlled trial. No between group differences were found for primary outcome measures SIS-mobility over 8 weeks ($P=0.233$) and 12 weeks ($P=0.958$), and LOS ($P=0.818$). We did find, however, a significant interaction effect, post intervention, for anxiety of the patient (β 1.87, SD 0.88; $P=0.034$) and depression of the caregiver (β 2.32, SD 0.77; $P=0.003$) in favour of the CARE4STROKE intervention group. Decreased anxiety of patients persisted at the 12-week follow-up (β 1.02, SD 0.40; $P=0.010$). In addition, this proof-of-concept trial did show that the CARE4STROKE program is feasible and safe to apply. Patients in the CARE4STROKE group exercised a median of 1190 minutes with a caregiver versus 480 minutes in the control group ($P=0.002$). However, total amount of exercise time (i.e. the time combined the patient exercised in therapy, with a caregiver, with a nurse and independently) did not significantly differ between intervention and control group. Our planned treatment contrast was therefore not fully reached.

The explorative qualitative study we performed alongside the CARE4STROKE trial is described in **chapter 6**. This study focused on how participants managed these exercises together. The research questions were: 1) How do the patient-caregiver couples exercise together? And 2) what does exercising together bring about, besides more hours of practice? Semi-structured interviews were conducted with seven patients and seven caregivers who participated in the CARE4STROKE intervention. The data were interpreted by using inductive thematic data analysis. Three different role-dynamics were found during caregiver-mediated exercises: 1) patient in control, 2) in concert, and 3) the caregiver as informal carer. In addition, three themes were identified about what exercising together brings about: a) tailor made exercises through active involvement, b) preparation for the home situation,

and c) opportunity to be involved. In conclusion, we can say that practicing together goes beyond just intensifying therapy. We advise participating staff in caregiver-mediated exercises to be aware of the role-dynamics and the effects this might have on patient or caregiver. In addition, these results show that caregiver-mediated exercises enhance individualization of the treatment plan and preparation for discharge from inpatient setting to the home situation.

Finally, in the general discussion (**chapter 7**) the main findings of chapters 2–6 are summarized. The discussion continues with a reflection on the results, recommendations for daily practice and recommendations for further research.

A key question is why our trial is neutral in terms of self-reported mobility and LOS? A first explanation might be lack of treatment contrast between experimental and control group with respect to treatment intensity. Another explanation could be that our primary outcome measures are not responsive enough for the therapy-induced improvements in this proof-of-concept trial with a limited number of participants. Although there was a trend towards significance with regard to SIS mobility suggesting that a larger sample may have turned our study from neutral to positive.

The favourable effects found on mood and qualitative data on transition from inpatient setting to the home situation suggest that CME might in the future fulfil a role as part of an early supported discharge intervention. CME could then provide the possibility of early discharge and good preparation combined with continuation of therapy and support in the home situation. We also argue that these positive effects justify proceeding with the concept of CME in a larger phase III or phase IV cost-effectiveness trial.

For future research we advise to use a cluster-randomized controlled trial design to overcome the problem of contamination (e.g. the possibility that patients in the control group copy the applied caregiver exercises). In addition, cost-effectiveness of e-health technology in combination of CME used to augment rehabilitation services should be studied further. To measure the effects of CME on psychosocial functioning and quality of transition from an inpatient setting to the home situation ('care transition') we advise to validate a measurement tool for this goal.

Concerning the development of future CME programs, we discussed a number of considerations: the dependency of CME on the availability of a caregiver, our advice to further explore the possibilities of CME in hospital and geriatric rehabilitation settings and the possibility to use CME in patients with other impairments after stroke or even other diagnosis.

Finally, we advise to study cross-cultural differences in the use of CME. At this moment, worldwide, CME programs exist that differ with regard to content, progressiveness and

purpose (in addition or as substitution of usual care). Knowledge exchange and examination of cross-cultural differences can support further development and implementation of CME.

Samenvatting

De meest voorkomende oorzaak van hersenletsel is een beroerte. Beroerte heeft twee verschijningsvormen: hersenbloeding of herseninfarct. De gevolgen variëren van lichte neurologische symptomen tot ernstige problemen in bijvoorbeeld gebruik van arm of been, spreken of cognitieve functies. Dit kan leiden tot beperkingen in bijvoorbeeld mobiliteit, algemene dagelijkse levensverrichtingen (ADL), communicatie en sociaal-maatschappelijk functioneren. De gevolgen van een beroerte hebben een grote impact op ervaren kwaliteit van leven van patiënten met een beroerte. Fysiek oefenen is een belangrijk onderdeel van het revalidatietraject na een beroerte. Verschillende meta-analyses hebben aangetoond dat meer oefenen na een beroerte leidt tot een betere functionele uitkomst ten aanzien van mobiliteit en ADL. Inventieve manieren om meer te oefenen na een beroerte worden daarom gezocht, zeker nu de middelen, waaronder personele bezetting voor revalidatie, steeds schaarser aan het worden zijn. Een manier om de hoeveelheid oefentijd te vergroten voor patiënten met een beroerte, is het betrekken van naasten bij het oefenen. Hiervoor is in Reade, in samenwerking met AmsterdamUMC locatie VUmc, een 'caregiver-mediated exercises' (CME) programma ontwikkeld, waarbij de patiënt met een beroerte en een naaste samen oefenen in aanvulling op de reguliere therapie. Een naaste is hierbij gedefinieerd als iemand die dichtbij de patiënt staat en die samen kan en wil oefenen met de patiënt, bijvoorbeeld een partner, familielid of vriend. Het samen oefenen kan zowel plaatsvinden in het ziekenhuis, het revalidatiecentrum, de geriatrische revalidatieafdeling in een verpleeghuis, als in de thuissituatie. Het samen oefenen wordt ondersteund door wekelijkse sessies met een getrainde fysiotherapeut.

CME heeft de potentie 'early supported discharge' (ESD) mogelijk te maken. ESD omvat een combinatie van vervroegd ontslag en ondersteuning en therapie in de thuissituatie. Theoretisch gezien zou CME het moment van ontslag uit de revalidatiesetting kunnen vervroegen. Men mag er immers van uitgaan dat als de toename van oefentijd leidt tot betere functionele uitkomst, de benodigde opnameduur waarschijnlijk zal verminderen. Omdat de kosten na een beroerte voor een belangrijk deel worden bepaald door opnameduur kan vervroegd ontslag door CME een interessante manier zijn om de kosten van opname en revalidatie te verminderen. In aanvulling hierop kan CME het oefenen thuis faciliteren en op die manier zorgen voor ondersteuning en therapie in de thuissituatie waarbij zowel patiënt als naaste betrokken zijn. Tot slot kan een CME-programma de overgang van revalidatiesetting naar huis mogelijk makkelijker maken, doordat patiënt en naaste beter weten wat de patiënt wel en niet kan in termen van mobiliteit.

Het doel van dit proefschrift was om het gebruik van CME na een beroerte te onderzoeken. Als start is met behulp van systematisch literatuuronderzoek een overzicht gemaakt van het wetenschappelijke bewijs met betrekking tot effectiviteit van CME-interventies die in het verleden zijn uitgevoerd. Vervolgens is het CARE4STROKE programma, een CME-interventie

ondersteund door e-health, ontwikkeld en beschreven in een toetsbaar en repliceerbaar behandelprotocol. Daarna is het effect van dit programma onderzocht in een gecontroleerd kosten-effectiviteitsonderzoek op de primaire uitkomstmaten zelfgerapporteerde mobiliteit en duur van opname. Tot slot zijn patiënten en naasten geïnterviewd over hun ervaringen met deelname aan het CARE4STROKE programma.

In **hoofdstuk 2** is het bewijs met betrekking tot effectiviteit van CME samengevat in een systematisch literatuuroverzicht met meta-analyse. Hiervoor zijn relevante databases doorzocht tot oktober 2015 op gerandomiseerde effectstudies, die CME gericht op het verbeteren van de motorische functies in patiënten na een beroerte vergeleken met standaard zorg, geen interventie, of een andere interventie die geen CME bevatte. Er werden negen studies gevonden, waarvan zes studies met in totaal 333 patiënt-naaste koppels geïncludeerd konden worden in de meta-analyse. Het combineren van de data voor meta-analyse was voor een beperkt aantal studies mogelijk als gevolg van verschil in uitkomstmaten en geringe methodologische kwaliteit. In de kwantitatieve analyse vonden we zeer lage tot gemiddelde kwaliteit bewijs in het voordeel van CME voor stabalans, loopafstand en kwaliteit van leven. Voor handvaardigheid, gemeten met de Wolf Motor Function Test, werd direct na de interventie een significant verschil ten nadele van de CME-groep gevonden (2 studies, lage kwaliteit bewijs). In de analyse werden geen significante verschillen gevonden voor de uitkomstmaten basis ADL (bijvoorbeeld wassen en kleden), uitgebreide ADL (gericht op bijvoorbeeld activiteiten in de keuken, tuinieren) en belasting voor de naaste bij vergelijking van de CME-groep met de controlegroep.

In tegenstelling tot de primaire analyse werd in een sensitiviteitsanalyse van CME-core studies een significant effect in het voordeel van CME gevonden voor basis ADL direct na de interventieperiode. CME-core refereert aan studies waarin CME de enige interventie was in contrast met andere studies ('non CME-core') waarin naasten ingezet worden om de uitvoer van een andere interventie te ondersteunen. Concluderend is er zeer lage tot gemiddelde kwaliteit bewijs, dat CME een meerwaarde kan hebben na een beroerte. De geïncludeerde studies zijn klein en heterogeen en daarom is toekomstig methodologisch hoogkwalitatief onderzoek gericht op (kosten)effectiviteit van CME noodzakelijk.

Gebruikmakend van de eerdere evidentie over CME is het CARE4STROKE programma ontwikkeld: een CME-interventie ondersteund door e-health door gebruik van een tablet-app en tele-revalidatie. Onze verwachting was dat deze innovatieve middelen zowel motiverend als ondersteunend zouden kunnen werken voor het patiënt-naaste koppel. De praktische uitwerking van het programma is ingevuld door een samenwerking van artsen, fysio- en ergotherapeuten, wetenschappers, studenten fysiotherapie en patiënt-naaste koppels.

Zoals beschreven in **hoofdstuk 3** is het CARE4STROKE programma een 8 weken durend programma waarin de patiënt met een beroerte oefent met zijn of haar naaste. De TiDieR (Template of Intervention Description and Replication) checklist is gebruikt om de elementen van het programma zoals inhoud, timing, intensiteit, selectie en screening van deelnemers, en procedures te beschrijven. De oefeningen en gebruik van de videoapplicatie worden in detail uitgelegd en de rol van de naaste en getrainde fysiotherapeut worden beschreven. Door de TiDieR checklist te gebruiken was het mogelijk deze complexe revalidatie-interventie in detail te beschrijven, zodat het oefenprogramma gerepliceerd kan worden door anderen.

Het CARE4STROKE programma is onderzocht in een proof-of-concept gerandomiseerde effectstudie. De opzet van deze studie is beschreven in **hoofdstuk 4**. Het primaire doel was om de effectiviteit en kosteneffectiviteit van het CARE4STROKE programma te onderzoeken. Patiënten met een beroerte die opgenomen waren in ziekenhuis, revalidatiecentrum of verpleeghuis werden op basis van loting toegewezen aan 8 weken CARE4STROKE programma in aanvulling op de reguliere zorg of aan alleen reguliere zorg. Hierbij waren de primaire uitkomstmaten 'zelfgerapporteerde mobiliteit', gemeten op het domein mobiliteit van de Stroke Impact Scale (SIS 3.0) en 'duur van opname' gerekend vanaf tijdstip van de beroerte tot ontslag uit revalidatiecentrum of verpleeghuis. Secundaire uitkomstmaten voor de patiënt waren de andere domeinen van de Stroke Impact Scale inclusief mate van ervaren herstel. Daarnaast werden met de aanbevolen meetinstrumenten uit de behandelrichtlijnen, kracht, selectiviteit, loopvaardigheid, zit- en stabalans, mobiliteit, (uitgebreide) activiteiten van het dagelijks leven, psychosociaal functioneren, vermoeidheid, en gezondheidgerelateerde kwaliteit van leven gemeten. Voor de naasten waren dit ervaren belasting, psychosociaal functioneren en kwaliteit van leven. De uitkomsten werden gemeten voorafgaand aan de interventie, 8 weken (direct na de interventie) en 12 weken na randomisatie. We verwachtten een significante afname van vijf punten (11%) op de SIS-mobiliteit in het voordeel van de CARE4STROKE interventiegroep. Rekening houdend met 10% drop-outs berekenden we dat 66 deelnemers nodig waren in de CARE4STROKE studie voor voldoende statistische power van 80%, en een alfa van $P<0,05$.

In **hoofdstuk 5** zijn de resultaten van de gerandomiseerde studie beschreven. Er werden geen significante verschillen gevonden voor de primaire uitkomstmaten SIS-mobiliteit op 8 en 12 weken. De opnameduur was ook niet significant verschillend tussen de beide groepen. Hiermee heeft deze proof-of-concept studie een neutrale uitkomst, waarbij CME veilig en uitvoerbaar bleek. We vonden wel een significant interactie-effect, na 8 weken, voor ervaren angst van de patiënt en ervaren somberheid van de naaste in het voordeel van de CARE4STROKE interventiegroep. De vermindering in ervaren angst bij patiënten hield aan bij de 12 weken follow-up meting. De patiënten in de CARE4STROKE interventiegroep oefenden

significant meer met een naaste dan patiënten in de controlegroep (mediaan 1190 minuten versus 480 minuten). De totale hoeveelheid oefentijd (de minuten geoefend tijdens therapie, zelfstandig, met een verpleegkundige en met een naaste bij elkaar opgeteld) verschilde echter niet significant tussen de CARE4STROKE interventiegroep en de controlegroep. Ons geplande behandelcontrast is hiermee niet gehaald.

Vervolgens is de exploratieve kwalitatieve studie, gericht op hoe de deelnemers het samen oefenen uitvoerden en hebben ervaren, beschreven in **hoofdstuk 6**. De onderzoeksvragen waren: 1) Hoe oefenen patiënt en naaste samen? en 2) Waar leidt het samen oefenen toe, behalve tot meer oefenmomenten? Er vonden semigestructureerde interviews plaats met zeven patiënten en zeven naasten uit de CARE4STROKE interventiegroep. Analyse vond plaats met inductieve thematische analyse. We vonden drie manieren waarop patiënt en naaste samen oefenden: 1) de controle lag bij de patiënt; 2) er was sprake van samenwerking; 3) de naaste nam de verantwoordelijkheid (in het verlengde van de rol als mantelzorger). De meerwaarde van het samen oefenen was in drie thema's in te delen, namelijk: 1) actieve betrokkenheid leidt tot personalisatie; 2) voorbereiding op de thuissituatie; en 3) betrokkenheid op elkaar. Concluderend kunnen we zeggen dat het samen oefenen verder reikt dan alleen een intensivering van de therapie. Het is van belang dat de fysiotherapeuten die de koppels begeleiden zich bewust zijn van de mogelijke rolverdelingen en wat voor effect het gezamenlijk oefenen kan hebben op de belasting van de patiënt of de naaste. Door de actieve betrokkenheid bij de oefeningen kan samen oefenen leiden tot verdere individualisering van het behandelplan en een betere voorbereiding op ontslag naar huis.

Tot slot worden in de algemene discussie in **hoofdstuk 7** de belangrijkste bevindingen van de voorgaande hoofdstukken samengevat. De discussie vervolgt met een kritische beschouwing op de resultaten, aanbevelingen voor de praktijk en aanbevelingen voor vervolgonderzoek.

De resultaten gepresenteerd in dit proefschrift laten zien dat CME ondersteund door e-health veilig uitgevoerd kan worden en gebruikt kan worden in de dagelijkse revalidatiepraktijk. De proof-of-concept gerandomiseerde effectstudie had een neutrale uitkomst met betrekking tot de primaire uitkomstmaten zelfgerapporteerde mobiliteit en opnameduur. Het behandelcontrast, of gebrek daaraan, is mogelijk een belangrijke factor hiervoor. Een andere verklaring zou kunnen zijn dat onze primaire uitkomstmaten niet responsief genoeg zijn voor de subtiele veranderingen die door CME worden geïntroduceerd in deze proof-of-concept studie met een beperkt aantal deelnemers. Er werd overigens wel een trend naar significantie gezien op de SIS-mobiliteit (zelfgerapporteerde mobiliteit).

De positieve resultaten op het gebied van stemming en transitie van revalidatiesetting naar de thuissituatie maken dat CME in de toekomst wellicht goed onderdeel zou kunnen zijn

van een ESD-interventie door de mogelijkheid van vroeg ontslag en goede voorbereiding op thuis te combineren met continueren van oefenen en het krijgen van steun. Wij denken ook dat deze positieve effecten rechtvaardigen om het concept CME in een grotere fase III of IV kosteneffectiviteitsstudie te onderzoeken.

Ten aanzien van de ontwikkeling en het gebruik van CME-programma's benoemen we in dit hoofdstuk een aantal overwegingen: de afhankelijkheid van de beschikbaarheid van een naaste om CME te kunnen uitvoeren, ons advies om de mogelijkheden van CME in ziekenhuis en geriatrische revalidatiesetting verder te onderzoeken en de mogelijkheid om CME in te zetten bij patiënten met andere gevolgen na een beroerte en zelfs bij patiënten met een andere diagnose.

Voor toekomstig onderzoek adviseren wij clusterrandomisatie op niveau van centra om te voorkomen dat delen van de interventie worden uitgevoerd door patiënten in de controlegroep. Daarnaast zal de kosteneffectiviteit van e-health technologie in combinatie met CME verder onderzocht moeten worden. Om de effecten van CME op psychosociaal functioneren en transitie naar de thuissituatie verder te onderzoeken zou het goed zijn als er een uitkomstmaat gericht op transitie van revalidatiecentrum naar de thuissituatie in het Nederlands vertaald en gevalideerd zou worden. Tot slot adviseren we om cross-culturele verschillen in het gebruik van CME te onderzoeken. Op dit moment bestaan er wereldwijd CME-programma's die verschillen qua inhoud, progressiviteit en doel (aanvulling of vervanging van reguliere therapie). Kennisuitwisseling en onderzoek naar de verschillen zal verdere ontwikkeling en implementatie van CME ondersteunen.

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About the author

CURRICULUM VITAE

Judith Vloothuis was born on October 16th 1981 in Hoorn, the Netherlands. In 1999 she graduated from high school 'Werenfridus' in Hoorn. Thereafter she studied medicine at the Academical Medical Center (AMC) in Amsterdam and became a medical doctor in 2005. From 2006–2010 she specialized in rehabilitation medicine. During this specialization she worked at rehabilitation centre the Trappenberg in Huizen, Medical center Alkmaar in Alkmaar and Rehabilitation centre Amsterdam in Amsterdam. As a rehabilitation physician, she continued to work in Rehabilitation centre Amsterdam in Amsterdam. This centre is now known as Reade, centre for rehabilitation and rheumatology. The focus of her work is with stroke and brain injury patients. Aside from her work as a rehabilitation physician, she works one day a week as a researcher. Her research work is supervised by professor Gert Kwakkel and his research group from as well Reade rehabilitation centre as Amsterdam University medical centre location VUmc. Together they started the CARE4STROKE project of which the results are described in the current thesis.

Judith lives together with her husband Jeroen and their son Alexander.

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