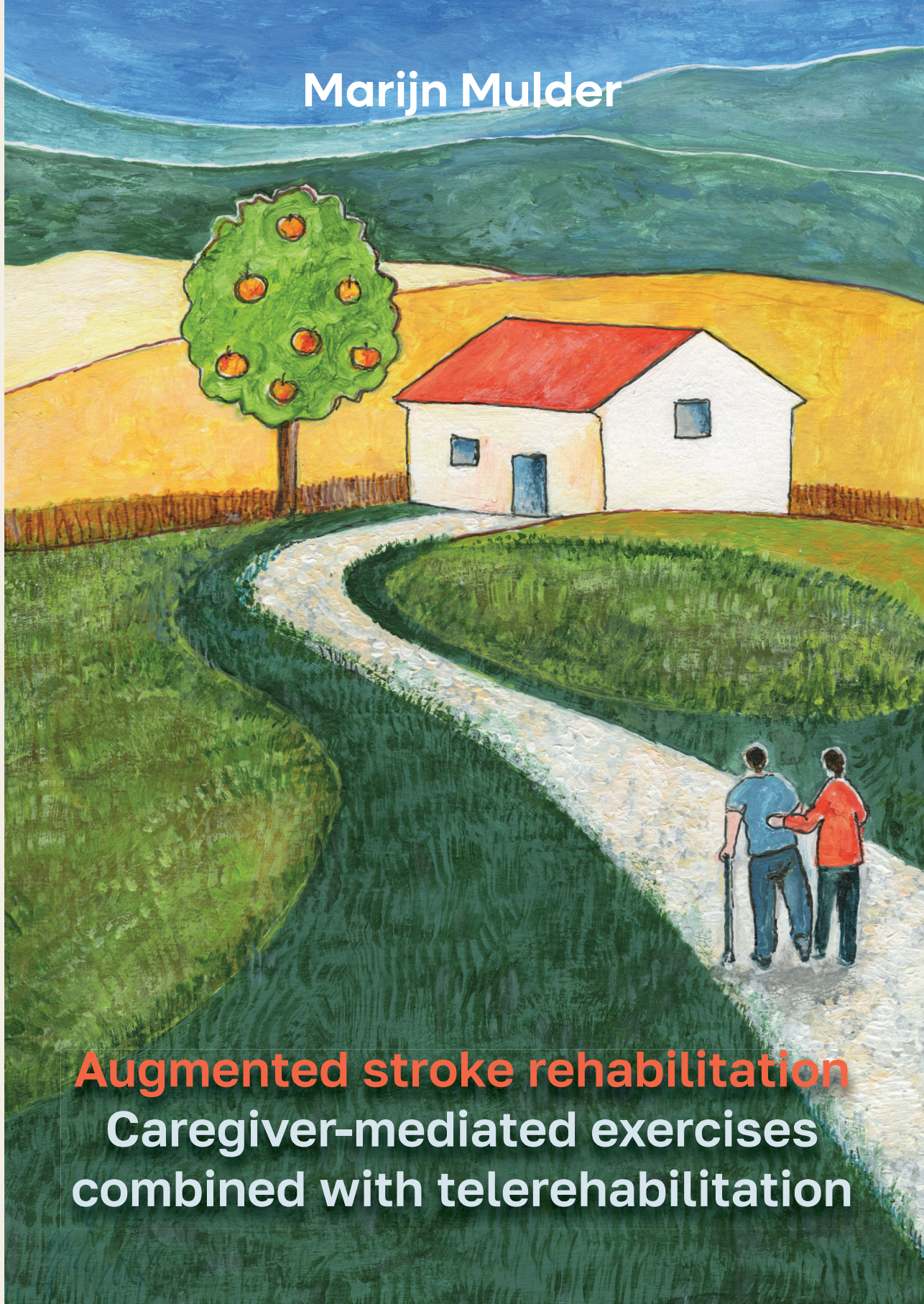
Marijn Mulder



Augmented stroke rehabilitation

Caregiver-mediated exercises combined with telerehabilitation

AUGMENTED STROKE REHABILITATION

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Thesis, VU University, Amsterdam, The Netherlands

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VRIJE UNIVERSITEIT

AUGMENTED STROKE REHABILITATION

Caregiver-mediated exercises combined with telerehabilitation

ACADEMISCH PROEFSCHRIFT

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de Vrije Universiteit Amsterdam,
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1

General introduction

Increasing the amount of task- and context-specific training likely enhances functional and motor outcomes after stroke including walking capacity and performance.[1,2] After discharge to the home setting, scheduled therapy stops or decreases sharply and the transition from inpatient care to the community is experienced as a significant hurdle by patients and their informal caregivers.[3,4] Early supported discharge (ESD), i.e. services aimed at accelerating discharge and to support continuity of stroke rehabilitation in the community, improves long-term independence in activities of daily living (ADL) and may reduce healthcare costs.[5] The main aim of this thesis is to investigate the added value of caregiver-mediated exercises (CME) combined with telerehabilitation services after stroke to augment the current dose of task- and context-specific training and to facilitate the transition from inpatient care to community and informal care. In the final section of this thesis, a list of abbreviations and a glossary are included to clarify key terms.

Stroke in the context of an ageing population

In 2021, almost 12 million people suffered a new stroke and nearly 94 million people were living with the consequences of stroke worldwide.[6] Absolute numbers of stroke incidence, prevalence, mortality and disability-adjusted life year rates continue to increase due to global ageing, population growth and unfavourable trends in several important stroke risk factors such as low physical activity and unhealthy diet. As a result, stroke remains the third leading cause of global disease burden.[6] When the current trends continue, it is expected that the global cost of stroke will almost double by 2050.[7] In the context of an ageing population, the demand for care is increasing while the relative supply of qualified healthcare personnel is decreasing. It is estimated that 1 in 5 persons of working age in the Netherlands should work in healthcare by 2030 to keep up with this rising demand and the projection increases to more than 1 in 3 by 2060.[8] In the Netherlands, the estimated cost for stroke is 1.4 billion euros with 83% of healthcare expenditure being spent on inpatient care.[9] After discharge from inpatient care, professional support tapers off. As a result of growing staff shortages in stroke rehabilitation and rising costs of care, there is increasing pressure on the number of available beds and to accelerate discharge to the home setting. Hence, stroke patients return home earlier in their recovery trajectory. While ESD services improve functional independence after stroke and may save costs, its effect on patient outcome is dependent on continuity of intensive multidisciplinary stroke rehabilitation at home.[5]

Stroke is characterized by acute neurological dysfunction, lasting more than 24 hours or leading to death, resulting from an acute focal brain injury by a vascular cause including cerebral ischemic stroke (ICD:8B11), intracerebral haemorrhage (ICD:8B00), subarachnoid haemorrhage (ICD:8B01) and cases of stroke in which the subtype of stroke has not been determined by neuroimaging or other techniques (ICD:8B20).[10] Following the International Classification of Functioning, Disability and Health (ICF) framework, stroke can result in residual impairments such as cognitive or motor impairment, activity limitations such as with self-care or walking, and participation restriction such as in social activities or work.[11] Motor impairment occurs in about 80% of acute stroke patients and is the most common impairment at the moment of hospital admission.[12] As a result, patients often remain dependent on others to execute their everyday activities, including bathing, making transfers and walking, even beyond six months poststroke when recovery is plateauing.[13-15] Recently, the European Stroke Organization (ESO) defined motor rehabilitation as "a process that engages people with stroke in order to benefit their motor function, activity capacity and performance in daily life. It incorporates principles of motor control in which patients learn to optimize and adapt their motor, sensory and cognitive functioning through appropriately dosed, repetitive, goal-oriented, progressive, task- and context-specific training".[16] Motor recovery after stroke is probably achieved through a combination of mechanisms that drive behavioural restitution, such as spontaneous neurological recovery within the first three months poststroke, and use-dependent mechanisms in which patients learn to cope with their underlying neurological deficits to accomplish a meaningful task.[16] Although prospective epidemiological studies on long-term outcomes of stroke are lacking, several cohort studies have reported that an estimated 70% of patients will achieve at least some return of their upper limb capacity poststroke,[17,18] whereas about 60% to 80% will regain at least some independence in walking[19-22] , while 60% to 70% will achieve independency in basic ADL.[23,24] Importantly, unilateral recovery of the most affected upper limb is poorly associated with recovery of basic ADLs, as activities are often taken over or compensated for by the less affected arm and ADL independence is mainly determined by lower limb functions.[25] This also underpins that above mentioned percentages of recovery are heavily dependent on underlying constructs of the measurement of outcome. In addition, regaining independence during basic ADL and walking does not generalize to reengagement in meaningful activities or independent mobility in the community, as these activities require additional behavioural and cognitive skills.

Independent mobility

Recovery of independent mobility is an important rehabilitation goal for patients poststroke[26-28] and a basic level of independent mobility is an important criterion for an ESD to the home setting.[29,30] Prognostic information about the time course of mobility recovery is important to increase knowledge and insight of patients and their families into the long-term implications of stroke and to set meaningful and attainable goals. Accurate prediction of independent mobility could also increase healthcare efficiency by improving triage and treatment decisions. The ICF has defined mobility as "moving by changing body position or location or by transferring from one place to another, by carrying, moving or manipulating objects, by walking, running or climbing, and by using various forms of transportation".[11] Independent walking can be predicted relatively early poststroke using clinical outcome measures of paretic leg strength and (sitting) balance.[19,21,31] However, independent mobility outside the home (i.e., community ambulation) includes being able to confidently negotiate curbs, uneven grounds and to cope with crowded environments.

About 75% of patients with stroke indicated, shortly after discharge, that the ability to go outside in the community is either essential or very important to them.[32] Consequently, community ambulation is considered to be an important final outcome of stroke rehabilitation.[33] Community ambulation is difficult to measure as it spans two levels of the ICF: 1) Activities; related to mobility, walking and using transportation; and 2) Participation; to use the ability to walk and move to exercise or as a means of transportation to participate in relevant social, domestic, leisurely or economic activities. **Figure 1.1** shows our theoretical model of candidate factors that may contribute to community ambulation. Adequate identification of prognostic factors for community ambulation before discharge from inpatient care could guide discharge planning, inform the organization of community services, and support the development of targeted poststroke rehabilitation interventions. **Chapter 2** provides a prognostic model for community ambulation outcome, six months after discharge from inpatient rehabilitation.

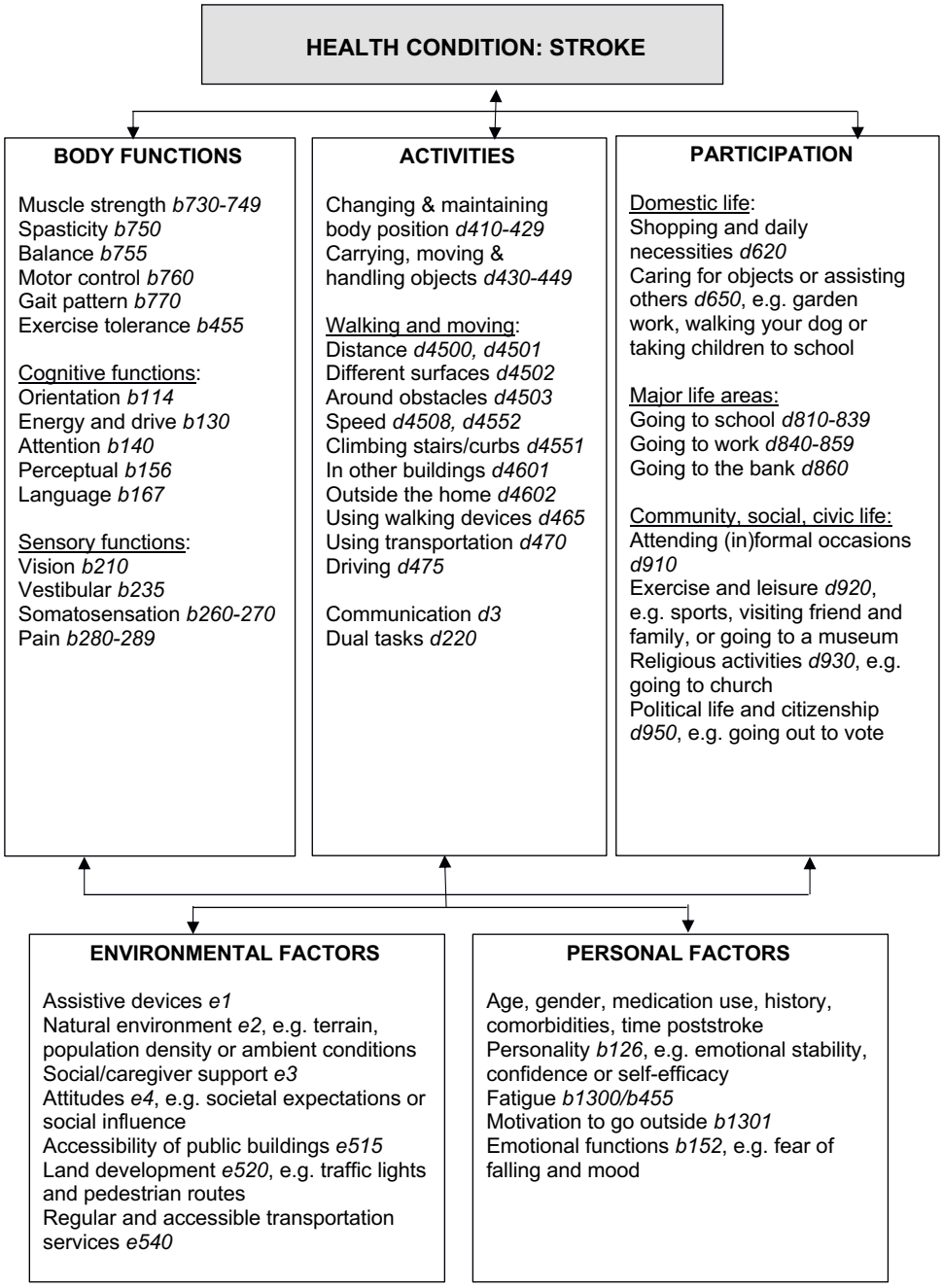


Figure 1.1. Theoretical model of factors contributing to community ambulation, categorized according to the International Classification of Functioning, Disability and Health (ICF), with ICF codes presented in parentheses.

Augmented rehabilitation

Stroke rehabilitation interventions are often complex and built up from multiple interacting components to enhance functional recovery.[34] Therapy-induced improvements of mobility and ADL independence poststroke is enhanced by task- and context-specific training and intensive practice.[12,35-38] Task-specific, goal-oriented and context-specific training facilitates motor learning, suggesting that training of meaningful activities within a patients' own environment can improve functional recovery and ensure retention of acquired skills.[16,34,39] Augmenting the intensity of training in terms of frequency, duration and number of hours spent in goal-oriented, progressive, task- and context-specific training may enhance mobility and independence in ADL, at least during the first six months poststroke.[1,2,37] Although there is little evidence to guide the choice for an optimal intensity of training, there is some evidence for a dose-response relationship.[40-42] Hence, patients should be provided with as much scheduled therapy as possible. Recently updated stroke guidelines currently advise three daily hours of task-specific therapy, without specific recommendations for weekend therapy.[43-45] Due to a lack of staff resources and insufficient time of available staff, patients often do not receive recommended amounts of task- and context-specific training.[46-49] Guideline adherence is not expected to improve with an increased demand for care and decreasing staffing levels in stroke rehabilitation. As a result, patients spend most of their time being inactive and alone.[50-52] Moreover, the length of inpatient stay after stroke is decreasing,[9] while access to ongoing rehabilitation therapies after discharge is often unavailable or delayed and insufficiently intensive.[53,54] Cost-effective strategies to augment task- and context-specific training and increase physical activity outside of scheduled face-to-face therapy are urgently needed. The ESO recently suggested that increasing the amount of task-specific practice by at least 20 additional hours may improve activity capacity including walking.[2,40] Theoretically, group therapy,[55] self-directed practice[56] and performing exercises with an informal caregiver (i.e., CME)[57] are strategies that could increase time spent in task- and context-specific training without substantially increasing human resources. In addition, telerehabilitation services can be used as an adjunct to support home-based practice and CME.[58] Telerehabilitation is broadly defined as "the use of information and communication technologies (ICT) to deliver rehabilitation services to people remotely in their homes or other environments",[59] for the purposes of screening, assessment, goal-setting, intervention, supervision/monitoring, prevention, education, consultation, and/or counseling.[58,60] Delivery of rehabilitation services can be achieved using synchronous (real-time, such as videoconferencing), asynchronous

(delayed delivery, such as messaging) or continuous formats (remote monitoring).[60,61] Facilitating technologies such as robotics[62] or virtual reality applications[63] fall within the definition of telerehabilitation if a connection or data flow is established between healthcare provider and recipient (i.e., patient and/or caregiver) to deliver remote rehabilitation services.[58,60] Unfortunately, the evidence for the superiority of these interventions aimed at augmenting the intensity of training, is still in debate.

Caregiver-mediated exercises

Training caregivers to become an exercise coach and perform CME may be a resource-efficient strategy to augment task- and context-specific training. In addition, informal caregivers or 'visitors' can be strong facilitators of physical activity outside of scheduled therapy.[64] We define an informal caregiver as an unpaid or partially paid person who voluntarily helps an impaired partner, family member, neighbour or friend with performing ADL. An early study by Galvin et al. (2011) showed that training family members to provide additional exercise therapy may result in improved community reintegration, decreased caregiver burden, and better outcomes on both the impairment and activity level.[57] In **chapter 3**, we will review and summarize the available evidence for CME interventions after stroke, up to 2015. Subsequently, we investigated the effect of a CME intervention combined with an e-health application with exercise videos in two parallel trials conducted in the Netherlands and Australia.[65,66] The CME paradigm combined with e-health tools, was specifically developed to allow an ESD to the home setting and augment training while limiting the need to increase the number of visits to rehabilitation facilities. In contrast to the Australian population, patients in the Netherlands often live relatively close to rehabilitation facilities. As a result, differences may exist in the organization and processes of local healthcare services. In addition, differences in terms of social, political and cultural norms with respect to the involvement of caregivers could exist. This raises the question whether cross-cultural differences exist with respect to the applicability and effectiveness of the CME paradigm in different countries and if adaptations are needed to fit the local healthcare system and cultural context. In **chapter 4**, the results of an individual patient data analysis are presented to compare differences across countries in terms of patient and caregiver characteristics, compliance with the intervention protocol, usual exercise dose and caregiver involvement, as well as processes of care such as length of inpatient stay, to obtain insight into cross-cultural differences with respect to the observed treatment effects.

Although differences may exist across countries, most patients who survive a stroke ultimately return to their own home. It is estimated that 74% to 80% of these patients require support from informal caregivers, usually a partner or family member.[67,68] Acknowledging that informal caregivers provide sustained support after discharge, they could be important allies in promoting long-term physical activity in the community and providing task-specific training after discharge from inpatient care. However, it is important to consider the impact of a CME program on the informal caregiver and to carefully monitor any potential negative consequences.

The impact on informal caregivers

Caregiving can have a significant negative impact on the psychosocial health of informal caregivers. It is estimated that prevalence of high caregiver burden ranges from 25% to 54% and continues for an indefinite period.[69] Depression rates are approximately 30% to 52% among informal caregivers of patients poststroke.[14] A longitudinal cohort study showed that caregivers experienced poorer psychological and emotional well-being when caring for a patient with depressive symptoms, suggesting an interdependent effect between patient and caregiver well-being.[70] Poor family functioning, as perceived by caregivers, is associated with higher depression rates.[71] However, little is known about the perspective on family functioning of patients poststroke and how they relate to the perception of their caregivers. Therefore, different perspectives on family functioning in both patients and their caregivers poststroke is investigated in **chapter 5**.

After discharge, professional support tapers off rapidly and family dynamics may change because of altered roles and vice versa. The transition from inpatient care to informal and community care is experienced as a significant hurdle and informal caregivers often feel unprepared for providing care at home.[3,4] Similar experiences are reported during the transition from intensive ESD services to community and informal care.[72] Active involvement of caregivers in stroke rehabilitation and addressing their goals and support needs including education and training, may therefore smoothen the transition between services.[72] However, a large number of face-to-face sessions with a therapist in a rehabilitation facility may not be feasible for informal caregivers and remote intervention delivery via telephone or web-based interventions have been suggested as a potentially beneficial alternative approach.[73]

Blended care

Blended care interventions, which combine face-to-face treatment with telerehabilitation support, may be a feasible and resource-efficient approach to support patient-caregiver dyads during CME. In addition, blended care is a promising paradigm to support the transition from professional face-to-face support to self-management in the community.[74] Caregivers' need for professional support is highest during preparation for discharge and in the first few months of adjustment at home,[75] suggesting that this may be the most appropriate phase for implementing a CME program. A blended care approach offers opportunities for more tailored support, for example by gradually reducing the frequency of face-to-face sessions and/or by shifting focus to remote monitoring and feedback, to meet the changing needs of patient-caregiver dyads over time. Furthermore, discharge from inpatient rehabilitation is often accompanied by a drastic reduction in scheduled therapy and patients often adopt a sedentary lifestyle in the community.[76] A deterioration in mobility has been reported in varying proportions of 21%,[77] 43%,[78] to 60%[79] of patients during the late subacute and chronic phases poststroke. Physical inactivity[77] and discontinuation of exercise therapy after discharge[78] were associated with a greater risk of deterioration. Engaging informal caregivers to motivate patients and promote physical activity may therefore be essential to prevent deterioration of mobility.

Stroke rehabilitation trials aiming to increase the amount of task-specific training are often conducted during inpatient rehabilitation, lack sufficient dosing combined with insufficient treatment contrast and have generally achieved neutral results.[40] Extending CME to the community with support of telerehabilitation, in a period when professional support stops or tapers off, may increase treatment contrast and improve long-term outcomes by preventing deterioration of functional mobility. Moreover, involving caregivers in goal setting and task-specific training, while monitoring their wellbeing, may improve the transition from inpatient care to community and informal care. In **chapter 6 and 7**, a protocol and the results of a randomized controlled trial (RCT) will be presented to study the effect of a CME program using a blended care approach, in addition to usual care. Compared to previous CME trials, there is an increased focus on joint goal setting and task- and context-specific practice during preparation for discharge and in the community to increase motivation, stimulate self-management and promote physical activity at home. Patient-caregiver dyads are supported by a web-based telerehabilitation system with individualized goals, exercise videos and a messaging environment to communicate (asynchronous) with their therapist. The training

program was specifically developed to achieve important milestones for community ambulation. Finally, in the general discussion, I will provide an overview of the results presented in this thesis and discuss directions for future research (**chapter 8**).

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2

Prospectively classifying community walkers after stroke: Who are they?

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ABSTRACT

Objective: To classify patients with stroke into subgroups based on their characteristics at the moment of discharge from inpatient rehabilitation in order to predict community ambulation outcome 6 months later.

Design: Prospective cohort study with a baseline measurement at discharge from inpatient care and final outcome determined after 6 months.

Setting: Community.

Participants: A cohort of patients (NZ243) with stroke, referred for outpatient physical therapy, after completing inpatient rehabilitation in The Netherlands.

Interventions: Not applicable.

Main Outcome Measures: A classification model was developed using Classification And Regression Tree (CART) analysis. Final outcome was determined using the community ambulation questionnaire. Potential baseline predictors included patient demographics, stroke characteristics, use of assistive devices, comfortable gait speed, balance, strength, motivation, falls efficacy, anxiety, and depression.

Results: The CART model accurately predicted independent community ambulation in 181 of 193 patients with stroke, based on a comfortable gait speed at discharge of 0.5 meters per second or faster. In contrast, 27 of 50 patients with gait speeds below 0.5 meters per second were correctly predicted to become noncommunity walkers.

Conclusions: We show that comfortable gait speed is a key factor in the prognosis of community ambulation outcome. The CART model may support clinicians in organizing community services at the moment of discharge from inpatient care.

INTRODUCTION

Stroke care is shifting from inpatient services towards community-based rehabilitation, and there is an increase in the number of trials focusing on community ambulation.[1,2] Community ambulation is a complex concept that refers to activities as well as social participation,[1,3] according to the International Classification of Functioning, Disability and Health.[4] It can be defined as "in-dependent mobility outside the home, which includes the ability to confidently negotiate uneven terrain, private venues, shopping centres, and other public venues."[5(p236)] Currently, however, no uniform definition or method of measuring community ambulation exists. Although being able to go outside is perceived as very important by most home-dwelling stroke survivors,[5,6] only 50% to 74% are actually walking independently in the community.[5,7-9] Persons who survived a stroke and are discharged home after inpatient rehabilitation are often dependent on others for community ambulation.[5,8,9]

Cohort studies that aim to predict independent community ambulation poststroke are needed to guide clinicians in organizing community services. These studies should meet recommended guidelines for conducting observational studies and prognostic modeling.[10,11] Community ambulation involves going outside to participate and resume roles that are crucial for community reintegration. Psychosocial functioning could have an important effect on participation and consequently on community ambulation poststroke,[1,12] whereas balance control[8,13-15] and gait speed[7-9,13,14,16] have been claimed as crucial determinants for community ambulation in cross-sectional studies. In a study among a cohort of community-dwelling persons with stroke, higher age, less physical activity, and poorer functional mobility predicted limited mobility (≤0.8 m/s) 1 year after inpatient care.[17] Unfortunately, cohort studies examining factors that predict community ambulation after inpatient care have been scarce[18-20] and difficult to compare, due to heterogeneity in the definition and measurement of community ambulation. In addition, most of the available studies were compromised by a small sample size[18,19] or did not consider physical functioning.[18,20]

The main objective of the present study was to classify patients with stroke into subgroups based on their characteristics at the moment of discharge from inpatient rehabilitation, in order to predict community ambulation 6 months later. We hypothesized that comfortable gait speed at discharge could predict community ambulation outcome. Additionally, we hypothesized that psychosocial functioning, balance control, lower extremity strength, and the use of assistive

devices could promote or restrict community ambulation outcome in patients with lower gait speeds at discharge.

METHODS

For the purpose of this prospective cohort study, data from the FIT-Stroke trial were analyzed.[21] A detailed trial description has been published earlier.[22] Potential predictors were measured at discharge from inpatient care (baseline). Community ambulation outcome was derived from the final follow-up assessment, 6 months after discharge.

Participants

The FIT-Stroke cohort consists of community-dwelling patients with stroke, referred for outpatient physical therapy after completing inpatient care. Patients were recruited between June 2008 and December 2010, from 9 rehabilitation centres in The Netherlands. Inclusion criteria were: verified stroke, having been discharged home, being able to walk 10 meters without physical assistance (Functional Ambulation Category 2≥3), and requiring outpatient physical therapy to improve walking ability and physical fitness. Exclusion criteria were: severe cognitive deficits (Mini-Mental State Examination <24 points), inability to communicate (Utrechts Communicatie Onderzoek item 19 <4 points), or large travel distance between the rehabilitation centre and the person's home (>30 km). The medical ethics committee of the University Medical Centre Utrecht approved the trial protocol, and all participants gave their informed consent. Reporting in this cohort study follows the STROBE statement.[10]

Dependent variable

Final outcome was assessed with the Community Ambulation Questionnaire (CAQ).[5] The CAQ measures self-reported levels of unassisted ambulation outside the home. Unassisted ambulation refers to independent ambulation, without physical assistance or supervision. According to this questionnaire, patients can be classified as (1) unable to walk outside unassisted; (2) only ambulant around the house (e.g., as far as the letterbox); (3) ambulation in the immediate environment (e.g., around the block); or (4) independent community ambulation (e.g., to visit a friend or shop). Patients in categories 1 to 3 were classified as noncommunity walkers, and patients in category 4 were classified as community walkers, in line with earlier

studies.[5,8,9,13,16]

Independent variables

Patient demographics, stroke characteristics, physical and psychosocial functioning were considered as potential baseline predictors, on the basis of literature and clinical judgment. A detailed description of predictor assessment has been published previously.[22] Patient demographics and stroke characteristics included sex, age, type of stroke (haemorrhagic or ischemic), history of stroke and time between stroke onset and discharge (wk). Physical predictors included: comfortable gait speed (5-meter timed walk),[23] standing balance (Timed Balance Test)[24] and strength and range of motion of the paretic leg (Motricity Index).[25] The use of orthotics (yes or no) and walking devices (yes or no) outside was also included. Comfortable gait speed was assessed over a practical distance of 5 meters. A previous study suggested that comfortable speed assessment is not affected by the choice of a 5- or 10-meter distance poststroke.[26] The mean speed (meters per second) was calculated over 3 repetitions. Psychosocial predictors included: motivation to walk in the community (self-report),[5] balance self-efficacy (Falls Efficacy Scale),[27] and anxiety and depression (Hospital Anxiety and Depression Scale).[28] Finally, to limit potential bias from treatment, intervention allocation was also included. To correct for collinearity, independent variables were removed if correlation coefficients (Spearman or Pearson r) were 0.70 or higher.[29]

Statistical analyses

A classification model was developed using Classification And Regression Tree (CART) analysis. CART is based on a binary recursive partitioning strategy.[30] The sample is stratified (partitioning) into 2 homogeneous subgroups (binary), with respect to the dependent variable. CART uses a forward approach to select the independent variable and associated cut-off value that results in the most effective split. The most effective split is determined by improvement in the Gini Index, a measure of homogeneity within and heterogeneity between subgroups.[31] This process of splitting is repeated (recursive) until patients within subgroups have a similar endpoint (Gini Index ≤ 0.01) or until the subgroups are too small to allow further splitting (growth limit ≤ 5 patients).[30] Patients with a missing value on the most effective splitting variable are classified using the most appropriate surrogate variable (i.e., the most similar alternative splitting variable). Model performance was investigated by calculating the

specificity, sensitivity, positive predictive value, negative predictive value, and overall accuracy, with their 95% confidence intervals (CIs). A 10-fold cross-validation procedure was applied to calculate the adjusted overall accuracy. In 10-fold cross-validation, a sample is randomly divided into 10 subsets, with 1 subset being treated as a validation set and the remaining subsets being used to train the model. This procedure is repeated for every subset, and the average misclassification error is calculated to provide a model performance statistic. Finally, to prevent over-fitting to our data an automatic pruning procedure was applied to select the most robust and stable model. Pruning was based on a maximum allowable difference of 1 standard error between the pruned tree and the full tree (with the smallest risk).[30,31] Data analyses were performed using IBM SPSS Statistics version 25.

RESULTS

The FIT-Stroke cohort consists of 250 community-dwelling patients with stroke. Final outcome of community ambulation could be determined in 243 patients. There were no significant differences between patients who completed the CAQ and those who were lost to follow-up (n=7), with the exception of higher Cumulative Illness Rating Scale scores among those lost to follow-up. During the baseline assessments, the average time after stroke was 3 months, and most patients lived in an urban environment (89.7%) together with a partner or caregiver (82.3%). At the final outcome assessment, a total of 193 patients (79.4%) reported that they were able to walk to shops and friends without assistance and were classified as community walkers. The remaining patients were unable to walk outside unassisted (n=25) or were only ambulant in the immediate environment (n=25) and were classified as noncommunity walkers. A baseline description of community walkers and noncommunity walkers is presented in **Table 2.1**. Significant baseline differences between community and noncommunity walkers were observed for all of the physical predictors. In contrast, balance self-efficacy was the only psychosocial predictor that differed significantly between the 2 groups. Most patients in both classes of the dependent variable reported that community ambulation was very important to them.

The CART model is presented in **Figure 2.1**. Collinearity diagnostics showed no cause for concern. Comfortable gait speed was the best predictor of community ambulation, with faster speed corresponding to a higher probability of achieving community ambulation.

Table 2.1. Baseline description of the sample

Independent variables	Community Walkers (n=193)	Noncommunity Walkers (n=50)	*p*-value
Allocated to intervention, n (%)	104 (53.9)	21 (42.0)	.134
Women, n (%)*	60 (31.1)	25 (50.0)	.012*
Age, mean ± SD	57.0±10.3	57.6±10.2	.684
Ischemic stroke, n (%)	157 (81.3)	41 (82.0)	.916
Time poststroke in wk, median (IQR)*	12 (8-16)	17 (14-23)	.001y
Recurrent stroke, n (%)	169 (87.6)	45 (90.0)	.831
Motivation: very important, n (%)	172 (89.1)	46 (92.0)	.550
Walking device use outside, n (%)**	95 (49.2)	45 (90.0)	<.001**
Orthotics use outside, n (%)**	56 (29.0)	32 (64.0)	<.001**
Comfortable gait speed in m/s (5MTW), mean ± SD**	0.89±0.29	0.49±0.24	<.001**
Standing balance (TBT), median (IQR)**	4 (3-5)	3 (2-3)	<.001**
Strength paretic leg (MI), median (IQR) **	75 (58-83)	51 (42-75)	<.001**
Balance self-efficacy (FES), median (IQR)**	103 (87-115)	85 (74-101)	<.001**
Anxiety (HADS), median (IQR)	3 (1-6)	4 (2-7)	.111
Depression (HADS), median (IQR)	4 (2-7)	5 (3-8)	.216

Abbreviations: 5MTW = 5-Meter Timed Walk; FES = Falls Efficacy Scale; HADS = Hospital Anxiety and Depression Scale; IQR = Interquartile Range; MI = Motricity Index; TBT = Timed Balance Test. * $p < 0.05$; ** $p < 0.01$.

CART classified patients into 3 subgroups according to their comfortable gait speed: those with gait speeds below 0.5 meters per second, those with gait speeds ranging from 0.5 to 0.8 meters per second and those with gait speeds above 0.8 meters per second. Patients with gait speeds below 0.5 meters per second were further classified according to the strength and range of motion of their affected leg. Those with a Motricity Index leg score above 45 points were more likely to regain independent gait in the community (47.6%) compared to those with lower Motricity Index leg scores. The predicted probability that patients with gait speeds ranging from

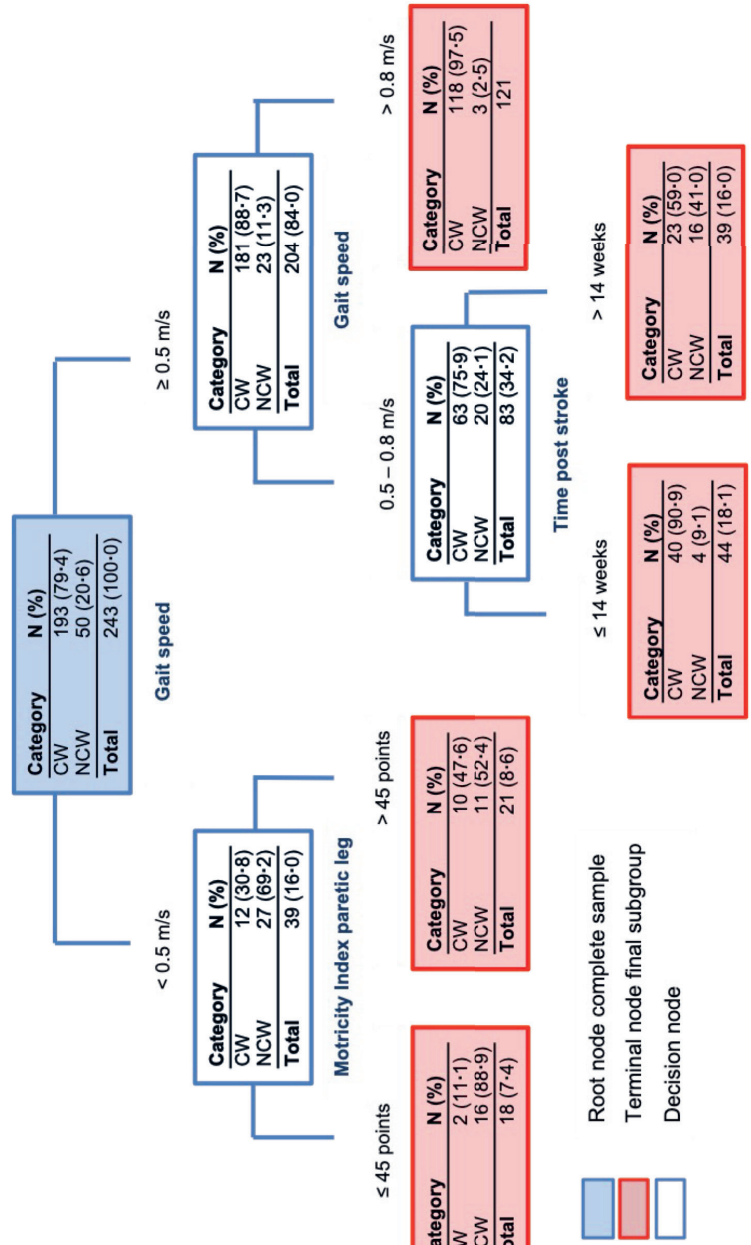


Figure 2.1. Classification tree for predicting community ambulation 6 months after inpatient rehabilitation.
Abbreviations: CW = Community Walkers; NCW = Noncommunity Walkers.

0.5 to 0.8 meters per second would become community walkers was 90.9% if they achieved this speed within 14 weeks after stroke onset. The predicted probability of becoming community walkers was lower in patients achieving this beyond this time frame (59.0%). Patients with gait speeds beyond 0.8 meters per second were predicted to become community walkers with a probability of 97.5%. The other independent variables were not selected by CART. Subsequently, an automatic pruning procedure was applied. The pruned tree is presented in **Figure 2.2**. The pruned tree shows that comfortable gait speed, at a cut-off value of 0.5 meters per second, was the most robust predictor of community ambulation outcome.

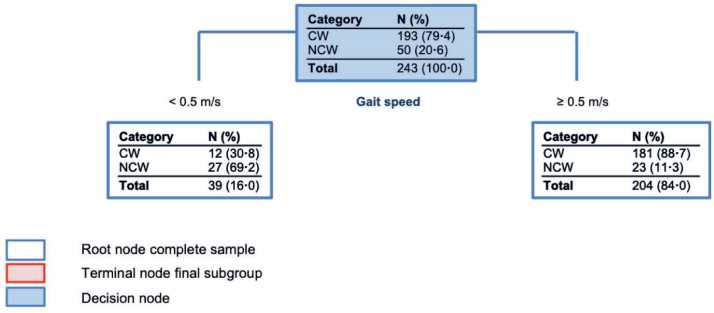


Figure 2.2. Classification tree after automatic pruning.
Abbreviations: CW = Community Walkers; NCW = Noncommunity Walkers.

Finally, model performance of the pruned tree was investigated, and outcomes are presented in **Table 2.2**. The CART model accurately predicted independent community ambulation in 181 of 193 patients with stroke (sensitivity 94%, CI 89-97) and 27 of 50 were correctly predicted to become noncommunity walkers (specificity 54%, CI 39-68). Overall accuracy of our model was 86% (i.e., misclassification risk 14%). Cross-validation of the CART model resulted in an adjusted overall accuracy of 79% (i.e., misclassification risk 21%).

Table 2.2. Model performance of the pruned classification tree

Model performance	Value	95% CI
Sensitivity	0.94	0.89-0.97
Specificity	0.54	0.39-0.68
Positive predictive value	0.89	0.85-0.91
Negative predictive value	0.69	0.55-0.81
Overall accuracy	0.86	0.81-0.90

Abbreviations: CI = Confidence Interval.

DISCUSSION

To the best of our knowledge, this is the first prospective cohort study using CART analysis to predict community ambulation after inpatient care. In addition, it is the first large cohort study to investigate physical and psychosocial predictors of community ambulation outcome poststroke. We found that comfortable gait speed was a key factor predicting community ambulation outcome. This strengthens earlier findings that clinically meaningful improvements in gait speed are closely associated with increased participation after stroke[32] and further emphasizes that gait speed is an important variable of outcome for estimating the effect of stroke rehabilitation.[2,33]

There has been some debate about the use of gait speed to discriminate between community walkers and noncommunity walkers.[3,13,15,16] However, longitudinal studies investigating the ability of gait speed to predict community ambulation have thus far been scarce.[19] We show that faster comfortable gait speeds at baseline are associated with an increased probability of achieving independent community ambulation. Community ambulation was best predicted by a cut-off value for gait speed of 0.5 meters per second at the time of discharge from inpatient care. This cut-off value is in line with the findings of a small cohort study that explored the prognostic value of gait speed by simple Mann-Whitney tests.[19] Patients with speeds above this cut-off value benefit most from outpatient physical therapy in terms of independent community

ambulation, although improvements are probably more likely when outpatient rehabilitation is initiated earlier poststroke.

It is particularly difficult to classify patients with gait speeds below 0.5 meters per second, suggesting that additional variables may predict community ambulation in these patients.[8] CART analysis allows differences between population subgroups to be considered, while regression modelling is biased towards the average member of a population. Nevertheless, a considerable proportion (30.8%) of patients with comfortable gait speeds below 0.5 meters per second, were incorrectly classified as noncommunity walkers. Our findings show that, within this population subgroup, strength and range of motion of the paretic leg may help in identifying those patients who are incorrectly classified as noncommunity walkers based on their gait speed alone. However, the number of patients with lower physical functions within our sample is insufficient to draw firm conclusions and this finding warrants further validation in a larger sample to test its robustness.

Study limitations

Several limitations of our study should be addressed. First, the moment of discharge from inpatient rehabilitation is determined by an arbitrary process and is often decided by non-neurological factors such as availability of support in the community. On average, the clinical measurements in our study were taken beyond the time window of spontaneous neurological recovery,[34] whereas an inception cohort that starts within the first days post-stroke is preferred in prognostic studies. Second, the FIT-Stroke cohort represents a large sample recruited from 9 rehabilitation facilities, thus increasing the potential to generalize. However, the patients presented with only mild physical, cognitive, and communicative problems. Moreover, all patients were receiving outpatient physical therapy, with relatively high adherence to the treatment programs.[21] Therefore, these findings might not be generalizable to more severely affected patients with stroke or to populations receiving lower treatment rates. Third, since CART analysis employs a recursive partitioning strategy, the predictors towards the bottom of the tree are less stable due to decreasing subgroup sizes. External validation of the CART model is required to investigate its performance and stability in other samples. Fourth, some potentially relevant predictors were not considered in the present study, such as walking distance, ethnicity, and environmental characteristics. Gait speed and walking distance may be equally relevant predictors of community ambulation poststroke.[13,15] However, walking

distance, was not included to prevent issues of collinearity. Future cohort studies should focus on identifying predictors for community ambulation outcome in different personal, social, and physical environments. Finally, community ambulation outcome was assessed by self-report, and patients were considered community walkers if they could walk to shops and friends without help or supervision. Although this questionnaire has been commonly used in recent studies, it may not capture the complex nature of community ambulation. Future studies should focus on the development of a uniform definition and method of measuring community ambulation poststroke.

CONCLUSIONS

The CART model may support clinicians in organizing community services at the moment of discharge from inpatient care. We show that comfortable gait speed is a key factor for outcome of community ambulation.

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Caregiver-mediated exercises for improving outcomes after stroke

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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.[1] Twelve months after stroke about 28% of people with stroke remain dependent in their basic ADLs, such as dressing, toileting, and indoor mobility.[2] Pettersen and colleagues reported that 32% of people with stroke living at home after three years were inactive in extended ADL.[3] 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.[4-11] One resource-efficient method to increase intensity of training could be to involve caregivers in exercise training.[12] 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.[13,14] 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,[5-7,9,10] and the higher the number of repetitions, the better the outcome.[4,8,11] Therefore, clinical guidelines recommend that people who are in a rehabilitation setting should have the opportunity to train intensively.[11,15-17] For example, the stroke guideline in the UK recommends a daily dose of 45 minutes of exercise therapy.[16] 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,[18-20] and on weekends, rehabilitation services (including exercise therapy) in most hospital and rehabilitation settings are not available.[21] 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.[22] 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".[23] 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 healthcare 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),[24,25] Functional Independence Measure (FIM),[26] modified Rankin Scale (mRS);[27,28] extended ADL measures, such as the Nottingham Extended Activities of Daily Living (NEADL) Index,[29] or Frenchay Activities Index (FAI).[30] When found, we combined scales with the same construct.
- Caregiver: measures of burden, for example Caregiver Strain Index (CSI).[31] 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),[32] Fugl-Meyer Assessment (FMA).[33-35]
- Gait and gait-related measures: walking speed, walking distance, Timed-Up-and-Go test (TUG),[36,37] Rivermead Mobility Index (RMI),[38-40] Berg Balance Scale (BBS).[41-44]
- Measures of upper limb activities or function, for example, Action Research Arm Test (ARAT).[45-47]
- Measures of mood and QoL of the patient, for example, measured by the Stroke Impact Scale (SIS),[48-50] and Hospital Anxiety and Depression Scale (HADS).[51-54]
- Measures of fatigue of the patient, for example, measured by the Fatigue Severity Scale (FSS).[55]
- 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,[51-54] or CarerQoL.[56,57]

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/).

We developed the MEDLINE search strategy with the help of the Cochrane Stroke Group Trials Search Coordinator (Brenda Thomas) and adapted this for the other databases. The MEDLINE search strategy is provided in **Supplemental Table 3A**. The other search strategies can be found in the published 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).

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.[58] 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 postintervention 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.[59]

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 pairwise 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 I2 statistic.[58] When there was substantial statistical heterogeneity (I2 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 **Supplemental Table 3B**). 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.[60,61] 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.[59]

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 in **Supplemental Tables 3C, 3D and 3E**.

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.[62] 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.[63-66] We identified 11 relevant systematic reviews, which we screened for trials.[67-77] In total, we identified 46 potentially relevant trials. The results of the search are summarised in **Figure 3.1**.

We were able to include nine trials for final analysis (see **Supplemental Table 3C**), and we included six trials in the meta-analysis.[62,78-82] We excluded three trials from the meta-analysis because of poor methodological quality[83,84] or no reporting of required data (i.e. means or SDs, or both, of outcome measures),[83-85] 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 (see **Supplemental Table 3D**). Two trials are ongoing (see **Supplemental Table 3E**).

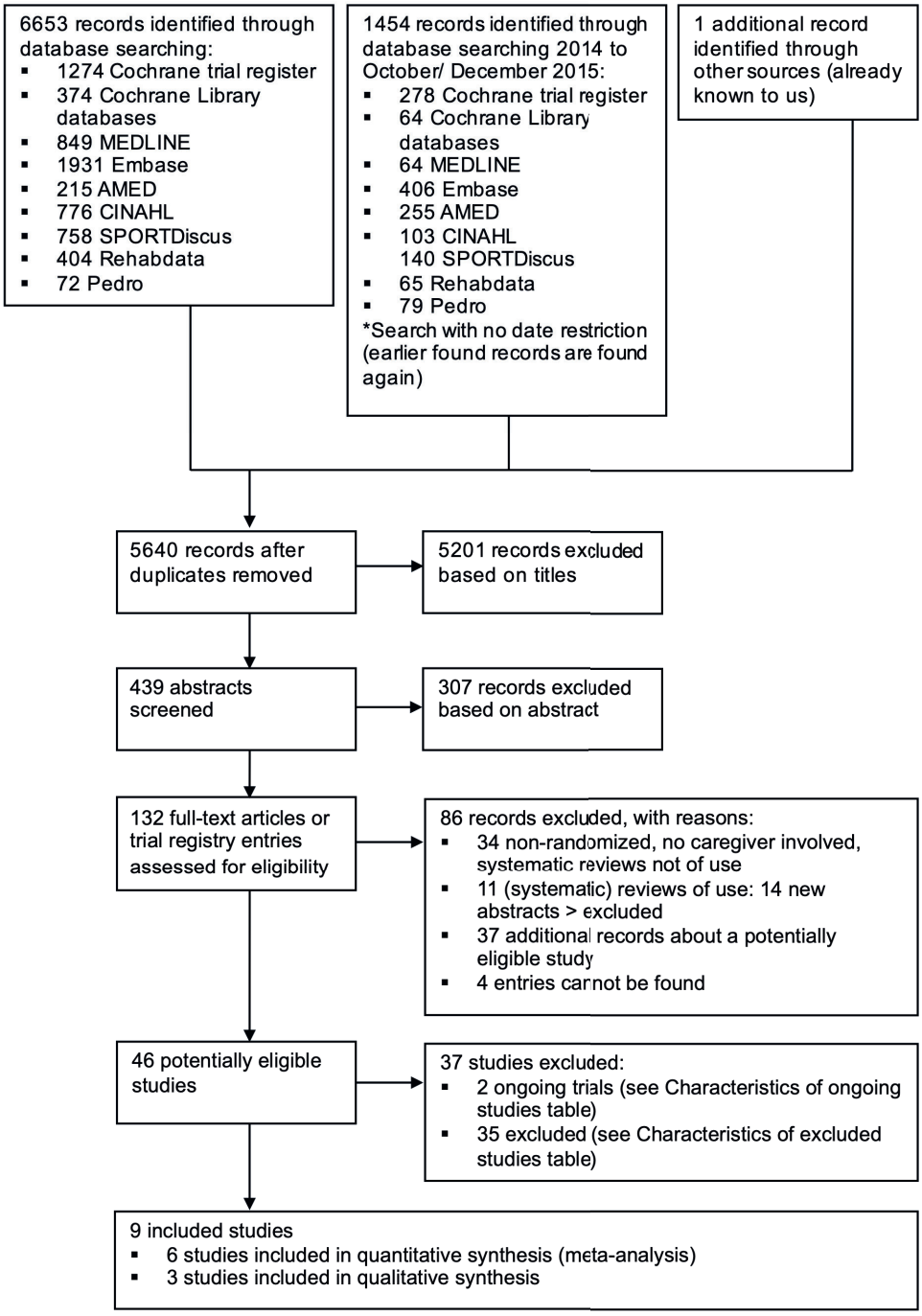


Figure 3.1. Study flow diagram

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.[84] Three studies defined inclusion or exclusion criteria for the caregiver, for example "willing to participate", "medically stable and physically able",[81] "being defined as primary caregivers",[80] and "caregivers were excluded if they were in poor physical health, had mental or behavioural disorders".[82] Four studies described an inclusion criterion for the patient about the caregiver: "live with family caregiver at home",[78] "patients with family support",[84] "had a caregiver who was prepared to be a non-professional coach (e.g., family member)",[79] and "availability of a family member to supervise home exercises".[85] Two studies gave information about the caregiver: "about 50% of the caregivers were nursing attendants",[80] and "majority were patients' spouse".[82]

Sample size

Five trials included fewer than 50 participants: 20 participants,[62,78] 24 participants,[85] 30 participants,[83] and 40 participants.[81] Four trials included more than 50 participants: 51 participants,[82] 55 participants,[80] 60 participants,[84] and 156 participants.[79]

Interventions

The content of the training and the timing was different between trials. Details of each intervention are summarised in **Table 3.1**. Two trials were aimed at the lower body,[62,81] five at the upper body,[78,79,83-85] and two at both upper and lower body.[80,82] Four studies included

patients within six months after stroke,[80,81,83,84] three studies included patients beyond six months after stroke,[62,79,82] one study included patients from two months after stroke or later,[78] one study included patients if they had a stroke in the last 24 months.[85] 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.[80,81,83,84]. The frequency, duration, and session length differed between studies, with training frequencies ranging from twice a week,[62,82] to every day,[78,81] with a duration per session ranging from 30 minutes[80] to three hours[85], and a programme duration ranging from 14 days[84] to six months[62]. In four trials, patients had weekly contact with the supervising therapist.[79,81-83] Two trials planned two to four sessions with a therapist.[78,80] One trial had 10 sessions with a therapist in 22 days.[85] One trial consisted of four groups, the amount of contact with the therapist differed between trial groups.[62] The frequency and duration of one trial was not clearly reported.[84] Three trials were carried out at home,[78,79,82] one trial was carried out in an inpatient setting,[84] three trials were carried out when patients were inpatient, outpatient, or at home,[62,81,85] and two trials were unclear about the location of the intervention.[80,83] 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, 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).

Table 3.1. Outline of included studies

Study ID	Form of training	Upper or lower body	Timing since stroke	Task caregiver	Routine care continued	Control group	Programme (duration, frequency, session length)	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 - 4 sessions	Home
Agrawal 2013	Exercise therapy	Upper	"Subacute stroke"	Encouragement, participating, and help	Yes	Usual care	4 weeks, 5 days/week, 60-90 minutes	Weekly	Inpatient?
Barzel 2015	CIMT	Upper	>6 months	Supervision, help, and maintaining training diary	No	Usual care, frequency of contact therapist the same	4 weeks, weekdays, 2 hours	5 x 60 minutes	Home
Dai 2013	Vestibular rehabilitation	Both	<6 months	Guidance and supervision (in 3rd and 4th week)	Yes	Usual care	4 weeks, 10 sessions per 2 weeks, 30 minutes	2 - 4 sessions in first 2 weeks	Inpatient?
Galvin 2011	Exercise therapy	Lower	Assessment 2 weeks poststroke	Encouragement and help	Yes	Usual care	8 weeks, daily, 35 minutes	Weekly	Inpatient or home
Gómez 2014	CIMT	Upper	<6 months	Monitoring and supervising	Yes	Usual care	14 days, daily*, 5.5 hours	1.5 hours/day	Inpatient
Souza 2015	CIMT: 1.5 hours with therapist, 1.5 hours 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

Table 3.1. Outline of included studies - *Continued*

Study ID	Form of training	Upper or lower body	Timing since stroke	Task caregiver	Routine care continued	Control group	Programme (duration, frequency, session length)	Contact with therapist	Place
Wall 1987	Exercise therapy	Lower	After discharge of rehabilitation	Supervision	No	No intervention	6 months, 2 days/week, 60 minutes	1 group: 2 sessions/week 1 group: 1 session/week 1 group: 'monitoring'	Outpatient or home
Wang 2015	Exercise program aimed at body functions, activities and participation	Both	>6 months	Encouragement and help	No	Usual care	12 weeks, 2 days/week (minimum) to daily, if possible, 50-60 minutes (minimum)	Weekly 90 minutes	Home

Abbreviations: 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 poststroke, unclear why.

Compliance

Five studies recorded compliance: "frequency of training and tasks completed was recorded",[82] "the amount of training was noted in a diary by patients' families",[78] "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",[81] "a log sheet per participant to record the total number of minutes completed per day",[83] and "compliance was assessed in all participants via a form (standard therapy group) or a training diary (home CIMT group)".[79] 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,[80,81,83,84] or instead of usual care.[62,78,79,82,85] Two studies included a control intervention,[78,85] seven included usual care as control,[62,79-84] one had no control intervention.[62] 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.[62,78,79,81,85] Two trials reported outcome measures during the intervention period.[62,80] 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 postintervention 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,[78,79,81,82] 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.[81] 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",[80] and one study included four paid workers.[82] 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.[86-120] See characteristics of excluded studies (**Supplemental Table 3D**). The most common reasons for exclusion were: interventions were educational for patient and caregiver but they performed no, or minimal, exercises together;[93-96,99,106,109,111,114,116-118] caregivers were involved and encouraged to participate but caregiver participation was not mandatory;[86,89,90,100,103,107,110,112,119,120] and the intervention concerned 'skill training'.[87,92,94,96,98,101,104,111] 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.[88,102,108,113] Because of their relevance for the topic of this review they are listed in the characteristics of excluded studies (**Supplemental Table 3D**). 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 (**Supplemental Table 3C**). See also **Figure 3.2** and **Figure 3.3** for a summary of the results.

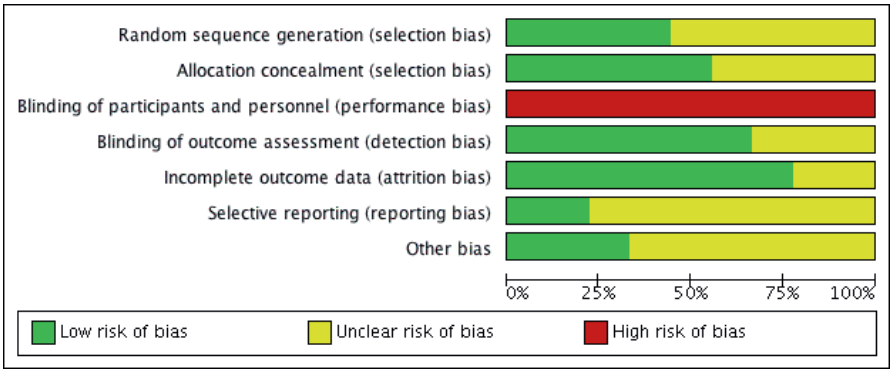


Figure 3.2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

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.[78,79,81,82] One study was unclear about the randomisation procedure but did provide sufficient information about allocation procedure.[85] The other four studies did not describe the randomisation procedure sufficiently.[62,80,83,84]

Blinding

Participant blinding

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

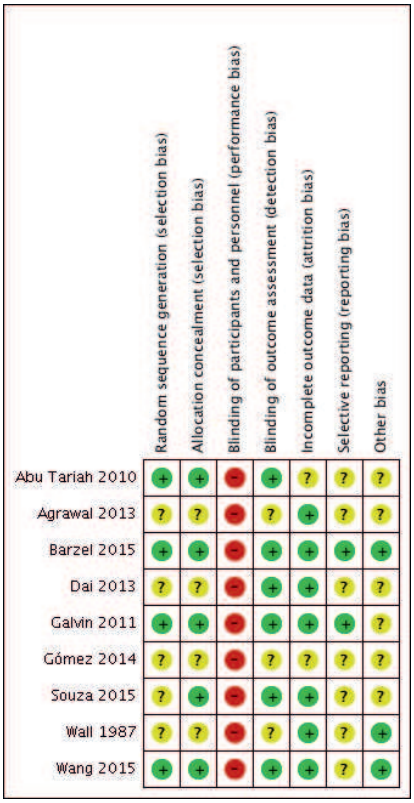


Figure 3.3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Investigator blinding

Six studies blinded the outcome assessors to treatment allocation.[78-82,85] Three studies did not report anything about an outcome assessor.[62,83,84] Five studies used participant-reported outcomes (questionnaires, report of number of falls).[79-82,85] For these outcomes, the assessor (patient or caregiver) was aware of the treatment allocation. This may have biased the results.

Incomplete outcome data

Three studies had no withdrawals and, therefore, reported complete outcome data.[62,82,83] Four studies had withdrawals, but reasons were well described and comparable in the intervention and control group.[79-81,85] One study reported only withdrawals in the control group.[78] 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.[84]

Selective reporting

For two included trials,[79,81] we identified a trial registry (NCT00666744) and published protocol.[121,122] Galvin (2011) reported no exclusion criteria in the trial paper in contrast to the protocol paper[122] and trial registration (NCT00666744). Not all outcome measures that were reported in the protocol paper of Barzel (2013) were reported in the trial paper,[79] 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.[78,80,85] Three trials did not report means or SDs for (a part of) the study outcomes.[81,83,85] 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.[84] We identified no other potential sources of bias for the remaining trials.[62,79,82]

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)[123] 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

A summary of findings for the main comparison ‘caregiver-mediated exercises compared with control intervention for people with stroke’ is provided in **Supplemental Table 3B**.

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).[79,81,82] We found no significant summary effect (mean difference (MD) 5.09, 95% CI -2.88 to 13.07; *p* =0.21; Table 3.2). One trial used the FIM.[80] The effect of CME on the FIM was not significant (MD 11.04, 95% CI - 1.59 to 23.67; *p* = 0.09; **Table 3.2**). 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.[79,81] 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 3.2**) or on the Instrumental Activities of Daily Living (IADL) (MD 0.02, 95% CI -0.72 to 0.76; *p* = 0.96; **Table 3.2**). 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[81] and six months' follow-up.[79] 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 3.2**), or measured with the IADL (MD 0.02, 95% CI -0.77 to 0.81; *p* = 0.96; **Table 3.2**) was 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.

Table 3.2. (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 ADL 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 ADL 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

Abbreviations: ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living. * Standardised mean difference.

Caregiver: measures of burden

End of intervention

One trial used the CSI to assess caregiver burden;[81] we found no significant effect (MD -0.50, 95% CI -1.81 to 0.81; $p = 0.46$; **Table 3.2**). Another trial used the Caregiver Burden Scale,[82] and again we found no significant effect (MD 1.30, 95% CI -4.88 to 7.48; $p = 0.68$; **Table 3.2**). 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.[81] 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.[81] 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.[78] 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.[81,82]. We found a significant summary effect (MD 6.35, 95% CI 1.64 to 11.06; p = 0.008; **Table 3.2**). One study assessed the Postural Assessment Scale for Stroke Patients[80] and found no significant effect of CME (MD 3.50, 95% CI -0.52 to 7.52; p = 0.09; **Table 3.2**). 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,[80] but more than half of the trials were of low risk of bias,[81,82] 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.[81] 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.[81,82] 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.[81] 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.[62,82] 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[82] and one trial with an unclear risk of bias.[62] 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.[78,79] However, there may be publication bias, because all studies excluded for meta-analysis were about upper limb training.[83-85] 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.[79] 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,[82] and one trial assessed only SIS hand function.[79] 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,[79] 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.[80] 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 3.3** 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 3.3. 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)

Abbreviations: SD = Standard Deviation

Dose of training

In three trials, the dose of training was comparable between the intervention and control groups.[62,78,85] In six trials, the dose of training in the intervention group was higher than the dose of training in the control group.[79-84] 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.[80,81,83,84] 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.[82] 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.[79] 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[80,81,83,84] versus trials that included patients beyond six months after stroke.[62,79,82] One trial included patients from beyond two months after stroke,[78] and another included patients directly after stroke;[85] 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,[78,79,83-85] and four of these trials were about CIMT.[78,79,84,85] However, Agrawal (2013), Gómez (2014), and Souza (2015) were not included in meta-analysis. Two trials were specifically aimed at the lower extremity.[62,81] 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 postintervention, 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).[62,81,83,85] Four trials studied the effect of another, existing intervention provided by the caregiver.[78-80,84] 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.[62,81,82] We found a significant summary effect for basic ADL postintervention 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 postintervention (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 postintervention 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).[62] 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.[81] 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.[83-85] All three trials were aimed at the upper extremity, with two trials applying CIMT.[84,85] For details of these trials, see the characteristics of included studies (**Supplemental Table 3C**). 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 3.4**.

Table 3.4. Results Agrawal 2013 (study not included in meta-analyses)

Outcome	Control group (mean scores)		GRASP 60 group (mean scores)		GRASP 90 group (mean scores)	
	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

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 (**Supplemental Table 3B**).

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.[6] 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.[79] 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 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.[124] 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.[79-84] Several systematic reviews have shown that a higher intensity of training can lead to better outcome in people with stroke in terms of ADL,[4-11] 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.[81,82,104] This may potentially increase feelings of self-efficacy and control of the caregiver.[125] 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.[81,82] Quality of the evidence was moderate. Reported mean change on the CSI from postintervention to follow-up was in favour of CME.[81] Veerbeek (2014) did show a significant homogeneous positive significant effect size on caregiver strain in its meta-analysis of trials about CME.[11] 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.[104] 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, task-oriented, and task-specific training in all phases post stroke.[11] 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.[4-11,75] Pollock and colleagues (2014) 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.[75] However, no conclusions could be drawn regarding to the total duration of the intervention due to substantial heterogeneity in the analyses.[75] 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.[6,10] In one trial, the intervention group received an extra 10 hours of treatment compared with the control group.[80] 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.[126-131] Pollock (2014) found evidence of greater benefit of an intervention associated with a shorter time since stroke onset.[75] 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 postintervention), 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,[78,79,83-85] and four of these trials were about CIMT.[78,79,84,85] CIMT has proven to be an effective therapy.[132] 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 (2015) 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.[85] 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 postintervention, but not at follow-up. This result is largely determined by a single study with a large number of participants,[79] and should, therefore, be considered with caution. Only two included trials were specifically aimed at the lower extremity.[62,81] 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.[80,82] 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.[133] 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'.[134] One of the excluded trials performed CME in both groups.[115] 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 healthcare, 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 (**Supplemental Table 3C**). 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,[78,79] trials with mobility exercises,[62,81,82] and other trials.[80] 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 (**Supplemental Table 3B**).

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.[135] 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.[81] However, more studies are needed to determine if CME can be cost-effective 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.[136] 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.[137] 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 out-come 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

Comparison 1: Caregiver-mediated exercises (CME) versus control - end of intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1. Patient: ADL measures: combined	4	295	Std. Mean Difference (IV, Fixed, 95% CI)	0.21 [-0.02, 0.44]
1.1 Barthel Index	3	247	Std. Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.09, 0.41]
1.2 Functional Independence Measure	1	48	Std. Mean Difference (IV, Fixed, 95% CI)	0.49 [-0.09, 1.06]
2. Patient: extended ADL measures: combined	2	196	Std. Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.21, 0.35]
2.1 Nottingham Extended ADL Index	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.33, 0.92]
2.2 IADL	1	156	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.31, 0.32]
3. Caregiver: burden: combined	2	91	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.45, 0.37]
3.1 Caregiver Strain Index	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.85, 0.39]
3.2 Caregiver Burden Scale	1	51	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.44, 0.66]
4. Measures of motor impairment: FMA lower extremity	1	40	Mean Difference (IV, Fixed, 95% CI)	3.10 [-2.02, 8.22]
5. Measures of motor impairment: FMA upper extremity	1	18	Mean Difference (IV, Fixed, 95% CI)	4.43 [-2.09, 10.95]
6. Gait and gait-related measures: balance: combined	3	139	Std. Mean Difference (IV, Fixed, 95% CI)	0.53 [0.19, 0.87]
6.1 Berg Balance Scale	2	91	Std. Mean Difference (IV, Fixed, 95% CI)	0.56 [0.14, 0.98]
6.2 Postural Assessment Scale for Stroke Patients	1	48	Std. Mean Difference (IV, Fixed, 95% CI)	0.48 [-0.09, 1.06]
7. Gait and gait-related measures: Six-Minute Walk Test	2	91	Mean Difference (IV, Fixed, 95% CI)	30.98 [-20.22, 82.19]

Comparison 1: CME versus control - end of intervention - *continued*

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8. Gait and gait-related measures: walking speed	2	71	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.03, 0.18]
9. Measures of upper limb activities or function: WMFT - functional ability	2	174	Mean Difference (IV, Random, 95% CI)	0.02 [-0.52, 0.55]
10. Measures of upper limb activities or function: WMFT - performance time	2	174	Mean Difference (IV, Fixed, 95% CI)	-1.72 [-2.23, -1.21]
11. Measures of upper limb activities or function: MAL - amount of use	2	174	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.36, 0.38]
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]
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]
14. Measures of mood and QoL: SIS - composite physical	1	51	Mean Difference (IV, Fixed, 95% CI)	12.40 [1.67, 23.13]
15. Measures of mood and QoL: SIS - strength	1	51	Mean Difference (IV, Fixed, 95% CI)	12.20 [-0.08, 24.48]
16. Measures of mood and QoL: SIS - ADL/IADL	1	51	Mean Difference (IV, Fixed, 95% CI)	11.4 [-1.11, 23.91]
17. Measures of mood and QoL: SIS - mobility	1	51	Mean Difference (IV, Fixed, 95% CI)	18.20 [7.54, 28.86]
18. Measures of mood and QoL: SIS - hand function	2	207	Mean Difference (IV, Fixed, 95% CI)	2.64 [-5.87, 11.15]
19. Measures of mood and QoL: SIS - memory	1	51	Mean Difference (IV, Fixed, 95% CI)	6.30 [-1.65, 14.25]
20. Measures of mood and QoL: SIS - communication	1	51	Mean Difference (IV, Fixed, 95% CI)	3.0 [-2.34, 8.34]
21. Measures of mood and QoL: SIS - emotion	1	51	Mean Difference (IV, Fixed, 95% CI)	2.10 [-4.35, 8.55]
22. Measures of mood and QoL: SIS - social participation	1	51	Mean Difference (IV, Fixed, 95% CI)	6.70 [-1.69, 15.09]
23. Measures of mood and QoL: SIS - general recovery	1	51	Mean Difference (IV, Fixed, 95% CI)	15.10 [8.44, 21.76]

Comparison 1: CME versus control - end of intervention - *continued*

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24. LOS - hospital	1	37	Mean Difference (IV, Fixed, 95% CI)	4.40 [-3.91, 12.71]
25. LOS - rehabilitation unit	1	20	Mean Difference (IV, Fixed, 95% CI)	12.0 [-10.88, 34.88]
26. Adverse outcomes: falls	1	48	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.10, 0.18]

Abbreviations: ADL = Activities of Daily Living; IADL = Instrumental ADL; FMA = Fugl-Meyer Assessment; WMFT = Wolf Motor Function Test; MAL = Motor Activity Log; QoL = Quality of Life; SIS = Stroke Impact Scale; LOS = Length Of Stay; CI = Confidence Interval.

Comparison 2: CME versus control - end of follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1. Patient: ADL measures: combined	2	196	Mean Difference (IV, Random, 95% CI)	2.69 [-8.18, 13.55]
1.1 Barthel Index	2	196	Mean Difference (IV, Random, 95% CI)	2.69 [-8.18, 13.55]
2. Patient: extended ADL measures: combined	2	196	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.17, 0.39]
2.1 Nottingham Extended ADL Index	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	0.51 [-0.12, 1.14]
2.2 IADL	1	156	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.31, 0.32]
3. Caregiver: burden	1	40	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.71, 1.91]
3.1 Caregiver Strain Index	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.71, 1.91]
4. Measures of motor impairment: FMA lower extremity	1	40	Mean Difference (IV, Fixed, 95% CI)	3.40 [-1.74, 8.54]
5. Measures of motor impairment: FMA upper extremity	1	18	Mean Difference (IV, Fixed, 95% CI)	2.75 [-8.24, 13.74]
6. Gait and gait-related measures: balance	1	40	Mean Difference (IV, Fixed, 95% CI)	8.40 [-1.04, 17.84]
6.1 Berg Balance Scale	1	40	Mean Difference (IV, Fixed, 95% CI)	8.40 [-1.04, 17.84]

Comparison 2: CME versus control - end of follow-up – *continued*

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7. Gait and gait-related measures: Six-Minute Walk Test	1	40	Mean Difference (IV, Fixed, 95% CI)	109.50 [17.12, 201. 88]
8. Gait and gait-related measures: walking speed	1	20	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.02, 0.22]
9. Measures of upper limb activities or function: WMFT - functional ability	2	174	Mean Difference (IV, Random, 95% CI)	0.08 [-0.46, 0.61]
10. Measures of upper limb activities or function: WMFT - performance time	2	174	Mean Difference (IV, Random, 95% CI)	1.85 [-8.78, 12.48]
11. Measures of upper limb activities or function: MAL - amount of use	2	174	Mean Difference (IV, Random, 95% CI)	0.21 [-0.65, 1.08]
12. Measures of upper limb activities or function: MAL - quality of movement	2	174	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.43, 0.37]
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]
14. Measures of mood and QoL: SIS - hand function	1	156	Mean Difference (IV, Fixed, 95% CI)	-2.20 [-12.46, 8.06]

Abbreviations: ADL = Activities of Daily Living; IADL = Instrumental ADL; FMA = Fugl-Meyer Assessment; WMFT = Wolf Motor Function Test; MAL = Motor Activity Log; QoL = Quality of Life; SIS = Stroke Impact Scale; CI = Confidence Interval.

Comparison 3: Timing poststroke - end of intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1. Patient: ADL measures: combined	4	295	Std. Mean Difference (IV, Fixed, 95% CI)	0.21 [-0.02, 0.44]
1.1 < 6 months	2	88	Std. Mean Difference (IV, Fixed, 95% CI)	0.44 [0.01, 0.86]
1.2 > 6 months	2	207	Std. Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.16, 0.39]

Abbreviations: ADL = Activities of Daily Living; CI = Confidence Interval.

Comparison 4: Mean change from postintervention - end of follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1. Patient: ADL measures: Barthel Index	1	40	Mean Difference (IV, Fixed, 95% CI)	2.3 [-3.95, 8.55]
2. Patient: extended ADL measures: Nottingham Extended ADL Index	1	40	Mean Difference (IV, Fixed, 95% CI)	4.00 [-0.99, 8.99]
3. Patient: extended ADL measures: Reintegration to Normal Living Index	1	40	Mean Difference (IV, Fixed, 95% CI)	4.3 [2.03, 6.57]
4. Caregiver: Caregiver Strain Index	1	40	Mean Difference (IV, Fixed, 95% CI)	1.1 [0.45, 1.75]
5. Measures of motor impairment: FMA lower extremity	1	40	Mean Difference (IV, Fixed, 95% CI)	0.30 [-2.21, 2.81]
6. Gait and gait-related measures: Berg Balance Scale	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.9 [-4.78, 2.98]
7. Gait and gait-related measures: Six-Minute Walk Test	1	40	Mean Difference (IV, Fixed, 95% CI)	43.3 [15.11, 71.49]
8. Other outcomes: Motor Assessment Scale	1	40	Mean Difference (IV, Fixed, 95% CI)	1.1 [-0.92, 3.12]

Abbreviations: ADL = Activities of Daily Living; FMA = Fugl-Meyer Assessment; CI = Confidence Interval.

Comparison 5: Sensitivity analysis - CME-core - end of intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1. Patient: ADL measures: Barthel Index	2	91	Mean Difference (IV, Fixed, 95% CI)	9.45 [2.11, 16.78]
2. Patient: extended ADL measures: Nottingham Extended ADL Index	1	40	Mean Difference (IV, Fixed, 95% CI)	5.5 [-5.83, 16.83]
3. Gait and gait-related measures: Berg Balance Scale	2	91	Mean Difference (IV, Fixed, 95% CI)	6.35 [1.64, 11.06]

Abbreviations: ADL = Activities of Daily Living; CI = Confidence Interval.

Comparison 6: Sensitivity analysis - CME-core - end of follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1. Patient: ADL measures: Barthel Index	1	40	Mean Difference (IV, Fixed, 95% CI)	9.0 [-1.29, 19.29]
2. Patient: extended ADL measures: Nottingham Extended ADL Index	1	40	Mean Difference (IV, Fixed, 95% CI)	9.5 [-1.83, 20.83]

Abbreviations: ADL = Activities of Daily Living; CI = Confidence Interval.

Comparison 7: Walking speed, different possibilities study of Wall

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1. Walking speed - caregiver-mediated exercises (CME) vs physiotherapy (PT) - end of intervention	2	61	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.07, 0.20]
2. Walking speed - CME vs PT - end of follow-up	1	10	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.04, 0.26]
3. Walking speed - CME vs no intervention - end of intervention	2	61	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.08, 0.19]
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]
5. Walking speed - CME and PT vs PT - end of intervention	2	61	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.06, 0.21]
6. Walking speed - CME and PT vs PT - end of follow-up	1	10	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.11, 0.31]
7. Walking speed - CME and PT vs no intervention - end of intervention	2	61	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.07, 0.20]
8. Walking speed - CME and PT vs no intervention - end of follow-up	1	10	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.11, 0.29]

Abbreviations: CME = Caregiver-Mediated Exercises; PT = Physiotherapy; CI = Confidence Interval.

Comparison 8: Extended ADL - analyses with Reintegration to Normal Living Index

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]
1.1 RNLI	1	40	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.59, 0.65]
1.2 IADL	1	156	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.31, 0.32]
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]
2.1 RNLI	1	40	Std. Mean Difference (IV, Random, 95% CI)	0.69 [0.05, 1.33]
2.2 IADL	1	156	Std. Mean Difference (IV, Random, 95% CI)	0.69 [0.05, 1.33]

Abbreviations: ADL = Activities of Daily Living; RNLI = Reintegration to Normal Living Index; IADL = Instrumental ADL; CI = Confidence Interval.

SUPPLEMENTARY MATERIAL

Supplement 3A. MEDLINE search strategy

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.
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/
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.

Supplement 3B. Summary of findings for the main comparison

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						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control intervention	Caregiver-mediated intervention				
Patient: ADL measures *Barthel Index (BI)* Scale 0 to 100 Follow-up: 2 studies; 3/6 months *Functional Independence Measure (FIM)* Scale 7 to 126 No follow-up	The mean BI score ranged across control groups from 78 to 84. 1 study: The mean FIM score in the control group was 65.	The mean BI 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).	-	BI: 247 (3) FIM: 48 (1) Total: 295	⊕⊕⊕⊖ **M**oderate	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 (CSI)* Scale 0 to 13 Follow-up 3 months *Caregiver Burden Scale (CBS)* Scale 22 to 88	The mean CSI score in the control group was 3.4. The mean CBS score in the control group was 46.6.	The mean CSI score in the intervention group was 0.50 higher (-0.81 to 1.81 higher). The mean CBS score in the intervention group was 1.30 lower (-4.88 to 7.48 lower)	-	CSI: 40 (1) CBS: 51 (1) Total: 91	⊕⊕⊕⊖ **M**oderate	Lower scores are better. Both studies at low risk of bias. Small total number of participants. SMD -0.04 (-0.45 to 0.37).

No follow-up						
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 *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)	⊕⊕⊕⊖ **M**oderate	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 (SIS) *SIS mobility scale* Scale 9 to 45 No follow-up	The mean SIS mobility score in the control group was 66.8.	The mean SIS 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 (-20.22 to 82.19).

Abbreviations: 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. *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).

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.

Supplement 3C. Characteristics of included studies *[ordered by study ID]*

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.	
Notes	-	
Risk of bias		
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) All outcomes	High risk	Participants and personnel cannot be blind for the intervention.
Blinding of outcome assessment (detection bias) All outcomes	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) All outcomes	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.
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		
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.
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		
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

Interventions	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.	
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		
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) **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		
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.
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, NIesulam. **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		
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 logbook 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. **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 logbooks. 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		
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		
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
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.

Interventions	**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).	
Notes	-	
Risk of bias		
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	-

Abbreviations: ADL = Activities of Daily Living; CIMT = Constraint-Induced Movement Therapy; CT = Computerized Tomography; IADL = Instrumental ADL; ITT = Intention-To-Treat; MRI = Magnetic Resonance Imaging; NDT = Neurodevelopmental Treatment; SD = Standard Deviation; SIS = Stroke Impact Scale; VR = Vestibular Rehabilitation.

Supplement 3D. Characteristics of excluded studies *[ordered by study ID]*

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.
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.

Abbreviations: CME = Caregiver-Mediated Exercises; RCT = Randomized Controlled Trial

Supplement 3E. Characteristics of ongoing studies *[ordered by study ID]*

ATTEND trial 2013	
Trial name or title	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-aug-13 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

Abbreviations: CME = Caregiver-Mediated Exercises; RCT = Randomized Controlled Trial

Care4Stroke trial 2014	
Trial name or title	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 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-apr-14 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 being done. This study is part of the Care4Stroke trial.

Abbreviations: CME = Caregiver-Mediated Exercises; RCT = Randomized Controlled Trial

4

Comparing two identically protocolized, multicentre, randomized controlled trials on caregiver-mediated exercises poststroke: Any differences across countries?

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ABSTRACT

Background: The evidence for rehabilitation interventions poststroke lack sufficient robustness. However, variation in treatment effects across countries have been given little attention.

Objective: To compare two identically protocolized trials conducted in different western countries in order to identify factors that may have caused variation in secondary trial outcomes.

Methods: Comparative study based on individual patient data (n = 129) from two randomized controlled trials, conducted in hospitals and rehabilitation facilities in the Netherlands (n = 66) and Australia (n = 63). Patients with stroke and their caregivers were randomly allocated to an 8-week caregiver-mediated exercises intervention (n = 63; 31 Australian and 32 Dutch) or to a control group (n = 66; 32 Australian and 34 Dutch). Patient characteristics, compliance, usual care and process measures were compared across countries. We examined if study setting significantly moderated the trial outcomes: Hospital Anxiety and Depression Scale, Fatigue Severity Scale and General Self-Efficacy Scale, measured at 8- and 12 weeks follow-up. In addition, we explored if factors that were significantly different across countries caused variation in these trial outcomes.

Results: Most patients suffered an ischemic stroke, were in the subacute phase and participated with their partner. Dutch patients were younger ($p = 0.005$) and had a lower functional status ($p = 0.001$). Australian patients were recruited earlier poststroke ($p < 0.001$), spent less time in exercise therapy ($p < 0.001$) and had a shorter length of stay ($p < 0.001$). The level of contamination was higher ($p = 0.040$) among Dutch controls. No effect modification was observed and trial outcomes did not change after controlling for cross-country differences.

Conclusions: The present study highlighted important clinical differences across countries whilst using an identical study protocol. The observed differences could result in a different potential for recovery and variation in treatment effects across trials. We argue that we can proceed faster to evaluating interventions within international pragmatic trials.

INTRODUCTION

Stroke affects approximately 104 million people worldwide and the global incidence of stroke is currently estimated at 11.9 million.[1] Stroke is a disabling condition with variable recovery patterns and a heterogeneous functional outcome.[2] Most patients require rehabilitation to assist functional recovery and optimize independence in daily life.[2,3] However, the current evidence for specific rehabilitation interventions poststroke lacks sufficient robustness and is largely based on findings from small, phase II, randomized controlled trials (RCTs).[3-5] Phase II RCTs are designed to estimate treatment effects with the lowest possible bias. Therefore, conflicting results across trials is assumed to result from either imprecision of effect estimates or true effect variation as a result of clinical heterogeneity.[6] Clinical heterogeneity refers to systematic differences in the outcomes studied or timing of outcome measurement, characteristics of patients (e.g. age, ethnicity, disease severity), interventions (e.g. content, dose, duration), or study setting (e.g. country, healthcare system, cultural context).[7] Further investigation of responder and non-responder groups or dose-response relationships is common within stroke recovery trials. However, variation in treatment effects across countries with a different healthcare system and cultural context have been given little attention.

In a recent collaboration, we simultaneously conducted two RCT's in Australia (ACTRN12613000779774) and the Netherlands (NTR4300). Both studies investigated the effect of a caregiver-mediated exercises (CME) intervention with e-health support,[8,9] which may be a valuable intervention to augment exercise therapy and improve functional outcome after stroke.[10,11] Although the primary outcome of both trials was neutral with respect to patients' self-reported mobility, different significant results regarding secondary psychosocial outcomes were found. The Dutch trial reported a significant decrease in caregiver depression and patient anxiety,[9] while the Australian trial reported a significant decrease in caregiver fatigue and increased caregiver self-efficacy.[8] Both trials had an identical study design that obeys CONSORT statements, used the same measurements of outcome and identical criteria of patient selection.[12] In addition, an identical intervention protocol in terms of content, dosing and treatment goals was used.[13] However, the studies were embedded within a different healthcare system and cultural context, making study setting the main source of heterogeneity for possible differences in outcome. Combining individual patient data from both trials allows us to investigate clinical heterogeneity and true effect variation across countries providing valuable information for future trial design and conduct.

The aim of the current study was to compare two identically protocolized trials in terms of design, outcome measurement, criteria of patient selection, and intervention protocol, applied in the Netherlands and Australia in order to identify factors that may have caused variation across countries in secondary trial outcomes. First, we hypothesized that the identical criteria of patient selection reduced patient heterogeneity. Second, we hypothesized that significant differences exist across countries in terms of usual exercise therapy and processes of care including length of inpatient stay and timing of recruitment. Finally, we hypothesized that study setting significantly moderated the secondary trial outcomes anxiety, depression, fatigue and self-efficacy.

MATERIAL AND METHODS

Study design

This study combined individual patient data from two identically protocolized, observer-blinded, multicentre RCTs in which patients with stroke and their appointed caregivers were randomly allocated to a CME intervention with e-health support in addition to usual care or to a control group that received usual care alone.[12] The two trials were simultaneously started in the Netherlands and Australia, respectively. The randomization procedures, sample size calculations and results of the separate trials have been published previously.[8,9] The medical ethics committee of the Slotervaart Hospital and Reade approved the Dutch study (NTR4300) and the local health research ethics board of Southern Adelaide Research Ethics Committee approved the Australian study (ACTRN12613000779774).

Definitions

- Imprecision is defined as random error in trial outcomes, as a result of sample variation. Hence, precision of effect estimates depends on the sample size, with smaller studies being less precise.[6]
- Methodological heterogeneity is defined as a difference across trials in the study design, outcome measurement tools or risk of bias. A higher degree of bias will lead to systematic error in trial outcomes.[6]
- Clinical heterogeneity is defined as a systematic difference across trials in the outcomes studied or timing of outcome measurement, characteristics of patients (e.g. age, ethnicity,

disease severity), interventions (e.g. content, dose, duration), or study setting (e.g. country, healthcare system, cultural context).[6,7]

- True effect variation is defined as variation in treatment effects as a consequence of clinical heterogeneity. True variation in trial outcomes is not explained by random or systematic error.[6,7]
- Study protocol is defined as a combination of the study design and intervention protocol. The design characteristics (e.g., blinding, randomization), study procedures, outcome measures, power calculation, criteria of patient selection and statistical analysis are protocolized in the study design. The essential elements of the trial intervention including its content, mode of delivery, dose, duration and monitoring of compliance are protocolized in the intervention protocol.
- Study setting is defined as the geographical location of a trial (i.e., country) including the healthcare system and cultural context in which it is embedded, and the context of individual study sites including their level of care (i.e., primary, secondary, tertiary), local healthcare processes and available resources including staff and expertise.[14]
- Contamination is defined as the receipt of active intervention amongst participants in the control arm of an RCT.[15]
- Pragmatic trials are defined as RCTs designed to determine the effect of an intervention under the usual conditions in which it will be applied,[16] more specifically the trial should 1) enrol a real-world population; 2) be conducted in a real-world setting; 3) include an appropriate comparison arm; and 3) capture relevant outcomes.[17]

Participant recruitment

Patients in the Netherlands were recruited from four hospital stroke units, two rehabilitation centres and seven rehabilitation wards of nursing homes in Amsterdam and its near surroundings. Patients in Australia were recruited from two hospital stroke units and one hospital rehabilitation unit in metropolitan Adelaide. Eligibility criteria for both patients and caregivers were: 1) 18 years or older; 2) able to understand the Dutch or English language; and 3) no significant signs of depression (Hospital Anxiety and Depression Scale [HADS] depression subscale < 11). Patients were eligible if they: 1) were diagnosed with stroke according to the WHO definition;[18] 2) experienced mobility limitations (Functional Ambulation Categories score < 5); 3) had sufficient cognition to follow instructions and provide informed consent (Mini-Mental State Examination [MMSE] > 18); 4) lived independently prior to stroke;

5) were planned to be discharged home; and 6) were willing and able to appoint a caregiver. Caregivers were eligible if they were: 1) willing to participate in CME; and 2) physically able to support the patient. Exclusion criteria for both patients and caregivers were: 1) a serious comorbidity that interfered with participation; and 2) not being medically stable. Participants were recruited in the early rehabilitation phase, following admission in a participating centre. All participants provided written informed consent prior to study enrolment.

Intervention

The C4S program consisted of an 8-week incremental training program with task-oriented and mobility-related exercises. An identical treatment protocol, including the intended dose, following the TIDieR guidelines was used.[13] Patient-caregiver dyads were asked to perform exercises together, at least five times a week for 30 minutes, within the clinical setting, outside or at home. In addition, participants were encouraged to exercise outside usual training hours. During a weekly face-to-face session with a trained physical therapist, dyads were instructed, evaluated and caregivers were educated to become an exercise coach. During the program, dyads were supported by an offline e-health application with instruction videos, in addition to usual care. The Australian and Dutch trials used respectively an English and Dutch version of the same video application.

Primary and secondary outcomes

Patients and caregivers in both trials were assessed using the same outcome measures, at baseline prior to randomization, and at 8- and 12-weeks follow-up. In both countries, outcome assessments were completed by an independent assessor blinded to treatment allocation. The primary outcome measure of both trials was the mobility domain of the Stroke Impact Scale (SIS 3.0).[19] The secondary outcome measures including their description and references has been published previously.[12] For the purpose of the current investigation, we selected the anxiety and depression subscales of the HADS,[20] the Fatigue Severity Scale (FSS)[21] and General Self-Efficacy Scale (GSES)[22] of both patients and caregivers to assess secondary trial outcomes of anxiety, depression, fatigue and self-efficacy.

To investigate systematic differences across countries in patient characteristics we used sex, age, living situation prior to stroke (alone or with someone), relationship with the appointed caregiver, type of stroke (ischemic or haemorrhagic), site of stroke (left or right hemisphere),

functional status measured with the modified Rankin Scale (mRS)[23] and cognition measured with the MMSE[24] at the moment of recruitment. Self-reported exercise minutes from diaries that were kept for 8 weeks following randomization, were used to investigate systematic differences in compliance and contamination (CME minutes) and usual exercise therapy (exercise minutes with a nurse, therapist and independent exercise minutes). Process measures that were compared across countries included timing of recruitment (days between stroke onset and randomization), timing of discharge (days between randomization and inpatient discharge) and length of inpatient stay (LOS) which was defined as the number of days between hospital admission and discharge from inpatient care.

Statistical analyses

Individual patient data from both trials were merged in one pooled database. First, systematic differences across the Dutch and Australian trials in terms of 1) patient characteristics; 2) compliance and usual exercise therapy; and 3) process measures; were compared using independent samples t-tests and we reported means and standard deviations in case of a normal distribution or used Mann-Whitney U tests and reported medians and interquartile ranges in case of a skewed distribution. A Chi-square test was used for categorical outcomes or a Fisher's exact test in case of few observations for individual cells (<10). Second, Linear Mixed Models were used to examine if the dichotomous variable 'country' was an effect-modifier that significantly moderated the secondary trial outcomes, with HADS anxiety, HADS depression, FSS and GSES as the dependent variables and treatment allocation, country, baseline score of the dependent variable and a treatment-by-country interaction term as covariates. A random intercept was included to adjust for the dependency of the repeated observations within subjects.[25] If a significant interaction was detected, treatment effects were reported separately for both countries. If no significant interaction was identified, the overall treatment effect was reported while controlling for country. Finally, patient characteristics and process measures that were systematically different across countries were successively added to the longitudinal model in order to explore if these factors may have caused variation in secondary trial outcomes. If the regression coefficient of treatment allocation changed by ≥10%, the covariate was considered to be a confounder and new candidate confounders were added to the longitudinal model.[26,27] A 2-tailed significance level alpha of 0.05 was used for all the statistical tests that were performed. Data were analysed using IBM SPSS Statistics version 25 for Windows.

RESULTS

Individual patient data of 129 patients and their appointed caregivers were included, of which 66 dyads were recruited in the Netherlands and 63 dyads in Australia. A total of 617/709 screened (87.0%) in Australia and 960/1082 screened (88.7%) in the Netherlands were excluded from participation. Patients were selected according to the same eligibility criteria, and no additional strategies were used to select or exclude patients. No significant difference (p = 0.054) was observed in the proportion of eligible patient-caregiver dyads that declined to participate in Australia, 29/709 screened (4.1%), compared to those that declined to participate in the Netherlands, 56/1082 screened (5.2%).

Systematic differences in patient characteristics

Table 4.1 presents the baseline characteristics of recruited patients in both countries. Patients in the Dutch trial were significantly younger (MD 7.7 years, CI 2.3-13.0; p = 0.005) and had a lower functional level (82% with a moderate to severe disability versus 54% in Australia) when compared to Australian patients. Although a higher proportion of patients were living alone prior to stroke in the Netherlands, this difference did not reach significance.

Systematic differences in compliance and usual care

Compliance with the intervention protocol did not differ across Australian (n = 31, Median 953 CME minutes, IQR 635-1390) and Dutch (n = 32, Median 1150 CME minutes, IQR 850-1500) intervention groups (p = 0.383). However, Australian controls reported significantly fewer CME minutes (n = 32, Median 60 minutes, IQR 5-495; p = 0.040) than Dutch controls (n = 34, Median 350 minutes; IQR 95-1065). Patients in Australia reported significantly (p = 0.04) less usual exercise minutes during the 8 weeks following randomization (n = 63, Median 2550 minutes, IQR 1478-3683) when compared to the Netherlands (n = 66, Median 3403 minutes, IQR 2220-3900). More specifically, patients in Australia reported less minutes in formal exercise therapy (Median 1080 minutes, IQR 473-1735; versus Median 2025 minutes, IQR 1368-2858; p < 0.001), but more independent exercises (Median 930 minutes, IQR 300-2408; versus Median 550 minutes, IQR 190-1200; p < 0.037). We found no significant difference (p = 0.114) in exercise time with a nurse (Median 0 minutes, IQR 0-140 and Median 35 minutes, IQR 0-173, in Australia and the Netherlands respectively).

Table 4.1. Differences in patient characteristics and process measures

Patient characteristics	The Netherlands (N = 66)	Australia (N = 63)	*p*-value
Age in years, mean (SD)	59.9 (14.8)	67.5 (15.8)	0.005*[a]
Sex, number of males (%)	41 (62.1)	40 (63.5)	0.872[c]
Type of stroke, N (%)			0.115[d]
Ischemic	50 (75.8)	54 (85.7)	
Haemorrhagic	16 (24.2)	8 (12.7)	
Both	0 (0.0)	1 (1.6)	
Site of stroke, N (%)			0.592[d]
Right hemisphere	37 (56.1)	39 (61.9)	
Left hemisphere	28 (42.4)	24 (38.1)	
Brainstem	1 (1.5)	0 (0.0)	
mRS disability (0-5), N (%)			0.001*[d]
1 no significant	1 (1.5)	2 (3.2)	
2-3 slight-moderate	11 (16.7)	27 (42.9)	
4-5 moderate-severe	54 (81.8)	34 (53.9)	
MMSE (0-30), median (IQR)	28.0 (25.0-29.0)	26.0 (24.0-28.3)	0.226[b]
Living alone, N (%)	20 (30.3)	10 (15.9)	0.059[c]
Caregiver, N (%)			0.280[c]
Partner	39 (59.1)	43 (68.3)	
Another caregiver	27 (40.9)	20 (31.7)	
Timing of recruitment in days, median (IQR)	37 (28-56)	14 (7-22)	<0.001*[b]
Timing of discharge in days, median (IQR)	69 (41-92)	18 (7-35)	<0.001*[b]
LOS in days, median (IQR)	112 (79-148)	34 (18-56)	<0.001*[b]

Abbreviations: IQR = Inter Quartile Range; SD = Standard Deviation; mRS = modified Rankin Scale; MMSE = Mini-Mental State Examination; LOS = Length Of inpatient Stay. * *P* <0.05. a = *P* values were calculated using independent samples t-tests; b = Mann-Whitney U tests; c = Chi-square tests; d = Fisher's exact tests.

Systematic differences in process measures

In **Table 4.1** process measures are presented for both countries. All process measures differed significantly across countries ($p < 0.001$). Patient-caregiver dyads in the Australian trial were recruited significantly earlier poststroke when compared to the Netherlands. Moreover, LOS was significantly shorter in Australia and as a result discharge occurred earlier in the program. Australian patients generally returned home in the first five weeks following randomization while Dutch patients returned home in the last two weeks or after completing the 8-week program.

Differences in secondary trial outcomes across countries

No significant interaction effects were observed between treatment allocation and the variable 'country' with respect to anxiety, depression, self-efficacy and fatigue of both patients and caregivers. The overall treatment effects of the C4S program with country as a covariate, and the interaction effects of treatment allocation and country are summarized in **Table 4.2**. The observed trial outcomes did not change after controlling for age, baseline functional status, or after controlling for usual exercise dose, timing of recruitment, timing of discharge and LOS.

DISCUSSION

To our knowledge, this is the first study in stroke rehabilitation that investigates cross-cultural clinical differences by comparing two identically protocolized phase II trials with respect to design, outcome measurement, patient selection and intervention conducted in two different Western countries. The present study shows that, despite identical criteria of patient selection, systematic clinical differences may be observed in study participants across countries. In addition, heterogeneity was observed in the level of contamination, amount of usual care and total length of inpatient stay. Awareness of clinical heterogeneity across countries is especially important when designing and conducting global trials. However, study setting did not moderate the secondary trial outcomes anxiety, depression, fatigue and self-efficacy suggesting that we can proceed faster to evaluating interventions within heterogeneous populations and study settings in pragmatic phase III and IV trials.

Table 4.2. Secondary treatment effects and study setting interaction effects.

Outcome measures patient	Beta (95% CI)	*P*-value[a] Treatment	*P*-value[a] Treatment*Country
HADS anxiety (0-21)	1.10 (0.01-2.20)	0.049*	0.220
HADS depression (0-21)	0.66 (-0.40-1.72)	0.222	0.470
FSS (1-7)	0.19 (-0.31-0.68)	0.462	0.505
GSES (10-40)	-0.42 (-1.99-1.14)	0.593	0.942
Outcome measures caregiver	**Beta (95% CI)**	***P*-value[a] Treatment**	***P*-value[a] Treatment*Country**
HADS anxiety (0-21)	0.23 (-0.94-1.41)	0.692	0.541
HADS depression (0-21)	0.94 (0.00-1.88)	0.050*	0.412
FSS (1-7)	0.18 (-0.19-0.54)	0.341	0.990
GSES (10-40)	-0.44 (-1.71-0.83)	0.493	0.703

Abbreviations: HADS = Hospital Anxiety and Depression Scale; FSS = Fatigue Severity Scale; GSES = General Self-Efficacy Scale. * P <0.05. a = P values were calculated using Linear Mixed Model analyses.

Patient heterogeneity was observed across countries with older age and a higher functional level at baseline in Australia when compared to the Netherlands. In general, age and functional status after stroke are factors known to influence discharge disposition and referral to inpatient rehabilitation after acute care on a hospital stroke unit (HSU).[28-30] In the Dutch study, participating HSUs were unable to recruit patients as a result of their fast discharge policies with a short LOS in the hospital. Hence, all patients were recruited from rehabilitation centres and rehabilitation wards of nursing homes. In contrast, Australian patients were recruited from acute HSUs as well as from hospital rehabilitation units which may explain the different casemix. In parallel, Australian patients were recruited earlier poststroke which is not unexpected within an acute setting. Age and functional status at admission are significant predictors of functional outcome after stroke.[28,31] Moreover, functional improvement is significantly associated with progress of time.[32] This suggests that age, functional status and

time poststroke at recruitment may be important effect modifiers that can cause variation in functional outcomes across trials despite following an identical study protocol.

The present study also shows that usual care is strongly dependent on features of the healthcare system and cultural context. To our knowledge, there are no recent studies reporting about practice variation in usual care across countries. We show that Australian patients spent less time in formal exercise therapy in both groups and total LOS was shorter when compared to the Netherlands. For the purpose of this study, LOS was defined as the number of days between acute hospital admission and final discharge home. Hence, this finding is not explained by timing of recruitment or level of care. The shorter LOS in Australia may be explained by the less severely affected population[33,34] or reflect differences in local healthcare policies with respect to rehabilitation services such as early supported discharge (ESD).[35] These findings are supported by lower costs of care observed in Australia, when compared to the Netherlands.[36] Although the emphasis on ESD has accelerated the interest in outpatient services,[37] most resources in stroke rehabilitation are focused on inpatient care.[35,38] As a result of the shorter LOS, Australian patients returned home faster following randomization which could explain the lower dose of formal exercise therapy during the 8 weeks thereafter. In stroke rehabilitation trials, the control group often receives 'usual care'. Unfortunately, the content, timing and dose of usual care is often poorly described.[39] Acknowledging that a difference in the amount of usual care delivered can result in a different potential for recovery[40,41] it is important to realize that these differences may exist across countries when designing global trials.

In the two trials, it was intended that controls received only usual care.[12,13] Although some contamination was present in the control groups of both studies, a significant difference was observed in its magnitude. The self-reported dose of CME within control groups was about 8 weekly minutes among Australian controls and 44 weekly minutes among Dutch controls, resulting in a larger treatment contrast in Australia. One of the most common sources of contamination within clinical trials is communication between trial arms, either between staff members or participants.[15] Such communication is more likely within an inpatient environment where patients are admitted to the same rehabilitation ward and providers of the intervention work closely together with other healthcare professionals. The earlier timing of discharge in Australia may therefore partly explain the lower level of contamination in this study. Another common source of contamination is when the intervention is already part of usual care to some extent.[15] Although the involvement of caregivers may differ across different social, cultural,

political and organizational contexts,[10] the total level of contamination is low and we have no data to support the structural use of CME in a usual care context in the Netherlands.

The present study highlighted important clinical differences across countries whilst using an identical study protocol. Although different significant results were reported in the separate trials regarding secondary outcomes of anxiety, depression, self-efficacy and fatigue,[8,9] we did not find a moderating effect of study setting on these trial outcomes. This suggests that treatment effects on secondary outcomes within small phase II trials may be imprecise and should be interpreted with caution. We argue that we should proceed faster to evaluating promising rehabilitation interventions poststroke in large phase III and IV trials. International collaboration to standardize study protocols including study design, outcome measurement and reporting is an important next step to improve robustness of trial outcomes in the field of stroke rehabilitation.[42-44] Awareness of clinical heterogeneity and consensus in trial conduct across countries through the international GAINS network is especially important when designing future global trials. First, we recommend that patients are recruited based on broad selection criteria, however at fixed times or within a narrow time window poststroke, and from multiple study settings to improve generalizability. Subsequently, responder analyses can be used to investigate and interpret a heterogeneous response to treatment. Second, the control condition should be monitored during the study period, and we should improve our reporting of 'usual care' including its specific content, dose and location. Third, careful consideration of the processes driving contamination is needed. Although cluster randomization is often mentioned as a solution, it could lead to patient heterogeneity across trial arms when patients are recruited from different study settings.[45] A balanced distribution of clusters over different settings or changes in trial conduct to reduce contamination could be considered. Finally, international consensus on parameters of trial conduct and reporting is essential for improving the quality of future stroke rehabilitation trials.

Strengths and limitations

Our individual patient dataset from two identically protocolized trials, independently conducted in two countries with a different healthcare system and cultural context, is unique. However, several study limitations should be acknowledged. First, the current study investigated differences across two Western, high-income countries and no generalizations can therefore be made to non-Western, low- or middle-income countries. Second, we did not collect information

on ethnicity, racial groups or comorbidities. Third, timing of recruitment was standardized based on the moment of admission to a participating rehabilitation ward. As a result, randomization, outcome measurement and initiation of the C4S program occurred at relatively arbitrary time points poststroke.

CONCLUSION

The present study highlighted important clinical differences across countries whilst using an identical study protocol, providing valuable information for future trial design and conduct. Theoretically, the observed clinical differences could result in a different potential for recovery and variation in treatment effects across trials. However, we did not find a moderating effect of study setting on the current secondary trial outcomes. We argue that we can proceed faster to evaluating promising interventions within large, pragmatic trials and give recommendations for designing future stroke rehabilitation trials.

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5

Agreement and differences regarding family functioning between patients with acquired brain injury and their partners

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ABSTRACT

Primary objective: To investigate the level of agreement and differences regarding the perception of family functioning between patients with acquired brain injury and their partners. Our hypothesis was that patients would report better family functioning than their partners.

Research design: Cross-sectional study.

Methods and procedures: Baseline data were used from 77 patient-partner dyads (87.0% stroke) who were participating in the ongoing CARE4Patient and CARE4Carer trials. Family functioning was assessed using the General Functioning subscale of the McMaster Family Assessment Device (FAD-GF). Agreement was assessed with intraclass correlation coefficient, a Bland-Altman plot, percentages absolute agreement and weighted kappa values. Differences were tested with Wilcoxon signed-rank tests.

Main outcomes and results: Patients and their partners differed in their perception of family functioning. Within-dyad agreement was poor regarding the overall FAD-GF scores with partners reporting significantly poorer family functioning compared to the patients (32.5% versus 18.2%). Agreement regarding the individual items ranged from slight to moderate.

Conclusions: Healthcare professionals should assess family functioning after stroke in both patients and their partners, and any discrepancies should be discussed with both members of the patient-partner dyad.

INTRODUCTION

Patients with acquired brain injury (ABI) typically suffer from complex problems, affecting both themselves and their caregivers. These may include physical, behavioural, cognitive, communicative and psychosocial problems, which can lead to loss of independence in everyday activities, reduced societal participation and poorer quality of life.[1] After inpatient care, most patients with stroke eventually return to their own home, and about 70% will be dependent on informal caregivers, usually family members.[2] The burden of care has a great impact on caregivers' physical and psychosocial well-being[2,3] with up to 65% of caregivers reporting health problems, high levels of strain and a decline in the quality of their social life.[4] Among caregivers, partners in particular have difficulties coping with the consequences of a brain injury.[5] Partners experience a sense of loss and need to adjust to a new relationship with the patient.[6,7] Changes in the relationship, lack of social support and changed roles of patients and partners may result in conflict, stress or even separation.[5,7] Both patients and caregivers experience negative consequences and there is an interdependent effect between patients with stroke and their caregivers on outcomes such as stress and quality of life.[8,9]

Family-centred interventions, aimed at both patients and caregivers, can result in better outcomes for the individual members of the dyad.[10-12] Evidence for outcomes concerning both members of the dyad together, such as family functioning, is still scarce. Family functioning comprises how family members work together and communicate with each other.[13] In patients with ABI, a negative perception of family functioning is associated with more depressive symptoms,[14] lower levels of activity,[15] and increased dependence in daily self-care[15] and home activities.[16] Poor family functioning, as perceived by caregivers, is associated with increased symptoms of anxiety and depression.[13,17-21] After an ABI, family functioning is often only assessed in caregivers, since patients may suffer from cognitive and communicative disorders.[11] Whether such a single measure is a valid representation of the perspectives of both members of the dyad is not clear, since little is known about the level of agreement and differences regarding perceived family functioning within dyads. To our knowledge, only two studies have reported on family functioning as perceived by both members of the patient-caregiver dyad, and their results are conflicting. One study found that patients reported better family functioning than their partners,[22] while another study found the opposite.[13] These contradictory results may be attributable to differences in the population they studied, e.g. the first study included only male patients and female partners, while the second study included not only partners but also other

caregivers. The further development of family-centred interventions for patients with ABI and their partners requires insight into the agreement about and differences in family functioning between these patients and their partners.

The objective of the present study was to examine how patients with ABI and their partners perceive their family functioning and to investigate agreement and differences regarding their perception of family functioning. We hypothesized that patients would report better family functioning than their partners.

MATERIALS AND METHODS

Design

For this cross-sectional investigation, data from two randomized controlled trials, CARE4Carer (NTR6197) and CARE4Patient (NTR5055), were combined. Designs, inclusion and exclusion criteria and trial interventions have been described in detail elsewhere and are briefly summarized here.[23-25] The medical ethics committee of the University Medical Centre Utrecht approved the CARE4Carer study. The CARE4Patient study was approved by the medical ethics committee of the Slotervaart Hospital and Reade. Reporting in this cross-sectional study follows the STROBE statement.[26]

Participants

In the ongoing CARE4Carer trial, patients with ABI (mostly stroke) and their partners are recruited during outpatient rehabilitation from hospitals and rehabilitation centres in the Netherlands. In the CARE4Patient trial, patients with ABI (mostly stroke) and their caregivers were recruited during inpatient rehabilitation from rehabilitation centres and nursing homes in the Netherlands. For the purpose of this study, only patient-partner dyads were selected. Participants, recruited until the end of 2018, were included in the current study. Inclusion criteria for patients and partners in both trials included: (1) aged 18 years or older, and (2) able to understand Dutch. Inclusion criteria for patients included: (1) having an ABI, and (2) living independently prior to the injury. Patients with neurodegenerative or progressive ABI were excluded from both trials. Additional in- and exclusion criteria were specified to ensure safety or determine suitability for the experimental interventions of the trials. Additional inclusion criteria for patients in the CARE4Patient trial were: (1) planned to be discharged home, (2) able

to follow instructions (Mini-Mental State Examination > 18), (3) having limited mobility (Functional Ambulation Category < 5), and (4) no significant symptoms of depression (depression subscale of the Hospital Anxiety and Depression Scale ≥ 11). In addition, patients and partners were excluded from CARE4Patient if they reported a serious comorbidity that interfered with participation or were medically unstable. Partners were excluded from the CARE4Carer trial if they: (1) were unable to use a computer, or (2) had no internet access. All participants gave written informed consent.

Measurements

In this study, we used baseline data from patients and partners participating in the CARE4Patient and CARE4Carer trials. Baseline measurements for CARE4Patient were taken during inpatient rehabilitation and those for CARE4Carer during outpatient rehabilitation. Family functioning was assessed using the General Functioning subscale of the McMaster Family Assessment Device (FAD-GF).[27] Patients and partners indicated their level of agreement (i.e., strongly disagree, disagree, agree, strongly agree) with 12 statements. Each statement was scored from 1 to 4, with higher scores reflecting poorer family functioning. A mean score of 2.0 or higher is defined as ineffective family functioning.[28] The Family Assessment Device (FAD) has good psychometric properties.[27-29] The FAD-GF has good reliability and validity[30] and the Dutch translation has good internal consistency.[31]

Patient and partner characteristics included demographics (age, sex, education, and employment), type of ABI, first or recurrent stroke, time since injury, being inpatient at a rehabilitation facility or living at home, communicative ability, anxiety and depression, and caregiver burden. Level of education was dichotomized into ‘higher education’ if participants had completed at least upper-level secondary school, and ‘lower education’ if they had completed lower-level secondary school or less. Communicative ability of the patients was dichotomized into presence or absence of communication restrictions, as indicated by a score of 3 or less on the Utrecht Communication Observation (UCO).[32] Anxiety and depression among both patients and partners were assessed using the Hospital Anxiety and Depression Scale (HADS).[33] The HADS consists of a 7-item anxiety and a 7-item depression subscale. Subscale scores above 7 suggest a mood disorder. Caregiver burden was assessed among partners with the Caregiver Strain Index (CSI).[34,35] The CSI consists of 13 items which can be

scored as ‘yes’ or ‘no’. The total score ranges from 0 to 13, with higher scores reflecting higher caregiver burden. A score of 7 or higher indicates substantial caregiver burden.

Statistical analyses

Normality of distribution of the data was assessed by Shapiro-Wilk tests and visual plots. Descriptive analyses were applied to describe the study sample, using means and standard deviations for normally distributed data and medians and interquartile ranges for non-normally distributed data. Independent samples t-tests, chi-square tests or Mann-Whitney U tests were conducted to test differences in demographic and psychosocial variables between effective and ineffective family functioning, in both patients and partners. The intraclass correlation coefficient (ICC) was used for measuring agreement within patient-partner dyads on their perception of family functioning. ICC estimates and their 95% confidence intervals (CIs) were calculated based on a single-rating, absolute agreement, two-way mixed-effects model. ICC values below 0.50 indicate poor agreement, values between 0.50 and 0.75 moderate agreement, values between 0.75 and 0.90 good agreement, and values greater than 0.90 excellent agreement.[36] A Bland-Altman plot was used to graphically display the level of agreement.[37] Agreement on individual items was evaluated as the percentage absolute agreement (exact patient-partner score matches). Weighted kappa values with quadratic weights were also calculated to determine item-level agreement within dyads. Kappa values below 0.00 indicate poor agreement, values between 0.00 and 0.20 slight agreement, values between 0.21 and 0.40 fair agreement, values between 0.41 and 0.60 moderate agreement, values between 0.61 and 0.80 substantial agreement, and values over 0.81 almost perfect agreement.[38] Wilcoxon signed-rank tests were used to test differences in the perception of general family functioning and regarding individual items. A two-tailed significance level alpha of 0.05 was used for all statistical tests. Data were analysed using IBM SPSS Statistics version 25 for Windows.

RESULTS

By the end of 2018, a total of 104 patients and their caregivers had been included in the ongoing CARE4Carer and CARE4Patient studies, 97 of whom provided complete data on family functioning for both members of the patient-caregiver dyad. CARE4Carer recruited 43 patients and their partners. CARE4Patient recruited 54 patients and their caregivers, of which 20

included other caregivers than partners. Those patient-caregiver dyads were excluded from the current study, resulting in a total of 77 patient-partner dyads. A description of their characteristics is presented in **Table 5.1**. Most patients had been diagnosed with stroke (87.0%), 8 of whom had had a recurrent stroke.

Table 5.1. Patients' and partners' characteristics (n = 77 dyads).

Characteristics	Patients	Partners
Age in years, mean (SD)	59.4 (8.7)	57.9 (9.1)
Male sex, n (%)	51 (66.2)	51 (66.2)
Higher education, n (%)	34 (44.2)	24 (31.2)
Employed before ABI, n (%)	53 (68.8)	47 (61.0)
Type of ABI, n (%)		
Ischemic stroke	45 (58.4)	
Haemorrhagic stroke	22 (28.6)	
Traumatic brain injury	8 (10.4)	
Oncology post-surgery	1 (1.3)	
Encephalitis	1 (1.3)	
Time since ABI in days, median (IQR)	80.0 (48.5-133.0)	
Living at home, n (%)	43 (55.8)	
Communication restrictions (UCO<4), n (%)	5 (6.5)	
Anxiety (HADS-A) [0-21], median (IQR)	5.0 (3.0-7.0)	5.0 (3.0-8.0)[a]
Anxiety (HADS-A) > 7, n (%)	18 (23.4)	21 (27.3)[a]
Depression (HADS-D) [0-21], median	5.0 (2.0-8.0)	4.0 (2.0-7.0)
Depression (HADS-D) > 7, n (%)	25 (32.5)	17 (22.1)
Caregiver burden (CSI) [0-13], mean (SD)		6.9 (2.6)
Caregiver burden (CSI) ≥ 7, n %		48 (62.3)

Abbreviations: FAD-GF = McMaster Family Assessment Device-General Functioning; ABI = Acquired Brain Injury; UCO = Utrecht Communication Observation; HADS = Hospital Anxiety and Depression Scale; CSI = Caregiver Strain Index. a = 1 missing.

Family functioning as reported by ABI patients and their partners

The median FAD-GF score of the patients was 1.50 (IQR = 1.17-1.83) reflecting a positive perception of family functioning. Fourteen patients (18.2%) had a score of 2.0 or higher, indicating ineffective family functioning. No significant differences were found between patients reporting effective and those reporting ineffective functioning (**Table 5.2**). The median FAD-GF score of the partners was 1.75 (IQR = 1.17-2.00) reflecting a positive perception of family functioning. Twenty-five partners (32.5%) reported ineffective family functioning. Partners reporting ineffective family functioning had significantly higher scores on caregiver burden ($t(75) = -3.84$; $p < .001$, $d = 0.92$), anxiety ($U = 306.0$; $p < .001$, $r = -0.42$) and depression ($U = 297.0$; $p < .001$, $r = -0.44$). In addition, partners reported ineffective family functioning when more time had passed since the brain injury ($U = 377.0$; $p = .003$, $r = -0.34$) and the patients were more often living at home ($X2 = 15.5$; $p < .001$, $r = 0.45$).

Table 5.2. Characteristics of patients and partners reporting effective versus ineffective family functioning (n = 77).

	Patients		**Partners**	
	Effective family functioning (n = 63)	Ineffective family functioning (n = 14)	Effective family functioning (n = 52)	Ineffective family functioning (n = 25)
Age in years, mean (SD)	59.4 (8.4)	59.3 (10.2)	58.7 (9.3)	56.1 (8.6)
Male sex, n (%)	40 (63.5)	11 (78.6)	21 (40.4)	5 (20.0)
Higher education, n (%)	27 (42.9)	7 (50.0)	16 (30.8)	8 (32.0)
Employed, n (%)	44 (69.8)	9 (64.3)	29 (55.8)	18 (72.0)
Time since ABI in days, median (IQR)	73.0 (46.0-131.0)	110.5 (72.3-137.8)	61.0 (37.0-117.3)	106.0 (80.5-153.0)*
Living at home, n (%)	32 (50.8)	11 (78.6)	21 (40.4)	22 (88.0)*
Anxiety (HADS) [0-21], median (IQR), (n=76)	5.0 (3.0-7.0)	4.5 (2.8-9.8)	4.0 (3.0-6.0)	9.0 (5.0-11.5)*
Depression (HADS) [0-21], median (IQR)	5.0 (2.0-8.0)	5.0 (3.5-8.3)	3.0 (1.0-6.0)	7.0 (4.0-10.0)*
Caregiver burden (CSI) [0-13], mean (SD)			6.2 (2.4)	8.4 (2.4)*

Abbreviations: HADS = Hospital Anxiety and Depression Scale; CSI = Caregiver Strain Index. * $P < 0.01$.

The perception of family functioning within dyads

Poor agreement within patient-partner dyads was observed for the FAD-GF scores (ICC = .45, 95% CI [.25, .61]). The Bland-Altman plot shows the difference between the FAD-GF scores of patients and partners (**Figure 5.1**). The mean difference between the scores was 0.11 and the 95% limits of agreement ranged from −0.85 to 1.07. The agreement between patients' and partners' scores was independent of the value of the mean score. A significant difference was observed between the FAD-GF scores of the patients and those of their partners (Z = 2.274, *p* = .023), with partners reporting poorer family functioning.

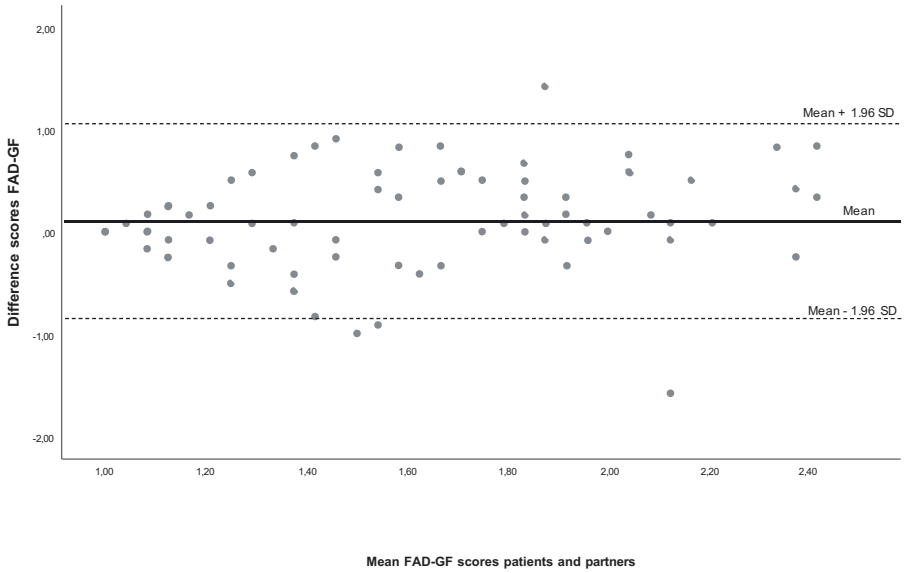


Figure 5.1. Bland-Altman plot of FAD-GF scores from patients and partners.

Agreement and differences regarding individual items of the FAD-GF are presented in **Table 5.3**. Within-dyad agreement for the individual items ranged from slight agreement on three items, to fair agreement on eight items and moderate agreement on one item, viz. '4. Individuals are accepted for what they are'. The lowest percentage of absolute agreement (36.4%) was found for item 5 'We avoid discussing our fears and concerns'. The item 'We don't get along well together' had the highest percentage of absolute agreement (71.4%) and a low weighted kappa (0.12). Further investigation revealed that the dyads showing less than perfect agreement

on this item had a greater discrepancy: in 5.2% of the dyads one member reported 'strongly agree' while the other member reported 'strongly disagree'. Significant differences were found for items 2, 3 and 8, with partners reporting poorer family functioning than patients.

Table 5.3. Agreement and differences on FAD-GF items within patient-partner dyads

	Patients	Partners	Agreement within dyads		Differences within dyads
FAD-GF items	Ineffective family functioning (%)	Ineffective family functioning (%)	Absolute agreement (%)	Weighted kappa (95% CI)	Wilcoxon signed-rank *p*-value
1. Planning family activities is difficult because we mis-understand each other	7.8	14.3	50.6	0.21 (0.01-0.41)	0.053
2. In times of crisis we can turn to each other for support	5.2	13.0	59.7	0.29 (0.07-0.50)	0.031*
3. We cannot talk to each other about the sadness we feel	5.2	14.3	51.9	0.22 (0.00-0.45)	0.026*
4. Individuals are accepted for what they are	7.8	11.7	58.4	0.45 (0.24-0.66)	0.170
5. We avoid discussing our fears and concerns	20.8	15.6	36.4	0.15 (-0.08-037)	0.509
6. We can express feelings to each other	10.4	11.7	54.5	0.34 (0.12-0.55)	0.588
7. There are lots of bad feelings in the family	5.2	6.5	59.7	0.37 (0.16-0.58)	0.654
8. We feel accepted for what we are	6.5	15.6	50.6	0.29 (0.04-0.53)	0.022*
9. Making decisions is a problem for our family	3.9	9.1	44.2	0.10 (-0.07-0.28)	0.097
10. We are able to make decisions about how to solve problems	3.9	2.6	62.3	0.27 (0.00-0.54)	0.157
11. We don't get along well together	2.6	3.9	71.4	0.12 (-0.09-0.33)	0.297
12 We confide in each other	3.9	7.8	55.8	0.21 (-0.04-0.46)	0.180

Abbreviations: FAD-GF = McMaster Family Assessment Device-General Functioning. * $p < 0.01$.

DISCUSSION

This is the first study to investigate agreement and differences between patients and their partners regarding their perception of general family functioning following a brain injury. We found that agreement within patient-partner dyads was poor. The perception of patients, primarily poststroke, and their partners differed, with partners reporting significantly poorer family functioning.

The objective of our study was to describe how patients with ABI and their partners perceive their family functioning. A previous study reported higher median scores on the FAD-GF in patients with stroke, indicating poorer family functioning, compared to our study.[14] King et al.[14] reported a significant association between patients' poorer family functioning and depressive symptoms, 2 years after discharge. We did not find this association, which may be attributable to the lower proportion of patients with ineffective family functioning in our sample (18.2% versus 33%). As regards the family functioning of partners, our findings are in accordance with previous research, which reported ineffective family functioning in about 30% of stroke caregivers.[13,18] Partners reporting ineffective family functioning in our study perceived higher burden and had more symptoms of anxiety and depression. This is also in line with previous studies, which reported associations between family functioning and anxiety and depression in partners.[13,17-21]

Agreement on general family functioning between the patients and their partners was poor (ICC = .45), which is lower than the agreement found in healthy dyads (ICC = .65).[39] A significant difference was observed between the FAD-GF scores of the patients and their partners, which is in accordance with a study which also reported poorer family functioning in partners compared to patients with stroke.[22] By contrast, our findings run counter to those from a previous study which reported significantly poorer family functioning in patients with stroke compared to their caregivers.[13] That study, however, also included caregivers other than partners. Partners may perceive poorer family functioning than other caregivers of patients with stroke.[40] Reports on the agreement and differences regarding individual items of the FAD-GF between patients with ABI and their partners have not been found in the current literature.

Our findings add to the scarce existing knowledge on the agreement and differences regarding family functioning. Low agreement between the perception of patients and their partners is also

found in other concepts, such as physical functioning of the patient, cognitive, emotional and behavioural changes and activities in daily living, where the partners are again more pessimistic.[41,42] The reason for this is unclear and requires further investigation.

The limitations of the current study should be mentioned. First, our study sample mainly consisted of patients with stroke (87.0%) and therefore these findings cannot be generalized to a broader population of patients with ABI and their partners. Second, this was a cross-sectional investigation and therefore the course of family functioning over time remains unclear. Third, patients and partners were excluded from the CARE4Patient trial if they reported significant symptoms of depression (HADS-D ≥ 11). Depressive symptoms may influence the agreement about and differences in perceived family functioning within dyads. Although few participants have been excluded due to symptoms of depression, our findings should be confirmed in a more heterogeneous sample with respect to depressive symptoms.

Patients with ABI (mostly stroke) and their partners differed in their perception of family functioning. Health care professionals should therefore assess family functioning in both patients with stroke and their partners. When family functioning can only be assessed in one member of a dyad, it is important to realize that perceptions within dyads may differ. We found that partners perceived poorer family functioning when more time had passed since the injury and when the patient had been discharged home. Family functioning is dynamic and likely to vary over time, as a result of changes in roles (e.g. from partner to caregiver) or depending on the post-injury phase (acute versus chronic).[14,19,43,44] Agreement about and differences in family functioning between patients and partners may also change over time. Family-centred interventions should be started early in the rehabilitation process, with repeated monitoring of the family functioning in both members of the dyad. Healthcare professionals should explore any discrepancies in the perception of family functioning and discuss these with both patient and partner.

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6

Can telerehabilitation services combined with caregiver-mediated exercises improve early supported discharge services poststroke? A study protocol for a multicentre, observer-blinded, randomized controlled trial

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ABSTRACT

Background: Recovery of walking ability is an important goal for patients poststroke, and a basic level of mobility is critical for an early discharge home. Caregiver-mediated exercises could be a resource-efficient strategy to augment exercise therapy and improve mobility in the first months poststroke. A combination of telerehabilitation and face-to-face support, blended care, may empower patient-caregiver dyads and smoothen the transition from professional support to self-management. The ARMed4Stroke study aims to investigate the effects of a caregiver-mediated exercise program using a blended care approach in addition to usual care, on recovery of mobility in the first 6 months poststroke.

Methods: A multicentre, observer-blinded randomized clinical trial in which 74 patient-caregiver dyads will be enrolled in the first 3 months poststroke. Dyads are randomly allocated to a caregiver-mediated exercises intervention or to a control group. The primary endpoint is the self-reported mobility domain of the Stroke Impact Scale. Secondary endpoints include care transition preparedness and psychological functioning of dyads, length of inpatient stay, gait-related measures and extended ADL of patients, and caregiver burden. Outcomes are assessed at enrolment, end of treatment and 6 months follow-up.

Results: During 8 weeks, caregivers are trained to become an exercise coach using a blended care approach. Dyads will receive a tailor-made, progressive training program containing task-specific exercises focusing on gait, balance, physical activity and outdoor activities. Dyads are asked to perform the training program a minimum of 5 times a week for 30 min per session, supported by a web-based telerehabilitation system with instruction videos and a messaging environment to communicate with their physiotherapist.

Conclusions: We hypothesize that the ARMed4Stroke program will increase self-reported mobility and independence in ADL, facilitating an early discharge poststroke. In addition, we hypothesize that active involvement of caregivers and providing support using blended care, will improve the care transition when professional support tapers off. Therefore, the ARMed4Stroke program may complement early supported discharge services.

BACKGROUND

In 2017, approximately 104 million people were living with the consequences of stroke.[1] Most patients have long-term disabilities and remain dependent on informal caregivers.[2] Stroke rehabilitation is typically front-loaded, with resources mainly focused on inpatient care.[3] After discharge, professional support tapers off and the majority of home-dwelling stroke patients are physically inactive.[4] Caregivers provide sustained support and could promote self-generated physical activity.[5] However, caregivers often feel unprepared for their new caregiving role[6] and nearly half of community-dwelling stroke patients continue to report unmet needs across a range of clinical domains including mobility and emotional well-being.[7] Improving the transition from inpatient stroke rehabilitation to the community is identified as a high priority topic by the World Stroke Organization.[8] Early supported discharge (ESD) services were developed to improve the transition and facilitate community reintegration by accelerating inpatient discharge and providing an equivalent level of rehabilitation at home.[9] Although the content of an effective service is not clearly defined, it has been shown that ESD can reduce disability and long-term dependency.[10] However, a basic level of mobility such as the ability to stand up from a chair is critical for the possibility of an early discharge.[11] In addition, patients still experience an abrupt and disjointed care transition when professional support from an ESD team dwindles and caregivers would benefit from more support and training.[12] Hence, strategies to improve mobility in the first months poststroke and smoothen the care transition are needed to facilitate and complement current ESD services.

Training caregivers to become an exercise coach and perform caregiver-mediated exercises (CME) may be a resource-efficient strategy to augment exercise therapy in the first 6 months poststroke.[13] Meta-analyses have shown that augmented exercise therapy and repetitive, progressive and task-oriented training can improve mobility and independence in activities of daily living (ADL) in the first 6 months poststroke.[14,15] In addition, involving caregivers in goal-setting and rehabilitation may smoothen the care transition by improving preparedness for discharge and enhancing self-efficacy in the home setting. A blended care approach, consisting of a combination of telerehabilitation and face-to-face support, is another promising paradigm to facilitate the transition from professional support to self-management.[16] Two recently conducted randomized controlled trials (RCTs) showed that CME supported by an offline application with exercise videos was feasible, safe, and effective in improving psychological outcomes.[17,18] In addition, dyads randomized to the CME intervention experienced a smooth

transition to the home setting.[19] Unfortunately, the intervention did not improve self-reported mobility, nor were significant differences found for secondary outcomes of physical functioning. The neutral outcome may be explained by insufficient treatment contrast between the intervention and control group in terms of total exercise time, as a result of contamination. Interestingly, the Australian trial did find a reduction in length of stay (LOS) in rehabilitation wards and a significant improvement of mobility and extended ADL in a per-protocol analysis of 20 patients that returned home during the intervention.[17] In addition to the CME program, this subgroup received telerehabilitation and home visits after discharge. Blended care and extending CME to the community, where caregivers can motivate the patient and provide continuity of exercises when professional support tapers off, could therefore be a promising addition to ESD services.

The Allied Rehabilitation using caregiver MEDiated exercises for Stroke (ARMed4Stroke) study investigates a CME program using a blended care approach, in addition to usual care. Compared to previous trials, there is an increased focus on joint goal-setting and rehabilitation in the home situation to increase motivation and stimulate self-management. The training program is developed to achieve important milestones for community ambulation[20,21] and dyads are supported by a web-based telerehabilitation system with individualized goals, exercise videos and a messaging environment to communicate with their physiotherapist.

The aim of this paper is to describe the ARMed4Stroke study design following the SPIRIT Statement. The multicentre, observer-blinded trial aims to assess the effects of the ARMed4Stroke program in addition to usual care, starting during the subacute phase poststroke.

We hypothesize that the ARMed4Stroke program will:

1) Increase patients' self-reported mobility;
2) Smoothen the care transition, resulting in reduced LOS and better preparedness for discharge;
3) Improve psychological functioning of patients and caregivers, such as mood and self-efficacy.

METHODS

Design

The ARMed4Stroke study is designed as a multicentre, observer-blinded, phase II, randomized controlled superiority trial with two parallel groups. Patient-caregiver dyads will be randomly allocated at a 1:1 ratio to 8 weeks of CME and telerehabilitation (ARMed4Stroke program) in addition to usual care, or usual care alone. The trial is registered since 11 December 2018 in the Netherlands Trial Register as NL7422. The study protocol was approved by the Medical Ethics Review Committee of VU Medical Centre on April 30th, 2019, and is registered with trial number 2019.081 - NL67357.029.18.

Setting

The multicentre study is conducted in the in- and outpatient clinics of 4 rehabilitation centres in the Netherlands: 1) Reade Rehabilitation, Amsterdam; 2) Roessingh, Centre for Rehabilitation, Enschede; 3) Sint Maartenskliniek, Nijmegen; and 4) Vogellanden, Zwolle. The Amsterdam UMC, location VU Medical Centre, is the initiator of this study in collaboration with Amsterdam Rehabilitation Research Centre | Reade and Roessingh Research and Development, Enschede.

Participants

Seventy-two patients with stroke, and 1 or 2 of their informal caregivers will be enrolled during in- or outpatient rehabilitation. The caregiver can be a partner, family member, or other person close to the patient. They are not healthcare professionals, nor are they paid for their efforts. 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”.[22] Subarachnoid haemorrhage, and stroke resulting from a brain tumour or traumatic brain injury are excluded as these subtypes differ in their prognosis.

Inclusion criteria for both patient and caregiver are: 1) 18 years or older; 2) written informed consent; 3) able to understand the Dutch language on sufficient level to understand instructions and complete the questionnaires; and 4) motivated for CME. Inclusion criteria for the patient

are: 1) < 3 months poststroke; 2) living independently prior to stroke; 3) discharged or planned to be discharged home; 4) able to follow instructions (Montreal Cognitive Assessment [MoCA] score > 21 points); and 5) able and willing to appoint an informal caregiver. An additional inclusion criterion for the caregiver is: being medically stable and able to support the patient. A trained physiotherapist will judge safety and determine if caregivers are physically and mentally able to support the patient during an intake exercise session. Exclusion criteria for both patient and caregiver will be a serious comorbidity that interferes with participation, e.g., premorbid restrictions in mobility as a result of a neurological disease, congestive heart failure or fractures of the lower extremity. Patients will not be enrolled in other clinical trials during the study period.

Baseline characteristics

Demographic and social characteristics of patients and caregivers will be recorded at baseline including: age, sex, country of birth, level of education, type and duration of relationship, living arrangement, work status, and comorbidities following the Cumulative Illness Rating Scale.[23] In addition, we will document stroke characteristics: type and location, stroke severity following the Bamford classification system,[24] date of stroke, previous stroke, hemiplegic side, presence of sensory deficits, hemianopia, neglect or aphasia, communicative ability following item 19 of the Utrecht Communication Observation,[25] and cognition following the MoCA.[26]

Study procedures

Every patient with stroke, starting in- or outpatient rehabilitation is screened for eligibility according to the inclusion and exclusion criteria by their rehabilitation physician and/or physiotherapist. Eligible dyads receive verbal and written information about the study. If a dyad wants to participate after a reflection period of 1 week, the intake exercise session is scheduled. Upon enrolment, informed consent will be signed by patient and caregiver(s) and primary and secondary endpoints are measured by an independent assessor (MM, CN). Following the assessments, an activity monitor is worn by the patient for 1 week and dyads are randomized to the intervention or control group at a 1:1 ratio using an online randomization module with a minimization algorithm to prevent unequal group sizes. The module will be managed by a researcher (EW, GK) from the initiating institute, not involved in inclusion, assessment or intervention delivery. Factors in the minimization include: 1) centre; 2) inpatient versus outpatient; 3) ≥70 years versus < 70; and 4) Functional Ambulation Category (FAC) 5 versus

FAC < 5. Primary and secondary endpoints are repeated by a blinded assessor (MM) at the end of treatment and 6 months follow-up (**Figure 6.1**: Study design).

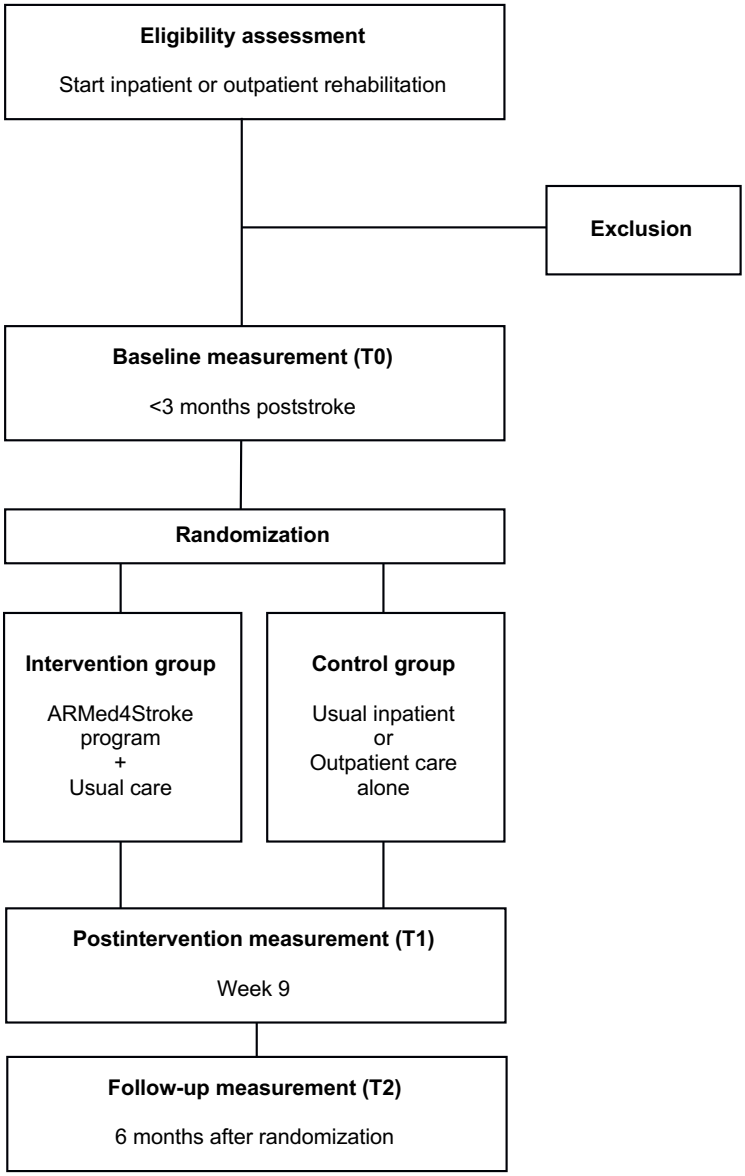


Figure 6.1. Study design

During the study period, serious adverse events will be recorded and reported to the Medical Ethics Review Committee of VU Medical Centre. Data collection is done using electronic Case Report Forms (eCRFs) within the Good Clinical Practice-proof, cloud-based clinical data management platform Castor EDC.[27] The study is monitored by the independent clinical research bureau from VU medical centre. Univariate checks, e.g., range checks, and conditional variables are built-in the eCRFs. The first participant was enrolled on September 2nd, 2019, and participants are currently being recruited and enrolled.

ARMed4Stroke intervention program

The ARMed4Stroke program consists of 8 weeks of complementary exercises executed with a caregiver (CME), in addition to usual care. A trained physiotherapist compiles a tailor-made, progressive training program, containing personal goals and task-specific exercises focusing on balance, gait, outdoor activities and physical training. A total of 31 goals and 80 exercises according to evidence-based physical therapy guidelines[28] were developed to achieve important milestones for community ambulation, based on expert's opinion and items of the hierarchical Mini-BESTest[29] and Rivermead Mobility Index (RMI).[30] Dyads are asked to perform the exercises minimally 5 times a week for 30 min per session. This intensity is in line with current exercise guidelines[28] and was shown to be feasible in previous CME studies.[17,18] Dyads are advised to execute their program outside usual training hours and during weekends, when patients are mostly inactive.[31,32]

Dyads are supported by a trained physiotherapist during at least 4 face-to-face sessions, scheduled every other week. During the first session, the program is explained in detail and explicit attention is given to information about the influence of physical activity and exercise on mood and health-related quality of life.[33] In addition, the role of caregivers and their benefits will be discussed. During subsequent sessions, the program is adapted according to the progress and personal goals of dyads, barriers are identified and addressed, and dyads are motivated to continue their exercise program. During the program, dyads are supported by exercise videos which are built into a web-based telerehabilitation system. Telerehabilitation poststroke should not be restricted to a time, place or device.[16] Therefore, the web-based system can be accessed on all devices with an internet connection including a computer, tablet or smartphone. In addition, dyads can communicate a-synchronically (i.e., exchange messages independent of time) with their physiotherapist. Therapists can use the telerehabilitation system to set-up goals

and exercises, monitor compliance and progress, give feedback and motivate participants. Physiotherapists were extensively trained in applying the program to optimize standardization.

Usual care

All participants will receive usual in- or outpatient physical therapy according to the Royal Dutch Guidelines of Physical Therapy.[28] Physical therapy sessions are designed to improve control of standing balance, physical condition, and walking competency. There are no restrictions with respect to content, time, or duration of therapy. Patients randomized to the control group will not have access to the ARMed4Stroke telerehabilitation module and no explicit attention is given to the involvement of caregivers in goal-setting and rehabilitation. An 8-week self-reported exercise diary is kept by all the participants to monitor compliance, record fall incidents and telerehabilitation use in a usual care context.

Outcome measures

Primary endpoint

The primary outcome is the mobility domain of the SIS version 3.0,[34] a stroke-specific questionnaire that evaluates self-reported health on 8 domains and a visual analogue scale (VAS). Items are scored on a 5-point Likert scale and domain scores are calculated ranging from 0 to 100.[35] The SIS has excellent clinometric properties in English[34,35] and Dutch.[36] The mobility domain consists of 9 questions about perceived ability to maintain balance, make transfers or walk in the community. The other 7 domains, the VAS and a composite physical domain are evaluated as secondary endpoints.

Secondary endpoints patient and caregiver

General Self-efficacy Scale (GSES). The GSES is a valid questionnaire to evaluate general self-efficacy beliefs.[37,38] The 10 items are rated on a 4-point scale and summed to produce a total score.

Preparedness for Caregiving Scale (PCS) and Transition Preparedness Scale (TPS). The PCS is a reliable and valid tool to assess transition preparedness in caregivers, to assume their new role and to handle the stresses of caregiving.[39] The PCS was translated to Dutch using forward- and back-translations and a modified version was developed to assess transition

preparedness in patients, the TPS. Psychometric evaluation of both scales is currently being conducted by the authors.

Hospital Anxiety and Depression Scale (HADS) and Computer Adaptive Tests (CAT). The HADS is a psychometrically robust measure to assess mood.[40,41] The scale consists of two 7-item subscales for anxiety and depression. In addition, anxiety and depression items of the Dutch-Flemish PROMIS item bank are administered with CAT.[42-44] CAT dynamically selects the optimal number of questions and the best next question, based on responses to previous questions.

Fatigue Severity Scale (FSS). The 9-item FSS is a reliable and valid instrument to assess fatigue. A mean item score is calculated ranging from 1 to 7.[45]

General functioning subscale of the McMaster Family Assessment Device (FAD-GF). The FAD-GF is a reliable and valid questionnaire to determine general family functioning.[46,47] A mean item score is calculated ranging from 1 to 4, based on 12 items. Perceptions of family functioning can differ and therefore the FAD-GF is administered to both patients and caregivers.[48]

Secondary endpoints patient

Length of stay (LOS). LOS is defined as the number of days between admission and discharge from the rehabilitation centre and will only be considered as a secondary endpoint for patients enrolled during inpatient rehabilitation.

Stroke Self-efficacy Questionnaire (SSEQ). The SSEQ is a reliable and valid measure of self-efficacy in relevant domains of functioning poststroke.[49] The SSEQ con-sists of 13 items with scores ranging from 0 to 10. Rasch analysis identified 2 dimensions: 1) Activity; and 2) Self-management;[50] and we will report these separate dimensions.

RMI. The RMI measures self-reported mobility post-stroke with 14 questions and 1 observation.[51] A total score of 0 to 15 is calculated. Psychometric properties of the English and Dutch version[51-53] have been established.

FAC score. Functional walking ability is evaluated with the 0 to 5 FAC score, a reliable, valid and responsive scale poststroke.[54] An assessor rates the level of independence, regardless of the use of assistive devices.

Six-minute Walking Test (6MWT) and Five-meter Walk Test (5MWT). The 6MWT[55,56] and 5MWT[57,58] are psychometrically robust tests to determine walking capacity poststroke. Distance walked during 6 min is recorded in meters. Mean gait speed is calculated in meters per second based on 3 repetitions. The 5MWT at a comfortable speed is recommended as the most responsive and convenient method of evaluating gait speed, when compared to fast speed or a 10-m distance.[59]

Leg section of the Motricity Index (MI-leg). The MI-leg is a reliable and valid tool to assess strength and range of motion of the paretic leg.[60,61] The test consists of 3 joint movements, i.e., ankle dorsiflexion, knee extension, and hip flexion which are rated on a 0 to 33 scale and summed. When the maximum score of 99 is achieved, 1 point is added.

Berg Balance Scale (BBS). The BBS measures balance during 14 tasks.[62] Items are rated on a 0 to 4 scale, and a total score is calculated ranging from 0 to 56. Reliability, validity and responsiveness are established poststroke.[62,63]

MOX-2 activity monitor. Physical activity will be measured for 7 days during wake hours using the MOX-2. The MOX-2 is a small, lightweight device and will be worn on the non-paretic thigh using an adhesive plaster. It measures 3D-accelerations during daily activities and mean daily physical activity is calculated over 1 week.

Nottingham Extended Activities of Daily Living index (NEADL). The NEADL is a 22-item reliable and valid test of extended ADL poststroke.[30,64,65] Rasch analysis did not support a unidimensional structure or polytomous scoring.[65] Therefore, the original dichotomous scoring method and domain scores: 1) mobility; 2) kitchen; 3) household; and 4) leisure, will be used.

Community Ambulation Questionnaire (CAQ). The CAQ measures the level of independent walking outside the home, i.e., without physical assistance or supervision.[66] Patients are categorized as: 1) unable to walk out-side unassisted; 2) only ambulant around the house (e.g., as far as the letterbox); 3) ambulant in the immediate environment (e.g., around the block); or 4) independent community ambulation (e.g., to visit a friend or shop).

The EuroQol 5D (EQ-5D). The 3-level version of the EQ-5D is a valid and reliable, generic measure of health-related quality of life poststroke.[67,68] The instrument consists of 5 dimensions: 1) mobility; 2) self-care; 3) usual activities; 4) pain/discomfort; and 5) anxiety/depression; and a VAS to assess perceived health.

Modified Rankin Scale (mRS). The mRS is a widely used 0 to 5 global rating scale of disability poststroke. An assessor rates the level of independence in pre-stroke activities. The scale has good reliability and validity post-stroke.[69]

Secondary endpoints caregiver

Caregiver Strain Index (CSI) and Care-related Quality of Life instrument (CarerQoL). Both the CSI[70-72] and the CarerQoL[73-75] are reliable and valid instruments to evaluate caregiver burden. The CSI consists of 13 items which are summed to produce a total score. The Carer-QoL consists of seven 3-level burden dimensions and a 0 to 100 VAS measuring happiness.

Power analysis

We expect a significant improvement of 10 points (10%) on the SIS mobility domain (mean 79.4, SD 14) in favour of the intervention group. We expect that minimally 30 patients are required per trial arm.[76] Including 20% drop-outs (for patients and caregivers), a sample size of 72 patient-caregiver dyads is needed to achieve sufficient statistical power of 80% using a two-tailed significance level alpha of $p < 0.05$. Currently, 26 participants have been enrolled in the ongoing trial.

Data analyses

Baseline characteristics will be presented in mean and standard deviation or median and interquartile range, depending on the normality of data distributions judged by visual plot and Shapiro-Wilk tests. Between-group differences will be studied to determine whether groups are comparable at baseline using non-parametric Wilcoxon signed rank sum tests when the data is not normally distributed, or student t-tests for independent samples in the presence of normally distributed data. The study endpoints will be compared between the intervention and control group at different time points using linear mixed model analysis. Time since stroke, group allocation, minimization factors and baseline value of the outcome measure will be added to

the longitudinal model. Intention-to-treat analysis will be applied, and all hypotheses will be tested two-sided using a critical value of < 0.05.

DISCUSSION

The ARMed4Stroke trial is a multicentre observer-blinded RCT that aims to investigate the effects of an improved CME program in addition to usual care on recovery of self-reported mobility poststroke. CME is a promising paradigm to improve psychological out-comes of patients with stroke and their caregivers. Unfortunately, two previous CME trials have failed to achieve sufficient treatment contrast in terms of augmented exercise time.[17,18] As a result, these trials were unable to show an improvement on mobility and other outcomes of physical functioning poststroke. The current trial aims to continue CME after inpatient discharge, in a period when professional support tapers off, reducing the impact of contamination and increasing treatment contrast. We hypothesize that the improved ARMed4Stroke program can increase self-reported mobility and independence, in addition to psychological improvements.

Although augmented exercise therapy can result in improved walking ability and independence in ADL,[14,15] it is critical to develop an active lifestyle to prevent deterioration and maintain physical function in the community.[77] Most people with stroke living in the community adopt a sedentary lifestyle[78] and even community-living people with only mild motor impairments, do not use their walking capacity to engage in physical activity.[4] The increased focus on personal goals and rehabilitation in a relevant context aims to heighten motivation. In addition, caregivers can provide patients with sustained support and motivate patients when professional support tapers off.[5] Hence, active involvement of caregivers in goal-setting and exercise therapy during the rehabilitation phase may promote long-term adherence to recommended physical activity levels and improve mobility outcome.

Telerehabilitation and CME may be resource-efficient strategies to augment exercise therapy and continue rehabilitation in the home setting. The current evidence suggests that telerehabilitation and CME are at least equally effective, when compared to usual care.[13,79-81] However, we would like to stress the importance of using these strategies to augment or extend rehabilitation instead of replacing traditional rehabilitation. Rehabilitation should start with professional face-to-face therapy to establish a good professional relationship and to provide

greater opportunity for progressive, goal-oriented treatment while ensuring safety. In addition, caregivers of patients with stroke need professional support during preparation for discharge and in the first few months of adjustment at home.[82] A blended care approach which combines telerehabilitation with face-to-face support may empower and better prepare patient-caregiver dyads for inpatient discharge and facilitate the transition from face-to-face therapy to self-management at home.

The ARMed4Stroke trials investigates a complex rehabilitation intervention with multiple interacting components and types of support. Physiotherapists are extensively trained in applying the ARMed4Stroke program and preparing patient-caregiver dyads for their roles in the intervention to optimize standardization, promote adherence to the multifaceted content and ensure an optimal quality of intervention delivery. However, healthcare policies and resources in terms of financial support and staffing can challenge implementation of these complex rehabilitation trials. Professional support, either face-to-face or using telerehabilitation, after discharge may not be reimbursed by health insurance. In addition, insufficient staffing and resources of rehabilitation centres can be barriers for both recruitment and intervention delivery. Another barrier for recruitment could be the absence of an informal caregiver to participate in CME. Although our definition of an informal caregiver is broad, the current intervention may not be suitable for patients with a limited social support system.

Several limitations of our design should be addressed. First, the aim of the current trial does not include an evaluation of cost-effectiveness. Theoretically, telerehabilitation and CME can be used to augment exercise therapy and provide sustained support after discharge with limited resource-use. However, there is currently insufficient evidence about the cost-effectiveness of these strategies.[13,79] Although no formal economic evaluation is planned, the protocol did include several secondary endpoints which can be used to evaluate cost-effectiveness including LOS, the EQ-5D and CarerQoL. Second, patient-caregiver dyads and physiotherapists cannot be blinded to treatment allocation. Therefore, our self-reported outcome measures may be subject to bias. However, the objective endpoints will be measured by a blinded assessor. Third, lack of blinding can result in contamination in terms of altered behaviour of the control group (i.e., CME and independent exercise time) and professionals (i.e., professional exercise time and telerehabilitation use). Therefore, the level of contamination will be monitored during the trial. Finally, we excluded patients with severe cognitive and/or communicative abilities to ensure that instructions are understood, safety is secured, and self-reported questionnaires can

be completed. Therefore, treatment effects may not be generalizable to more severely affected patients.

CONCLUSION

In conclusion, the ARMed4Stroke clinical trial investigates the effects of an improved CME program with an increased focus on personal goals, rehabilitation in the home situation, and combined with web-based telerehabilitation services poststroke. The ARMed4Stroke study is an important next step before proceeding to a larger phase III/IV cost-effectiveness trial.

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7

Allied Rehabilitation using caregiver-MEDiated exercises combined with telerehabilitation for Stroke (ARMed4Stroke): A randomised controlled trial

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ABSTRACT

Objective: To assess the added value of caregiver-mediated exercises combined with telerehabilitation in addition to usual care compared to usual care alone on the self-reported mobility outcome after subacute stroke.

Design: Multicentre, observer-blinded, parallel randomised controlled trial. An off-site researcher allocated treatments using minimisation.

Setting: Four rehabilitation centres in the Netherlands.

Participants: Forty-one patient-caregiver dyads within 3 months poststroke.

Intervention: Eight-week blended care program with caregiver-mediated mobility exercises for 2.5 h per week supported by telerehabilitation and four face-to-face sessions in addition to usual care.

Main measures: Self-reported mobility domain of the Stroke Impact Scale postintervention. Secondary outcomes were functional outcome, dyads' psychosocial wellbeing, care transition to the community post-intervention and after 6 months.

Results: Forty-one dyads (21 intervention, 20 control) were randomised, and 37 (n = 18; n = 19) were analysed following intention-to-treat. The Stroke Impact Scale mobility was not significantly different between groups postintervention (B 0.8, 95% CI -6.8-8.5, $p = 0.826$). The secondary outcomes, namely, (a) caregivers' quality of life postintervention ($p = 0.013$), (b) caregivers' symptoms of depression postintervention ($p = 0.025$), and (c) independence in leisurely activities at 6 months ($p = 0.024$), showed significant benefits in favour of caregiver-mediated exercises with telerehabilitation. A significant difference favouring controls was found in self-reported muscle strength at 6 months ($p = 0.002$).

Conclusions: Caregiver-mediated exercises combined with telerehabilitation yielded no differential effect on our primary outcome self-reported mobility. Although the trial is underpowered, current findings are in line with previous trials. Future studies should further explore beneficial effects of caregiver involvement in stroke rehabilitation targeting psychosocial wellbeing.

INTRODUCTION

Recovery of independent mobility (e.g. walking and maintaining balance) is a top priority of patients poststroke.[1] In addition, independent mobility determines to a great extent the ability to return home[2] and level of dependence on informal caregivers. It is estimated that approximately 75% of stroke survivors achieve independent mobility.[3] However, a risk of mobility deterioration exists when professional support tapers off.[4,5] Intensive, repetitive task training promotes recovery of mobility and independence in ADL in the first 6 months poststroke[6,7] and is recommended by clinical guidelines worldwide. Although the optimal dose remains unclear, the evidence suggests that more is better.[8] The recently updated National Institute for Health and Care Excellence (NICE) guideline for stroke in the United Kingdom recommends at least 3 h of individualised motor/functional therapy a day.[9] Unfortunately, patients often do not receive recommended amounts of training as a result of low staffing levels and time spent in non-patient activities.[10] Training of patient-caregiver dyads to perform task-specific exercises together, i.e. caregiver-mediated exercises, has the potential to augment training without increasing costs.[11] In this trial, a dyad refers to a patient and informal caregiver pair. Blended care, i.e. combining face-to-face support with telerehabilitation, may be a promising approach to provide tailored support to dyads and facilitate the transition to self-management at home.[12] Moreover, informal caregivers can provide sustained support after discharge and promote continued activity in the community.

The primary objective of this randomised controlled trial was to assess the added value of caregiver-mediated exercises combined with telerehabilitation in addition to usual care after subacute stroke on patients' self-reported mobility outcome when compared with usual care alone. Secondary objectives were to assess the differential effects on patients' functional outcome, dyads' psychosocial wellbeing and on the care transition in terms of length of stay and preparedness for discharge.

METHODS

We conducted a multicentre, observer-blinded randomised controlled trial with two parallel groups (trial registration NTR7664, 11 December 2018). The study protocol with the acronym Allied Rehabilitation using caregiver-Mediated exercises combined with telerehabilitation for Stroke (ARMed4Stroke) was extensively described and published previously.[13] No protocol

changes were made after trial commencement, and no protocol violations were found during monitoring visits. The Medical Ethics Review Committee of VU Medical Centre approved the study protocol on 30 April 2019 (2019.081 — NL67357.029.18), and all participants gave written informed consent. Recruitment started in September 2019 and ended in September 2022, with the last follow-up measurement in January 2023. The current report of results follows the CONSORT statement.[14]

Patients and caregivers were recruited from four rehabilitation centres in the Netherlands during in- or outpatient care: (a) Reade Centre for Rehabilitation and Rheumatology, Amsterdam; (b) Roessingh, Centre for Rehabilitation, Enschede; (c) Sint Maartenskliniek, Nijmegen; and (d) Vogellanden, Zwolle. Eligibility was determined in the first week of admission by a rehabilitation physician or physical therapist. Inclusion criteria were as follows: aged ≥18 years; willing to participate and able to understand Dutch on a sufficient level to understand instructions; complete self-reported questionnaires; and provide written informed consent. Additional inclusion criteria for patients were ≤3 months poststroke according to the WHO definition[15] excluding subarachnoid haemorrhage, living independently pre-stroke, planned to be discharged home or living at home, able to follow instructions (Montreal Cognitive Assessment >21) and willing and able to appoint a caregiver. Caregivers were defined as persons close to the patient (e.g. partner, family and friend) who were not practicing healthcare professionals nor were they paid for their efforts. Caregivers were eligible if they were mentally and physically able to support the patient, as determined by a trained physiotherapist during an intake exercise session. Exclusion criteria for both were a serious comorbidity that interfered with the intervention (e.g. lower extremity fracture) or not being medically stable. After baseline assessment by a blinded observer (MM), an off-site researcher (EW) randomly allocated eligible dyads to the Armed4Stroke intervention in addition to usual care or to usual care alone using an online randomisation module with a minimisation algorithm. Covariates in the minimisation were as follows: (a) centre; (b) inpatient vs outpatient; (c) age ≥70 vs <70; and (d) functional ambulation categories <5 vs 5. The off-site researcher informed the physiotherapist about the assigned intervention. Physiotherapists and dyads could not be blinded to treatment allocation.

The ARMed4Stroke intervention was an 8-week progressive, task-specific exercise program focused on mobility in addition to usual care after subacute stroke. Mobility training was supervised by an informal caregiver, supported using blended care with a minimum of four

face-to-face sessions scheduled every other week and asynchronous support via the online telerehabilitation platform Telerevalidatie.nl.[16] The physiotherapist composed a tailor-made exercise program in face-to-face consultation with dyads. Dyads were asked to perform exercises together for a minimum of 5 × 30 min per week and were encouraged to train outside of usual training hours and in weekends. During caregiver-mediated exercises, dyads had access to their tailored exercise program with exercise videos, personal instructions, mobility milestones and a messaging environment for asynchronous consultation via the telerehabilitation platform. During face-to-face sessions, patients and caregivers were trained and educated; treatment fidelity was discussed; barriers or facilitators were addressed; progress was evaluated; novel goals were identified; and the exercise program was modified accordingly. Patients in both study arms received usual mobility exercise therapy following guidelines from the Royal Dutch Society for Physical Therapy.[17] Multidisciplinary teams and supporting staff were instructed that content, frequency, and duration of regular therapies should be scheduled as usual in both arms. Patients in the control group did not have access to the ARMed4Stroke module on the telerehabilitation platform, and no explicit attention was given to caregiver involvement. All participants kept an 8-week diary to monitor compliance, fall incidents and estimate treatment contrast. Participants reported daily mobility-related exercise minutes with an informal caregiver, with a nurse, in therapy and self-directed exercise time. In addition, telerehabilitation use and fall incidents were recorded weekly.

Outcomes were assessed by a blinded observer at baseline (≤3 months poststroke), 8 weeks (postintervention) and 6 months follow-up. The primary outcome was the self-reported mobility domain of the Stroke Impact Scale 3.0 after 8 weeks. The mobility domain consists of nine questions about perceived ability to maintain balance, make transfers, walk and climb stairs. Questions are rated on a 5-point Likert scale, and a domain score (0-100) is calculated. The Stroke Impact Scale has excellent psychometric properties.[18] Secondary outcome measures were described in our study protocol, including references.[13] Secondary outcomes to establish effects on patients' functional outcome were the other domains of the Stroke Impact Scale, Rivermead Mobility Index, Functional Ambulation Category, 6 min walking distance, 5 m comfortable walking speed, Motricity Index Leg Score, Berg Balance Scale, Nottingham Extended ADL Scale, Community Ambulation Questionnaire and modified Rankin Scale at 8 weeks and 6 months follow-up; and the mobility domain of the Stroke Impact Scale at 6 months. Differential effects in dyads' psychosocial wellbeing were evaluated at 8 weeks and 6 months follow-up using the Stroke Self-efficacy Questionnaire and EuroQol-5D for patients, modified

Caregiver Strain Index, Care-related Quality of Life Instrument (seven dimensions and Visual Analogue Scale) for caregivers, General Self-efficacy Scale, Hospital Anxiety and Depression Scale, PROMIS Computer Adaptive Tests for anxiety and depression, Fatigue Severity Scale and the general functioning subscale of the McMaster Family Assessment Device for both patients and caregivers. Differential effects in the care transition were evaluated at 8 weeks and 6 months follow-up using the Transition Preparedness Scale for patients and Preparedness for Caregiving Scale for caregivers and using length of stay defined as the number of days between hospital admission and discharge home.

Statistical Analyses

Success of observer-blinding was tested by comparing actual with guessed allocation using Cohen's κ statistic. Baseline differences between groups were evaluated using Chi-squared tests, independent samples t-test or non-parametric Mann-Whitney U tests, where appropriate. Treatment effects were evaluated according to intention-to-treat and compared between groups at different time points using a linear mixed model for continuous outcomes and generalised estimating equations for ordinal outcomes. Differences in the care transition were only analysed in participants recruited during inpatient rehabilitation. Group allocation, time, a group-time interaction term and baseline values of the dependent were included as covariates. All hypotheses were tested using a two-tailed significance level alpha of 0.05. Data were analysed using IBM SPSS Statistics version 28. Sample size calculation showed that 72 dyads were required to achieve sufficient statistical power (80%) to detect a significant between-group difference of 10 points (10%) on the mobility domain of the Stroke Impact Scale (mean 79.4, SD 14) using a two-tailed significance level alpha of 0.05, including a 20% drop-out rate.[13] Due to the unexpected halt of recruitment in March 2020 and the subsequent slowdown of recruitment after restarting the trial during the COVID-19 pandemic, an unplanned futility analysis of the primary outcome was performed when sources of funding ended in September 2022. A conditional power of 20% was used to establish futility. The adjusted p-value for the efficacy analysis was based on 41 patients of the required 72 patients. Using the Lan-DeMets alpha spending function for the Pocock boundary, the adjusted p-value was equal to 0.035.[19]

RESULTS

A total of 41 dyads were recruited (**Figure 7.1**: CONSORT flowchart) and randomised to the ARMed4Stroke group (n = 21) or usual care alone (n = 20). Low agreement was observed between blinded guesses from the assessor and actual treatment allocation (κ=0.219, p = 0.161), indicating successful blinding.

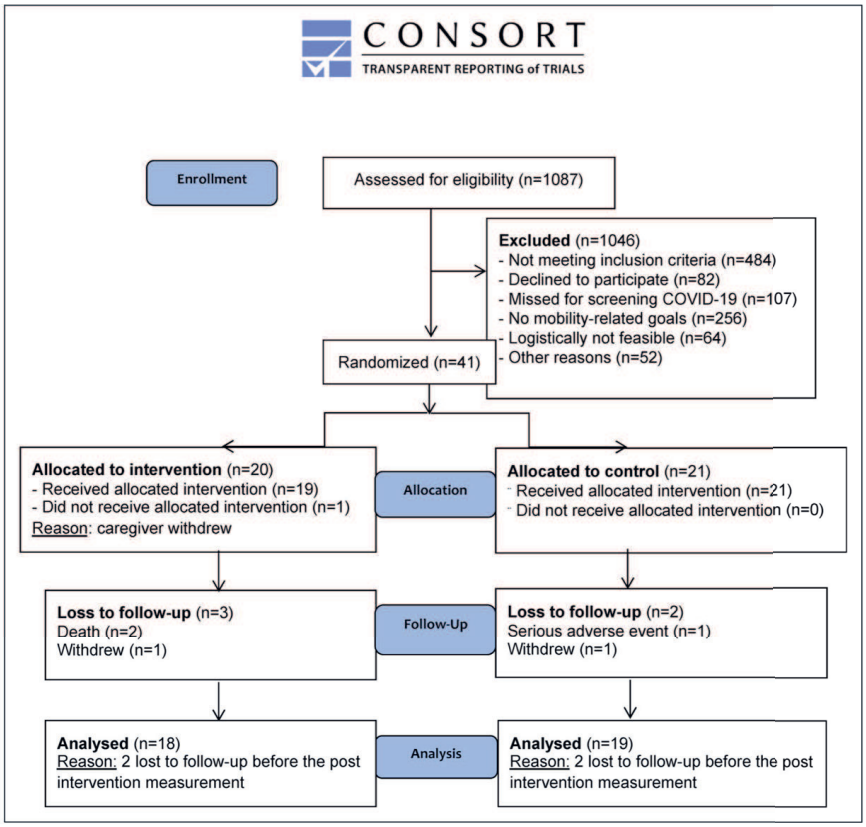


Figure 7.1. CONSORT 2010 flow diagram

Self-reported mobility-related exercise minutes (caregiver-mediated, self-directed, in therapy and with a nurse) during 8 weeks are reported in **Table 7.1**.

Table 7.1. Total self-reported exercise minutes during 8 weeks

Self-reported exercise minutes	Usual care median (IQR)	ARMed4Stroke median (IQR)	*p*-value
With a therapist	1445 (740-2633)	1420 (720-2250)	0.778
Self-directed	1005 (873-1880)	1950 (750-2690)	0.540
With a nurse	30 (0-295)	0 (0-20)	0.101
Caregiver-mediated	435 (235-1145)	1260 (930-1980)	0.006*

Abbreviations: IQR = Interquartile Range * $p < 0.05$

Median caregiver-mediated exercise minutes in the ARMed4Stroke group slightly exceeded the intended dose of 1200 min, and a significant treatment contrast was observed ($p < 0.006$). No significant contrast was observed in the total mobility-related exercise time ($p = 0.221$) with a median of 3875 min (IQR 2185-6605) in the usual care group compared to 5010 min (IQR 4060-6120) in the ARMed4Stroke group. In the usual care group, five falls were reported compared to four falls in the ARMed4Stroke group ($p = 0.703$).

Baseline characteristics are presented in **Table 7.2**. Patients had an average age of 62 years (SD 10.2), while the caregivers' mean age was 59 years (SD 11.5). Approximately 56% of our patients were male, and almost 15% of them were not born in the Netherlands. Most patients (90.2%) were recruited during inpatient rehabilitation, participated with their partner (95.1%) and were on average 56 days (SD 16.6) poststroke. A significant between-group difference was observed in stroke classification ($p = 0.036$), with a higher proportion of lacunar strokes in the ARMed4Stroke group. No significant baseline differences were observed in our primary outcome measure (MD −9.91, 95% CI −22.77-2.95, $p = 0.127$) or secondary outcome measures.

Table 7.2. Baseline characteristics

Patient	Control (N = 20)	ARMed4Stroke (N = 21)	*p*-value
Sex, female/male	8/12	10/11	0.623
Mean age (SD), years	63.0 (8.9)	61.3 (11.5)	0.608
Education, low/high[1]	7/13	9/12	0.606
Country of birth, Dutch/other	17/3	18/3	1.000
Living arrangement, alone/together	1/19	1/20	1.000
Working before stroke, yes/no	9/11	15/6	0.086
CIRS (0-52), median (IQR)	4.0 (2.0-5.0)	2.0 (1.0-4.0)	0.164
Rehabilitation phase, in/outpatient	17/3	20/1	0.343
Mean time poststroke (SD), days	56.8 (17.1)	55.2 (16.6)	0.775
Stroke type, haemorrhagic/ischaemic	6/14	7/14	0.819
Stroke location, right hemisphere/ left hemisphere/brainstem/cerebellum	10/7/2/1	18/2/1/0	0.051
Recurrent stroke, yes/no	1/19	1/20	1.000
Aphasia, yes/no	1/19	1/20	1.000
Hemianopia, yes/no	3/17	0/21	0.107
Bamford, LACS*/PACS/POCS/TACS	10/6/1/3	18/3/0/0	0.036*
MoCA (0-30), mean (SD)	26.3 (2.3)	25.6 (2.0)	0.314
Caregiver	**Control (N = 20)**	**ARMed4Stroke (N = 21)**	***p*-value**
Sex, female/male	10/10	11/10	0.879
Mean age (SD), years	60.2 (12.2)	58.4 (10.9)	0.624
Education, low/high1	9/11	9/11	1.000
Country of birth, Dutch/other	19/1	16/4	0.184
Relationship to patient, partner/other	19/1	18/2	0.606
Living together, yes/no	20/0	19/2	0.488
Median duration relationship (IQR), years	39.5 (26.3-45.0)	35.5 (22.0-43.8)	0.492
Working (before stroke), yes/no	10/10	16/5	0.082
CIRS (0-52), median (IQR)	0.5 (0.0-2.0)	2.0 (0.0-4.0)	0.247

Abbreviations: SD = Standard Deviation; IQR = Interquartile Range; CIRS = Cumulative Illness Rating Scale; LACS = Lacunar Stroke; PACS = Partial Anterior Circulation Stroke; POCS = Posterior Circulation Syndrome; TACS = Total Anterior Circulation Stroke; MoCA = Montreal Cognitive Assessment. [1] Education: low = none / primary school / secondary school / intermediate vocational education; high = higher vocational education / college / university. *$p < 0.05$.

The absolute mean values (SD) of our primary and secondary outcomes at different time points and between-group results of the linear mixed model and generalised estimating equations analyses corrected for baseline score are presented in **Table 7.3**. No significant differences were observed between groups for the primary outcome measure, Stroke Impact Scale mobility, after 8 weeks (B 0.8, 95% CI −6.8-8.5, $p = 0.826$). Conditional power was calculated, and futility (<0.2) was established (0.066). We concluded that extending recruitment by applying for novel funding would not result in efficacy, and the project team decided to stop the trial.

After 8 weeks, no significant differential effects were observed in patients' functional outcome or psychosocial wellbeing. We did observe significant beneficial effects in caregivers' psychosocial well-being, following the Care-related Quality of Life Instrument (seven-dimension score $p = 0.013$ and Visual Analogue Scale $p = 0.042$) and depression domain of the Hospital Anxiety and Depression Scale ($p = 0.025$) after 8 weeks. After 6 months of follow-up, we observed a significant between-group difference in terms of the functional outcome on the leisure domain of the Nottingham Extended ADL scale ($p = 0.024$) in favour of the ARMed4Stroke group and on the strength domain of the Stroke Impact Scale ($p = 0.002$) favouring the control group. No significant beneficial effects were observed in psychosocial wellbeing after 6 months. Within the subgroup of patients recruited from an inpatient setting, no significant differential effects were established in the care transition. A non-significant difference was observed between groups in the length of stay with a mean stay of 91.0 days (SD 29.0) in the usual care group compared to 83.9 days (SD 23.4) in the ARMed4Stroke group (MD 7.06; SE 8.98; 95% CI −11.24-25.35; $p = 0.438$).

Table 7.3. Results of the intention-to-treat analyses corrected for the baseline score

Outcome measures	Control (N=20)			Intervention (N = 21)			Between-group effect sizes T1		Between group effect sizes T2	
	T0	T1	T2	T0	T1	T2	B (95% CI)	*p*-value	B (95% CI)	*p*-value
Primary outcome measure										
SIS mobility (0-100)	61.3 (21.9)	82.7 (15.6)	85.5 (16.7)	71.2 (18.2)	86.0 (13.1)	85.1 (12.0)	0.8 (-6.8-8.5)	0.826	3.6 (-4.1-11.3)	0.354
Secondary outcome measures										
SIS strength (0-100)*	41.8 (23.1)	52.4 (20.7)	62.5 (23.1)	44.6 (21.6)	52.6 (22.5)	51.0 (26.6)	5.4 (-4.7-15.4)	0.289	16.2 (6.1-26.4)	0.002
SIS memory (0-100)	85.9 (14.9)	91.1 (10.2)	90.1 (11.3)	85.5 (14.9)	88.0 (14.2)	88.2 (15.7)	2.5 (-4.0-9.1)	0.444	1.2 (-5.5-7.8)	0.725
SIS emotion (0-100)	60.7 (7.1)	60.5 (6.9)	68.3 (12.7)	64.8 (10.0)	63.3 (8.0)	64.0 (10.1)	-1.1 (-7.3-5.0)	0.712	6.0 (-0.2-12.3)	0.059
SIS communication (0-100)	92.9 (12.8)	93.7 (9.3)	94.5 (6.6)	92.3 (9.1)	91.9 (10.3)	91.2 (10.8)	1.3 (-3.0-5.6)	0.554	2.7 (-1.7-7.0)	0.224
SIS ADL (0-100)	53.4 (15.1)	64.0 (15.3)	71.2 (17.0)	60.1 (17.1)	72.4 (14.9)	79.5 (12.5)	-4.5 (-12.5-3.6)	0.272	-5.1 (-13.3-3.0)	0.210
SIS hand (0-100)	27.1 (32.5)	37.5 (37.0)	55.0 (34.8)	31.9 (36.1)	55.5 (33.7)	62.4 (33.5)	-13.0 (-29.4-3.4)	0.119	-3.2 (-19.8-13.4)	0.704
SIS participation (0-100)	46.4 (24.5)	58.9 (12.9)	63.4 (21.7)	42.1 (23.1)	61.8 (18.8)	68.8 (20.8)	-4.2 (-16.2-7.9)	0.492	-6.9 (-19.1-5.3)	0.266
SIS recovery (0-100)	41.4 (16.4)	53.5 (16.9)	55.6 (21.4)	44.9 (17.5)	57.3 (18.0)	66.5 (14.6)	-0.5 (-9.5-8.5)	0.911	-7.9 (-17.0-1.2)	0.087
SIS physical (0-100)	49.6 (17.4)	63.6 (16.3)	71.6 (17.5)	56.4 (16.1)	70.9 (13.8)	74.2 (13.3)	-2.0 (-8.8-4.8)	0.554	1.9 (-5.0-8.7)	0.588

RMI (0-15)	9.3 (3.8)	12.3 (2.8)	12.9 (2.4)	9.6 (3.3)	12.8 (2.0)	13.6 (1.2)	-0.4 (-1.5-0.7)	0.493	-0.6 (-1.8-0.5)	0.253
FAC (0-5)	3.6 (1.3)	4.6 (0.9)	4.9 (0.5)	3.6 (1.0)	4.8 (0.4)	5.0 (0.2)	-1.9 (-4.1-0.3)	0.091	-1.1 (-4.8-2.6)	0.556
CAQ (0-3)	0.8 (1.2)	2.1 (1.2)	2.1 (1.3)	0.6 (1.1)	2.1 (1.2)	2.5 (1.0)	0.1 (-1.2-1.4)	0.860	-1.1 (-2.6-0.5)	0.174
5MWT speed, m/s	0.56 (0.33)	0.89 (0.37)	0.97 (0.47)	0.55 (0.25)	0.90 (0.29)	0.95 (0.33)	-0.1 (-0.2-0.1)	0.474	0.0 (-0.2-0.2)	0.903
6MWT distance, meters	231.9 (133.9)	329.7 (135.4)	343.0 (136.5)	198.4 (106.3)	316.1 (117.9)	329.6 (125.8)	-13.3 (-76.1-49.5)	0.669	-3.4 (-67.6-60.8)	0.915
BBS (0-56)	41.4 (13.9)	51.8 (5.0)	52.7 (4.9)	43.7 (11.8)	52.0 (4.6)	53.4 (3.8)	-0.4 (-1.9-1.1)	0.608	-0.6 (-2.2-1.0)	0.478
MI leg (0-100)	55.3 (19.6)	66.4 (19.3)	68.5 (22.3)	50.9 (17.1)	67.7 (23.3)	67.2 (24.9)	-6.7 (-15.8-2.3)	0.141	-1.6 (-11.0-7.8)	0.732
NEADL mobility (0-6)	1.3 (1.8)	3.9 (1.7)	4.1 (2.0)	1.7 (1.7)	3.9 (1.8)	4.9 (1.0)	0.1 (-1.0-1.1)	0.890	-0.7 (-1.7-0.40	0.188
NEADL kitchen (0-5)	2.0 (1.6)	3.8 (1.4)	4.2 (1.0)	2.5 (1.7)	4.4 (1.2)	4.4 (1.0)	-0.3 (-1.1-0.4)	0.349	0.0 (-0.7-0.7)	0.969
NEADL household (0-5)	0.8 (1.1)	2.1 (1.6)	2.6 (1.8)	1.1 (1.3)	2.5 (1.5)	3.3 (1.3)	-0.2 (-1.2-0.8)	0.668	-0.4 (-1.4-0.6)	0.399
NEADL leisure (0-6)*	2.9 (0.6)	3.4 (0.7)	4.0 (0.9)	2.5 (1.0)	3.7 (0.7)	4.4 (1.0)	-0.5 (-1.1-0.0)	0.052	-0.6 (-1.2--0.1)	0.024
mRS (0-5)	3.3 (0.7)	2.4 (0.7)	1.8 (0.9)	3.2 (0.6)	2.1 (0.7)	1.5 (0.7)	1.0 (-0.1-2.2)	0.068	1.1 (-0.5-2.7)	0.189
TPS (0-32)	17.8 (7.8)	21.3 (7.5)	22.9 (6.4)	17.2 (7.2)	20.2 (6.3)	20.6 (6.8)	1.0 (-2.7-4.7)	0.596	2.0 (-1.8-5.8)	0.306
SSEQ Activity (0-80)	45.7 (15.3)	58.8 (14.8)	65.5 (14.1)	47.3 (19.3)	58.2 (12.1)	63.8 (10.6)	1.1 (-6.0-8.3)	0.749	1.5 (-5.7-8.7)	0.678

SSEQ Self-Management (0-50)	35.7 (6.7)	36.1 (7.8)	36.3 (8.6)	34.1 (8.6)	34.9 (8.5)	35.8 (9.4)	0.3 (-4.1-4.8)	0.887	-0.2 (-4.7-4.4)	0.944
GSES (10-40)	32.1 (4.6)	32.8 (6.4)	34.7 (4.9)	32.8 (6.4)	32.9 (5.0)	33.1 (4.8)	1.1 (-1.8-4.0)	0.452	2.8 (-0.2-5.7)	0.064
EQ-5D (0-10)	3.3 (1.5)	3.0 (1.5)	2.1 (1.4)	3.5 (1.5)	2.8 (1.5)	2.6 (1.6)	0.3 (-0.5-1.2)	0.442	-0.3 (-1.2-0.5)	0.462
EQ-5D-VAS (0-100)	57.3 (17.3)	63.4 (14.3)	73.4 (17.1)	56.3 (19.9)	64.3 (16.5)	74.1 (15.6)	0.6 (-8.4-9.7)	0.892	0.1 (-9.0-9.3)	0.975
FSS mean (1-7)	3.8 (1.1)	3.6 (1.2)	3.8 (1.4)	3.9 (1.4)	4.0 (1.5)	4.2 (1.7)	-0.3 (-1.1-0.5)	0.491	-0.2 (-1.0-0.6)	0.580
FAD-GF mean (1-4)	1.5 (0.5)	1.4 (0.4)	1.5 (0.4)	1.6 (0.5)	1.5 (0.5)	1.6 (0.6)	-0.0 (-0.3-0.2)	0.716	-0.1 (-0.3-0.2)	0.648
HADS anxiety (0-21)	4.0 (3.7)	3.8 (3.7)	3.4 (1.9)	3.9 (2.8)	3.9 (3.0)	3.6 (3.4)	-0.6 (-2.3-1.0)	0.444	-0.5 (-2.1-1.2)	0.576
HADS depression (0-21)	4.2 (2.9)	3.8 (2.6)	3.9 (3.5)	4.8 (4.0)	3.8 (3.4)	3.7 (3.3)	0.5 (-1.3-2.3)	0.580	0.8 (-1.0-2.6)	0.379
PROMIS anxiety (-∞-∞)	51.5 (6.8)	52.0 (7.5)	51.4 (6.2)	52.5 (6.4)	51.8 (6.7)	50.6 (8.2)	1.1 (-2.6-4.7)	0.558	1.5 (-2.0-5.1)	0.389
PROMIS depression (-∞-∞)	51.2 (6.9)	49.9 (7.0)	53.5 (6.6)	49.7 (6.9)	50.0 (7.1)	50.8 (7.8)	-0.4 (-41-3.2)	0.813	1.6 (-2.1-5.2)	0.388

Secondary outcome measures - caregiver										
CSI (0-13)	5.5 (2.1)	5.8 (2.8)	4.9 (3.5)	5.8 (2.8)	6.1 (2.1)	4.7 (2.5)	-0.4 (-1.9-1.1)	0.604	0.1 (-1.5-1.7)	0.890
CarerQoL-7D (0-14)*	11.7 (2.0)	9.9 (2.1)	11.4 (1.7)	11.7 (2.2)	11.4 (1.5)	11.1 (2.6)	-1.4 (-2.5--0.3)	0.013	0.1 (-1.0-1.2)	0.866
CarerQoL-VAS (0-10)*	7.5 (1.1)	6.7 (1.4)	7.6 (0.9)	7.1 (1.1)	7.5 (0.8)	7.4 (1.3)	-0.7 (-1.3-0.0)	0.042	0.1 (-0.5-0.8)	0.697
HADS anxiety (0-21)	3.6 (2.2)	3.7 (3.7)	3.6 (2.5)	4.2 (2.7)	4.0 (2.5)	4.1 (3.0)	0.4 (-1.6-2.3)	0.714	0.1 (-1.9-2.1)	0.929
HADS depression (0-21)*	1.9 (2.6)	3.2 (2.9)	2.5 (2.4)	3.5 (3.5)	2.6 (3.0)	2.6 (2.4)	1.8 (0.2-3.4)	0.025	0.9 (-0.7-2.5)	0.245
PROMIS anxiety (-∞-∞)	52.3 (5.7)	51.7 (6.1)	51.9 (4.5)	51.1 (5.5)	51.2 (3.9)	51.6 (5.3)	0.0 (-3.0-3.1)	0.984	-0.3 (-3.5-2.8)	0.825
PROMIS depression (-∞-∞)	50.2 (5.3)	49.2 (5.6)	51.0 (4.9)	50.7 (5.6)	50.1 (4.4)	51.7 (5.4)	0.2 (-2.7-3.1)	0.894	-0.3 (-3.3-2.7)	0.866
PCS (0-32)	18.3 (5.5)	18.9 (8.0)	19.2 (6.3)	18.9 (5.0)	17.9 (4.6)	17.4 (6.9)	1.6 (-2.2-5.4)	0.396	2.7 (-1.1-6.5)	0.156
FSS mean (1-7)	2.5 (1.0)	3.2 (1.2)	2.8 (1.0)	2.9 (1.2)	3.3 (1.1)	2.6 (1.6)	0.4 (-0.3-1.0)	0.259	0.5 (-0.2-1.2)	0.155
FAD mean (1-4)	1.5 (0.4)	1.6 (0.4)	1.5 (0.4)	1.4 (0.4)	1.5 (0.4)	1.5 (0.4)	0.1 (-0.1-0.4)	0.270	0.0 (-0.2-0.3)	0.935
GSES (10-40)	33.5 (4.5)	34.3 (3.8)	33.5 (3.7)	33.6 (5.2)	35.0 (4.0)	34.5 (3.8)	-0.3 (-2.5-1.9)	0.777	-0.5 (-2.8-1.7)	0.632

Abbreviations: SD = Standard Deviation; B = Beta; CI = Confidence Interval; SIS = Stroke Impact Scale; RMI = Rivermead Mobility Index; FAC = Functional Ambulation Categories; 5MWT = 5-M Walk Test; 6MWT = 6-Min Walk test; BBS = Berg Balance Scale; MI = Motricity Index; NEADL = Nottingham Extended ADL; mRS = modified Ranking Scale; TPS = Transition Preparedness Scale; SSEQ = Stroke Self-Efficacy Questionnaire; GSES = General Self-Efficacy Scale; EQ-5D = EuroQol 5-Dimensions; VAS = Visual Analogue Scale; FSS = Fatigue Severity Scale; FAD-GF = Family Assessment Device-General Functioning; HADS = Hospital Anxiety and Depression Scale; PROMIS = Patient-Reported Outcome Measurement Information System; CSI = Caregiver Strain Index; CarerQoL = Care-related Quality of Life Instrument; PCS = Preparedness for Caregiving Scale. *$p < 0.05$

DISCUSSION

The main finding of this multicentre, randomised con-trolled trial is that our intervention yielded no significant differential effect on the primary outcome, patients' self-reported mobility following the Stroke Impact Scale after 8 weeks, when compared to usual care alone. Within the subgroup of patients recruited during inpatient care, we found no clear benefits with respect to the care transition to the community. We did observe an added value on patients' independence in leisurely activities after 6 months and care-givers' psychosocial wellbeing at 8 weeks in line with previous trials.[20–22]

Caregiver-mediated exercises combined with telerehabilitation in addition to usual care did not result in an improvement of patients' self-reported mobility after 8 weeks when compared with usual care nor after 6 months follow-up. Despite the lower number of subjects recruited than foreseen in the study protocol, we found no trend in the futility analysis. The neutrality of findings is supported by the absence of beneficial effects on secondary functional outcome measures, with the exception of independence in leisurely activities at 6 months. These findings are in line with several other caregiver-mediated exercise studies poststroke,[20,21,23] but runs contrary to another small sampled trial by Galvin et al.[24] The effect estimates reported by Galvin et al., however, were not adjusted for baseline imbalances and may be overly optimistic. Our hypotheses were based on beneficial effects of augmenting task-specific training. Although it should be acknowledged that estimations of treatment contrast were based on self-report and not on the actual number of repetitions of task-specific training, the exercise time did not differ significantly between groups, which may explain the neutral results. Cluster randomisation could prevent issues of contamination in future studies. In addition, informal caregivers may already provide training in usual care. To achieve sufficient contrast, a higher dose may be required, or our protocol may be complemented with other resource-efficient strategies, such as self-directed,[25] circuit-class[26] or peer-to-peer training. Finally, future trials should consider sensors to objectively measure activity and record both scheduled and active therapy time.

We additionally hypothesised that active involvement of caregivers and providing blended care support would empower dyads and improve psychosocial wellbeing as well as the care transition to the community.[13] We found no beneficial effects on patients' psychosocial wellbeing; however, our study yielded positive differential effects in caregivers' wellbeing, namely, improved quality of life and reduced depressive symptoms after 8 weeks. Despite the

multiple-comparison problem for these secondary outcomes, the results are in line with previous caregiver-mediated exercises trials poststroke.[20,21] Moreover, the majority (70%) of studies investigating mobility-directed, caregiver-mediated exercises reported improved caregiver outcomes in terms of psychological wellbeing or reduced burden.[27] Improved psychosocial wellbeing of caregivers may be linked to their active involvement in rehabilitation care, resulting in more insight and knowledge, improved skills to support the patient, feelings of empowerment and reduced uncertainty. Future caregiver-mediated exercise studies poststroke should explore more in-depth how caregivers experience their involvement in rehabilitation care before proceeding to a larger trial to validate these findings.

Our final secondary objective was evaluated within a subgroup of patients recruited from inpatient care. We hypothesised that active caregiver involvement and provision of blended care support would smooth the care transition to the community by improving preparedness for discharge and reducing length of stay.[13] We found no evidence to support our hypotheses with no significant differences in dyads' preparedness for discharge. We did observe an important non-significant difference of 1 week in length of stay favouring the ARMed4Stroke group, which could potentially reduce costs of care. The lack of significant effects may be explained by variation in length of stay between settings and patients corresponding to the relatively high standard deviations observed. Although these findings should be interpreted with caution, we recommend that future trials are sufficiently powered and include an economic evaluation to explore this further.

This study reports findings from a multicentre, randomised controlled trial with a rigorous study design, and the selection of outcome measures follows international consensus statements.[28] However, several study limitations should be acknowledged. First, this study is underpowered as a result of COVID-19 restrictions. We observed some positive trends on secondary outcome measures, namely, the functional ambulation categories, modified Ranking Scale and Nottingham Extended ADL leisure scale after 8 weeks. At 6 months, a trend was observed towards better perceived recovery and patients' self-efficacy. However, these trends show considerable variability and should be interpreted with caution. Second, our primary outcome measure may suffer from a ceiling effect and may be insufficiently sensitive to quantify change in mild stroke patients.[29] Future mobility-directed studies should consider 6 min walking distance or 10 m comfortable walking speed measurement as a primary outcome measure. Third, a significantly higher proportion of lacunar strokes was seen in the intervention group.

These patients may have had a slight prognostic advantage but may also have suffered more from a ceiling effect. Fourth, patients were recruited at arbitrary time points poststroke, which could have resulted in a type II error. Fifth, our patients were relatively young and mostly recruited from inpatient clinics, limiting generalizability to other settings. However, diversity in ethnic background and gender in this sample supports the external validity. Finally, further investigation is required to study the long-term effects of our program.

Clinical message

- The ARMed4Stroke program did not result in improved self-reported mobility.
- Involving caregivers in task-specific training did not lead to a higher perceived burden compared to usual care.
- Involvement of caregivers in rehabilitation may improve caregivers' psychosocial wellbeing.

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8

General discussion

Safely carrying your (grand)child up the stairs or taking a walk with your dog - restoring independence in mobility is an important rehabilitation goal for stroke patients and their caregivers. Physical therapy is a key discipline to deliver interventions aimed at mobility recovery and stroke patients should be provided with as much scheduled therapy as possible.[1] However, patients do not receive recommended amounts of task- and context-specific training and scheduled therapy stops or its frequency decreases sharply after discharge to the home setting. Early supported discharge (ESD) services can improve long-term independence in mobility and self-care tasks by providing intensive multidisciplinary stroke rehabilitation at home.[2] Unfortunately, there is no adequate integrated healthcare model for stroke to support the continuum of stroke rehabilitation and available services and resources vary between and within countries.[3,4] Moreover, national healthcare budgets are being reduced in the Netherlands while the demand for care continues to increase. Hence, effective strategies to safely increase the amount of training and to facilitate continuity of care without increasing already limited healthcare resources are urgently needed. It is estimated that roughly 90% of stroke survivors ultimately return to their own home and are largely dependent on informal caregivers to carry out their everyday activities.[5,6] Within available rehabilitation services, whether in-clinic or at home, there is insufficient attention for the transition of care to informal caregivers.[7-9] The current thesis focuses on caregiver-mediated exercises (CME) combined with telerehabilitation services to augment the current dose of task- and context-specific training and to facilitate the transition from inpatient care to community and informal care. Furthermore, this thesis sheds light on the importance of engaging caregivers in the entire cycle of stroke rehabilitation including assessment, goal setting, and intervention. In this chapter, we will reflect on our results within the context of the contemporary focus on healthcare efficiency and home-based care. We argue that stroke rehabilitation should be reimagined to support high intensity, high dosed rehabilitation and future research should focus on promising alternative models of care including telerehabilitation and caregiver-mediated exercises.

Who will achieve independent mobility in the community poststroke?

In the community environment, limited mobility restricts long-term participation in meaningful social and community activities.[10] The ability of a patient to safely transfer from a bed to a chair is an important prerequisite for an ESD to the community.[11] In addition, recovery of independent walking is the most common goal of inpatient stroke rehabilitation.[12] Good (sitting) balance and lower limb strength are consistently identified in the literature as

significant prognostic factors for independent walking measured with the Functional Ambulation Category (FAC).[13-15] However, patients that achieve independent walking may have persistent limitations in walking speed, distance and complex walking skills preventing them from safely crossing streets allowing to reach the nearest supermarket or bus stop. In **chapter 1** we provided a theoretical model for community ambulation (i.e., independent mobility outside the home which includes the ability to confidently navigate the community environment) following the ICF framework. In **chapter 2**, we presented a prognostic model for final community ambulation outcome, six months after being discharged home. Patients were classified as community walkers if they were able to walk to shops or friends without assistance. Patients were classified as non-community walkers if they were unable to walk outside unassisted (i.e., household walkers) or were only ambulant around the house or in the immediate environment (i.e., limited community walkers).[16-18] We investigated a prospectively collected dataset from a cohort of 243 stroke patients who were able to walk without physical assistance at discharge from inpatient rehabilitation. Most patients (79.4%) achieved a positive outcome in terms of independent community ambulation six months later. Independent community ambulation was predicted based on a comfortable walking speed of 0.5 m/s or faster with a sensitivity of 94% and a specificity of 54%. The same cut-off value was identified in a cross-sectional study to discriminate between household and community walking.[18] This finding suggests that this minimum walking speed upon discharge is a prerequisite for walking performance in the community, as an implicit reflection of dynamic balance and quality of gait. While walking speed can be used by clinicians during discharge planning and to better inform patients and their families about their future prospects, it should be acknowledged that even patients with only slight walking speed limitations may still have an increased fall risk, fear of falling and reduced walking activity in the community compared to healthy controls.[19] In addition, our model was too pessimistic for patients who walked at slower speeds than 0.5 m/s. The accuracy of our model, with relatively low specificity and negative predictive value, is in line with recent models predicting independent walking using FAC.[14,15] This could be explained by heterogeneity in the timeline and extent of spontaneous recovery poststroke, especially between patients who are initially more severely affected.[20] However, our study was largely conducted beyond the time window of motor recovery.[21] Within the slower subgroup, return of independent community ambulation is likely attributable to the adoption of compensatory strategies. For example, patients may start to use a walking device or learn to shift more weight to the less affected leg to improve balance. It is also possible that a gradual increase in therapists' or caregivers' perception of safe mobility progressively allows independent

community ambulation despite slower speeds.[22,23] Alternatively, initial walking speed may have been underestimated in some patients due to fear of falling. This is supported by better motor function of the affected leg as measured with the Motricity Index in patients with a positive outcome despite initial slow speed. In a recent study a similar mechanism of "over-compensating" was described in a subgroup of patients who adopted an asymmetrical gait pattern despite mild impairment which was explained by low confidence in gait safety.[24] Finally, patients may experience different environmental demands such as varying speed requirements for crosswalks.[25] Acknowledging that (un)limited community ambulation is not precisely defined and is probably dependent on varying personal and environmental characteristics, future research should combine self-reported measures, monitoring data and psychological information (e.g. balance self-efficacy) to gain more insight into the complex nature of community ambulation poststroke. High-quality, large datasets in which investigators use the same outcomes are needed to improve prognostic models for independent mobility and to allow better phenotyping. The development of dynamic models and use of machine learning techniques may improve prediction of individual trajectories of mobility recovery,[26] which may allow personalized treatment decisions and improve early triage from acute stroke settings.

Can we improve independent mobility in the community poststroke?

Repetitive task- and context-specific training likely enhances motor learning and mobility recovery poststroke.[27-29] Consequently, task-specific training and walking practice is recommended by clinical stroke guidelines worldwide.[30] Alarmingly, patients poststroke often do not receive recommended amounts of 45 daily minutes of physical therapy and thus fail to utilize their optimal recovery potential.[31-33] In addition, recently updated stroke guidelines have doubled recommended amounts to 3 daily hours of functional therapy (i.e., physical therapy and occupational therapy).[1,34] Within the context of growing shortages of qualified healthcare personnel and a rising demand for care, strategies to increase the amount of practice without substantially increasing financial and human resources are essential. Training informal caregivers to become an exercise coach and perform task-specific exercises with the patient (i.e., CME) may be a resource-efficient approach to intensify practice and thus improve recovery of independent mobility in the community poststroke. In this thesis, we investigated the effect of CME on mobility and functional recovery poststroke. Our Cochrane review in **chapter 3** showed no beneficial summary effect sizes for CME in terms of independence in basic or extended activities of daily living (ADL). The findings presented in this review were

based on a small number of trials with substantial clinical heterogeneity, limiting meta-analyses. We did report very low to moderate quality, significant evidence that CME may improve standing balance, walking distance and self-reported mobility, physical functioning and general recovery. We also reported potential significant benefits on basic ADL independence in a sensitivity analysis which only included trials focused on the lower extremity. Our review called for further high-quality research into the efficacy of CME. Hence, we proceeded with the development of a CME protocol focused on mobility recovery poststroke.[35,36] We studied the effects in the CARE4STROKE trials, two proof-of-concept trials conducted in parallel in the Netherlands and Australia.[37,38] No significant differential effects for CME versus usual care were found in terms of mobility or functional recovery. A sensitivity analysis, involving a subgroup of patients who completed CME in the community setting with telerehabilitation support in Australia, did suggest a positive trend towards improved mobility and a significant beneficial effect on extended ADL.[37] In **chapter 6 and 7**, we presented the protocol and results of the ARMed4Stroke trial in which we investigated the effects of a CME program combined with telerehabilitation support. We increased our focus on task- and context-specific practice in the community by adding relevant exercises and milestones for community ambulation. In line with previous findings, we found no beneficial effect of CME on mobility or functional recovery poststroke, except for extended ADL independence in leisurely activities. The neutral results are supported by an absence of significant effects in two large pragmatic trials conducted in India[39] and rural China.[40] Before jumping to the conclusion that CME has no added value to improve independent mobility in the community, some issues need to be considered. First, we define CME as a person with stroke performing task- and context-specific exercises together with an informal caregiver under the auspices of a physical or occupational therapist. Caregivers in the ATTEND[39] and RECOVER[40] trials did receive training on how to assist CME as part of a broad rehabilitation intervention. However, the actual performance of CME was only encouraged and not the intervention type of interest in these trials. Second, the modified Rankin Scale (mRS) dichotomized into a “good” (mRS 0-2) or “poor” (mRS 3-5) outcome[39,40] and the self-reported mobility domain of the Stroke Impact Scale[37,38] may be insufficiently sensitive to detect a significant improvement in functional independence or mobility, respectively. In addition, use of the mRS in stroke trials is problematic as its reliability has been shown to be insufficient and dichotomization increases the risk of incorrectly concluding that a treatment is ineffective.[41] However, neutral results were supported by an absence of significant effects on secondary outcome measures of mobility and functional recovery.[37-40,42] Third, our hypothesis of improved mobility recovery is based on increasing task- and context-specific practice. In the

ATTEND[39] and RECOVER[40] trials, dosing was not protocolized. In contrast, caregivers provided 16 to 20 hours of CME over a period of 8 weeks in the CARE4STROKE trials.[37,38,42] However, no significant difference was observed in total number of hours spent in task-specific training, suggesting that we were not successful in intensifying practice. Between-group differences in self-reported practice were especially prominent in terms of more nurse-led exercise time in control groups, suggesting contamination bias. Future trials should consider cluster randomization to prevent contamination. In addition, although previous trials were not designed to demonstrate non-inferiority, it should be noted that a CME program yielded similar outcomes in terms of mobility and functional recovery compared to usual care. This suggests that CME may be a promising alternative, (cost-)effective strategy to deliver task- and context-specific training. Fourth, context of intervention delivery in terms of geographical and cultural differences between countries could determine the relevance, feasibility and effectiveness of CME. Differences in healthcare systems such as timing of discharge and access to adequately dosed ESD services, outpatient rehabilitation or home-based therapy, may determine the relevance of CME. Social and cultural differences in terms of family dynamics, social network composition, employment, other roles and responsibilities, as well as travel distance to the rehabilitation facility may impact on the feasibility of CME. In **chapter 4**, we combined individual patient data from the two identically protocolized CME trials conducted in the Netherlands and Australia, to learn about possible differences in healthcare systems and culture such as intensity of usual care, length of stay, patient casemix, living situation and caregiving relationship. Country of intervention delivery did not modify the trial outcomes despite significant differences across countries in usual therapy dose, length of stay, patients' age and functional status and timing of recruitment poststroke, nor did outcomes change after adjusting for these variables. Recruitment took approximately 1 year in Australia compared to 2 years in the Netherlands. Importantly, the proportion of patient-caregiver dyads who were excluded and the proportion who declined to participate was comparable, suggesting that need for CME was similar across countries. Also, a significant difference between groups in self-reported CME time in both countries, with intervention groups approaching the intended dose, suggested that CME was feasible in both countries. Finally, we observed promising secondary findings regarding increased independence in extended ADL and improved psychosocial wellbeing in both patients and caregivers. These findings warrant further investigation, as our trials were not sufficiently powered to draw definitive conclusions.

Should we burden caregivers with an active role in stroke rehabilitation?

Most patients who survive a stroke are discharged home, either directly after acute care or following an extended period of inpatient stroke rehabilitation.[43,44] In the community, the responsibility of continuing care including assistance with ADLs shifts heavily onto informal caregivers. Assuming an informal caregiving role can be burdensome, with elevated levels of stress reported in 25% to 54% of stroke caregivers.[45,46] Substantial caregiving burden can result in negative psychological and social consequences including increased symptoms of depression[47-49] and anxiety,[47,49] reduced quality of life,[45,47] social support[50] and participation in meaningful activities,[51,52] as well as negative changes in quality of the relationship between stroke caregiver and recipient.[50] In **chapter 5**, we investigated the level of agreement and differences in perspective between patients and their partners on family functioning poststroke in a cross-sectional investigation based on aggregated baseline data from two randomized controlled trials. We concluded that perceptions differed significantly, with partners reporting poorer family functioning. About 30% of partners in this cohort reported ineffective family functioning and these partners reported higher caregiving burden and worse mood. In addition, partners more often reported ineffective family functioning when more time had passed since stroke onset and when patients were discharged home. These findings highlight the importance of monitoring family functioning and psychological wellbeing in both patients and informal caregivers poststroke. In addition, standardized follow-up and assessment of caregivers after discharge could help identify vulnerable caregivers who require additional support. Difficulty of caregiving tasks and hours spent caregiving (i.e., objective burden) is associated with increased stress and psychological burden (i.e., subjective burden) throughout the caregiving trajectory.[46,49,51] While CME may be an attractive, resource-efficient solution to augment task- and context-specific practice, it is imported to consider any potential negative consequences in terms of caregiver wellbeing. In our Cochrane review in **Chapter 3**, we reported no significant adverse effect of CME on perceived caregiving burden. These findings were based on two trials and none of the included studies reported on other measures of caregiver wellbeing such as mood or quality of life. In **Chapter 7**, we reported no significant negative effect of CME combined with telerehabilitation on perceived caregiving burden. In fact, to our knowledge, there are currently no trials reporting any negative effect of CME and one trial even reported reduced levels of strain.[53] In the ARMed4Stroke trial (**chapter 7**), we did report a significant differential effect in terms of improved quality of life and reduced depressive symptoms in caregivers postintervention. These unexpected promising findings are in line with results from

the CARE4STROKE trials.[37,38] In these studies, different positive psychological effects were observed, with caregivers reporting less fatigue,[37] higher self-efficacy[37] and reduced depressive symptoms.[38] In the Australian sensitivity analysis, a positive trend towards improved mood was observed using a combined anxiety and depression scale. Beneficial effects of CME in terms of caregiver psychological wellbeing may be explained by early involvement of caregivers in rehabilitation goal setting and intervention. Informal caregivers often feel overwhelmed following discharge from inpatient care and receive little preparation for their new caregiving tasks.[54] In a qualitative study investigating the experiences of patients and caregivers who participated in the CARE4STROKE trial,[55] both members of the dyad valued the active involvement of caregivers during stroke rehabilitation. Patients and caregivers described how CME provided them with an opportunity to individualize rehabilitation goals and exercises, to actively contribute to the recovery process, to gain insight and acquire skills which helped them in the home setting. Future studies should focus on identifying which caregiver profiles benefit most from structured involvement and how care systems can remain inclusive for patients without informal support.

Directions for future research and practice

Current demographic and epidemiological trends worldwide, including a growing number of stroke patients, rising costs of care and persistent shortages of qualified healthcare personnel, calls for a drastic change in our view on rehabilitation after stroke. In line with these trends, Dutch healthcare policy is shifting focus from inpatient professional care to home-based informal care, self-care and virtual care.[56] Therefore, I expect that, over the next 10 years, stroke rehabilitation will shift to the community setting and telerehabilitation will play an increasingly important role in monitoring and supporting patients at home. While the current evidence-base supports home-based rehabilitation after stroke,[2] effectiveness is heavily dependent on delivery of multidisciplinary rehabilitation at the same intensity as prescribed for inpatient rehabilitation. These ESD services are currently not part of routine practice in the Netherlands. In addition, evidence-based stroke rehabilitation whether provided in clinic or at home, requires challenging, high-intensity practice of walking and walking-related activities to improve mobility.[57] However, only a limited number of studies to date have succeeded in significantly intensifying task-specific training by at least 20 hours[58] and changing clinical practice.[59,60] A recently published trial reported promising functional gains following 90 hours of motor rehabilitation during 3 weeks in the chronic phase poststroke, however, the intervention was

not cost-effective after nine months.[61] Future research should focus on promising, alternative models of care such as telerehabilitation and CME to deliver high intensity motor rehabilitation at home including an economic evaluation.

A pragmatic CME trial

A home-based, challenging, high intensity, caregiver-mediated exercises intervention warrants evaluation of (cost-)effectiveness in a sufficiently powered, pragmatic, cluster-randomized controlled trial. Patients with stroke should be recruited using broad inclusion criteria from acute hospital settings to enhance early involvement of informal caregivers. Subsequently, a case manager should be assigned to the intervention group to coordinate the home-delivered training intervention. In the home setting, patients and caregivers receive home visits from a trained physical therapist for one hour a week for twelve weeks. Sessions are focused on context- and task-specific training in (supporting) walking and walking-related activities. In addition, face-to-face therapy is supplemented by two (a)synchronous telerehabilitation sessions a week of one hour with a focus on exercise progression, needs assessments, personalized goal setting and customized training and education. Patient-caregiver dyads receive a tailor-made training program with instruction videos of progressively challenging, high intensity (community) mobility exercises. Patients and caregivers should perform exercises together (i.e., CME) for one hour daily and patients are encouraged to also perform self-directed exercises to further intensify daily practice. Progression in the intensity of exercises during CME can be achieved by using wearable sensors and target thresholds such as a minimum number of steps taken during CME, in line with a recent trial by Peters and colleagues (2025) who showed impressive improvements in walking distance, speed, balance and quality of life by increasing energy expenditure during physical therapy sessions.[62] Physical therapists can monitor participants remotely using these wearables to inform the (a)synchronous sessions. This home-based, high intensity, caregiver-mediated, training intervention would result in a dose of 120 hours over a period of twelve weeks, including 84 hours of CME and 36 hours of blended care support. The primary outcome measures to evaluate intervention effectiveness should focus on clinically relevant community ambulation classification. In addition, outcome measurement of caregivers' mood perception and quality of the transition from inpatient care to community and informal care should be included. Finally, an economic evaluation should be included to evaluate cost-effectiveness. Aligning with contemporary policy trends, a stepped wedge design could also be considered to support implementation of

an ESD service. However, the government should provide reasonable compensation for the efforts of informal caregivers, including financial compensation and flexible work leave arrangements.

In conclusion, stroke rehabilitation must be reimagined not only from the patient's perspective, but also from that of the informal caregiver. A home-based rehabilitation model - offering **early involvement of caregivers, tailored education and training using a blended care approach, and a challenging, high-intensity training program of walking- and walking-related activities** - may reduce caregiver burden, support sustainable care, and improve outcomes for both patients and their informal caregivers.

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List of abbreviations and glossary of terms

LIST OF ABBREVIATIONS

ABI	Acquired Brain Injury
ADL/IADL	(Instrumental) Activities of Daily Living
ARAT	Action Research Arm Test
BBS	Berg Balance Scale
BI	Barthel Index
CAQ	Community Ambulation Questionnaire
CarerQoL	Care-related Quality of Life instrument
CART	Classification And Regression Tree analysis
CAT	Computer Adaptive Tests
CI	Confidence Interval
CIMT	Constraint-Induced Movement Therapy
CME	Caregiver-Mediated Exercises
CRF	Case Report Form
CSI	Caregiver Strain Index
ESO	European Stroke Organization
EQ-5D	EuroQoL
ESD	Early Supported Discharge
FAC	Functional Ambulation Categories
FAD-GF	Family Assessment Device – General Functioning
FAI	Frenchay Activities Index
FIM	Functional Independence Measure
FMA	Fugl Meyer Assessment
FSS	Fatigue Severity Scale
GSES	General Self-Efficacy Scale
HADS	Hospital Anxiety and Depression Scale
HSU	Hospital Stroke Unit
ICC	Intraclass Correlation Coefficient
ICD	International Classification of Diseases
ICF	International Classification of Functioning, Disability and Health
ICT	Information and Communication Technologies
KNGF	Koninklijk Nederlands Genootschap voor Fysiotherapie
LOS	Length Of (inpatient) Stay

MD	Mean Difference
MI	Motricity Index
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
mRS	modified Rankin Scale
NDT	Neuro Developmental Treatment
NEADL	Nottingham Extended ADL index
NICE	National Institute for Health and Care Excellence
PCS	Preparedness for Caregiving Scale
QoL	Quality of Life
RCT	Randomized Controlled Trial
RMI	Rivermead Mobility Index
SD	Standard Deviation
SIS	Stroke Impact Scale
SMD	Standardized Mean Difference
SSEQ	Stroke Self-Efficacy Questionnaire
SSQoL	Stroke-Specific Quality of Life scale
TPS	Transition Preparedness Scale
TUG	Timed Up and Go test
UCO	Utrecht Communication Observation
VAS	Visual Analogue Scale
WHO	World Health Organization

GLOSSARY OF TERMS

Activities: the execution of a task or action by an individual (ICF).[1]

Activity capacity: relates to what an individual can do in a "standardized" environment.[1]

Activity performance: what the person actually does in his or her "current" (usual) environment.[1]

Balance: The act of maintaining, achieving or restoring a state of control during any posture or activity.[2]

Behavioural restitution: a return toward more normal patterns of motor control with the impaired body part(s) as seen in pre-stroke state.[3,4]

Behavioural adaptation: occurs when the movement or task is executed with the impaired body part, but an alternative atypical movement pattern is used. Behavioural adaptation results in deviating quality of movement compared to non-disabled individuals.[3,4]

Behavioural compensation: occurs as adaptation, in which the impaired body part is used in an atypical way to accomplish a movement or a motor task; or as substitution, in which different atypical body part(s) or body segment(s) are used to accomplish a task.[3,4]

Blended care: refers to a hybrid model of healthcare in which traditional "offline" face-to-face care is combined with "online" telerehabilitation support.

Body functions: the physiological functions of body systems (ICF).[1]

Caregiver-mediated exercises (CME): a person with stroke performing task-specific exercises together with an informal 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 (safely) perform the exercises and by evaluating and monitoring them on a regular basis. In this thesis, the task-specific exercises are aimed at improving Activities of Daily Living (ADL) including mobility, such as making transfers, standing, and walking.

Clinical heterogeneity: a systematic difference across trials in the outcomes studied or timing of outcome measurement, characteristics of patients (e.g. age, ethnicity, disease severity), interventions (e.g. content, dose, duration), or study setting (e.g. country, healthcare system, cultural context) (adapted from Higgins et al., 2024).[5]

Community ambulation: independent mobility outside the home, which includes the ability to confidently negotiate uneven terrains, private venues, shopping centres, and other public venues.[6] Three levels of independent community ambulation are distinguished in the literature: 1) Most limited community walkers (i.e., ambulant as far as the letterbox); 2) Least limited community walkers (i.e., ambulant in the immediate environment); and 3) Unlimited community walkers (i.e., ambulant in a shopping centre and/or places of special interest). If a patient is not ambulant outside the home, they are considered non-community walkers or household walkers.[6]

Contamination: the receipt of active intervention amongst participants in the control arm of a randomized controlled trial.[7]

Early supported discharge (ESD): services aimed at accelerating discharge from hospital and providing continuity of coordinated multidisciplinary stroke rehabilitation in the home setting.[8]

E-health: electronic processes and communication technology which support healthcare practice. E-health includes but is not limited to electronic medical records and technology-delivered self-managed consumer education and training (e.g., therapy software apps used independently at home with no data transfer to a rehabilitation provider).[9]

Environmental factors: factors that make up the physical, social and attitudinal environment in which people live and conduct their lives (ICF).[1]

Exercise intensity: amount of time spent in **task-specific training** which includes frequency (i.e., number of sessions per day/week), duration (i.e., time period over which an intervention is delivered) and number of minutes/hours of task-specific training which can be quantified per session, per week or as the total amount of training.[10] This definition excludes other dosing elements including number of repetitions and physiological effort or aerobic intensity.

Family functioning: comprises how family members work together and communicate with each other.[11]

Impairments: problems (the negative term) in body functions and structures.[1]

Imprecision: random error in trial outcomes, as a result of sample variation. Hence, precision of effect estimates depends on the sample size, with smaller studies being less precise.[5]

Informal caregiver: an unpaid or partially paid person who voluntarily helps an impaired partner, family member, neighbour or friend with performing ADL. An informal caregiver is not a practicing healthcare professional.

International Classification of Functioning, disability, and health (ICF): a classification that provides a standardized framework to categorize health and health-related conditions.[1]

Length of stay: the number of days between acute hospital admission and final discharge home.

Lower extremity: refers to the part of the body from the hip to the toes. The lower extremity includes the hip, knee, and ankle joints, and the bones on the thigh, shank, and foot; and the muscles and ligaments spanning over these joints.[2]

Methodological heterogeneity: a difference across trials in the study design, outcome measurement tools or risk of bias. A higher degree of bias will lead to systematic error in trial outcomes.[5]

Mobility: moving by changing body position or location or by transferring from one place to another, by carrying, moving or manipulating objects, by walking, running or climbing, and by using various forms of transportation.[1] Mobility includes changing and maintaining body position (d410-d429), carrying, moving, and handling objects (d430-d449), walking and moving (d450-d469), and moving around using transportation (d470-d489).[1,2]

Motor control: the process whereby the central nervous system produces purposeful coordinated movements to interact with the rest of the body and the environment.[3]

Motor function: body functions related to muscle force and endurance, control over and coordination of voluntary movements, and movement patterns associated with walking, running or other whole-body movements.[1,3]

Motor learning: the changes, associated with practice or experience, in internal processes, that determine a person's capability for producing a motor skill.[3]

Motor recovery: the extent to which motor functions and activities have returned to their pre-stroke state.[3,4]

Motor rehabilitation: a process that engages people with stroke to benefit their motor function, activity capacity and performance in daily life. It is necessary for all people with residual motor disability whose goal is to enhance their functioning, independence and participation. Motor rehabilitation strives to reduce motor impairments and improve functioning in activities through learning- and use-dependent mechanisms. The trajectory of motor and functional recovery varies between patients and stages of recovery. At early stages, behavioural restitution of motor function depends on the underlying mechanisms of spontaneous neurological recovery. At later stages, further functional improvements can be achieved by compensations. Motor rehabilitation is guided by regular assessment of motor function and activity using consensus-based measures, including patient-reported outcomes. Results are discussed with the patient and their caregivers to set personal goals. The core element of motor rehabilitation incorporates principles of motor control in which patients learn to optimize and adapt their motor, sensory and cognitive functioning through appropriately dosed, repetitive, goal-oriented, progressive,

task- and context-specific training. Motor rehabilitation supports people with stroke to maximize health, well-being and quality of life.[3]

Participation: involvement in a life situation (ICF).[1]

Phases in stroke recovery: Hyperacute: from 0 to 24 hours post stroke onset; Acute: between 1 and 7 days; Early subacute: between 7 days and 3 months; Late subacute: between 3 and 6 months; Chronic: beyond 6 months poststroke.[3,4]

Pragmatic trial: a randomized controlled trial designed to determine the effect of an intervention under the usual conditions in which it will be applied.[12] More specifically, the trial should: 1) enrol a real-world population; 2) be conducted in a real-world setting; 3) include an appropriate comparison arm; and 3) capture a relevant outcome.[13]

Spontaneous neurological recovery: improvement in function and activities that is independent of specific targeted treatment and occurs within a restricted time-window of the first 3 months after stroke onset. It is considered an endogenous repair process that presumably relies on residual intact neural architecture as a template for reorganization.[3]

Stroke: a clinical syndrome typified by rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin.[14] Following the International Classification of Diseases and related health problems (ICD-10), this definition includes subarachnoid haemorrhage (I60), intracerebral haemorrhage (I61) and cerebral ischemic stroke (I63).[15]

Study protocol: a combination of the study design and intervention protocol. The design characteristics (e.g., blinding, randomization), study procedures, outcome measures, power calculation, criteria of patient selection and statistical analysis are protocolized in the study design. The essential elements of the trial intervention including its content, mode of delivery, dose, duration and monitoring of compliance are protocolized in the intervention protocol.

Study setting: the geographical location of a trial (i.e., country) including the healthcare system and cultural context in which it is embedded, and the context of individual study sites including their level of care (i.e., primary, secondary, tertiary), local healthcare processes and available resources including staff and expertise.[16]

Task-specific training: an intervention focused on improvement of performance in tasks through goal-directed practice and repetition. The focus is often on training of functional tasks rather than impairment.[4]

Telerehabilitation: refers to the use of Information and Communication Technologies (ICT) to deliver rehabilitation services to people remotely in their homes or other environments,[17] for the purposes of screening, goal setting, assessment, intervention, prevention, supervision/monitoring, education, consultation, and/or counseling.[8,18] Telerehabilitation encompasses synchronous (real-time delivery), asynchronous (delayed delivery) and continuous (remote monitoring) formats or a combination of these formats (hybrid). Telerehabilitation may include a range of emerging technologies (audio/telephone, video conferencing, digital app platform, wearable sensors, virtual reality, robotics) with a connection or data flow between healthcare provider and patient/caregiver to deliver rehabilitation services over a distance.[8,19]

True effect variation: variation in treatment effects as a consequence of clinical heterogeneity. True variation in trial outcomes is not explained by random or systematic error.[5]

Walking: moving along a surface on foot, step by step, so that one foot is always on the ground, such as when strolling, sauntering, walking forwards, backwards, or sideways.[1] Following the **ICF** framework, walking includes walking short distances (d4500), long distances (d4501), on different surfaces (d4502) and around obstacles (d4503).[1]

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Summary

Stroke is one of the leading causes of disease burden worldwide, with increasing morbidity and mortality rates due to population ageing and unfavourable trends in vascular risk factors. Many stroke survivors experience long-term impairments in motor function, limiting their independence in mobility and restricting participation in society. Regaining independent mobility within the community is considered a key goal of stroke rehabilitation. As a result of the increased care demand and staff shortages, rehabilitation facilities face increasing pressure to accelerate discharge to the home setting. Early supported discharge (ESD) services can reduce length of stay (LOS), improve functional outcome and facilitate the transition from inpatient rehabilitation to the community. However, the effectiveness of ESD depends on the continuation of intensive, task-specific rehabilitation at home. Although intensive task- and context-specific training is recommended, actual therapy dose remains below guideline targets, particularly after discharge. Hence, cost-effective ways to increase the intensity of training and support the transition to the home setting are required.

One cost-effective strategy to increase training dose could be to actively involve informal caregivers in task- and context-specific training through caregiver-mediated exercises (CME). In addition, caregivers provide sustained support after discharge from inpatient care. Training patients and informal caregivers through a combination of face-to-face support and telerehabilitation (i.e. blended care) could further help the transition of care by improving insight and preparing for self-management and informal caregiving at home. The main aim of this thesis was to investigate the added value of CME combined with telerehabilitation services after stroke to augment the current dose of task- and context-specific training and to facilitate the transition from inpatient rehabilitation to community and informal care.
The studies presented in this thesis address different but complementary aspects of stroke recovery and rehabilitation, ranging from prognostic modelling to intervention development and evaluation. Specifically, this thesis (1) identifies prognostic factors for community ambulation, (2) synthesizes the evidence for CME interventions, (3) compares international implementations of CME with e health support, (4) explores family functioning within patient-caregiver dyads, and (5) evaluates a blended care CME program (ARMed4Stroke) in a multicentre, randomized controlled trial (RCT).

Chapter 2 aimed to classify patients with stroke into clinically relevant subgroups based on their characteristics at discharge from inpatient rehabilitation to predict community ambulation outcome six months later. A prospective cohort design and classification and regression tree

analysis was used for prognostic modelling. This study, based on a cohort of 243 patients with stroke, demonstrated that comfortable gait speed at discharge is a key predictor of community ambulation outcome. A cut-off value of 0.5 m/s was identified as the most robust threshold, with a sensitivity of 94% and specificity of 54%. The overall model accuracy of 86% was reduced to an adjusted accuracy of 79% after cross-validation. The findings presented in this chapter highlight the importance of early assessment of walking capacity and support the use of gait speed as a simple and clinically relevant prognostic indicator when organizing home-based rehabilitation and community services.

A CME program may be a resource-efficient approach to improve long-term patient and caregiver outcomes by increasing the intensity of training and supporting patient and caregiver empowerment during the transition from inpatient rehabilitation to the home setting. In **chapter 3**, we summarized the available evidence for CME interventions poststroke up to 2015, in a systematic review and meta-analysis. The overall objective was to investigate if CME can improve functional ability and health-related quality of life in people with stroke, and to determine the effect on caregiver burden. Nine RCTs were identified and data from six trials, including 333 patient-caregiver dyads, were included in the meta-analyses. The results showed inconclusive evidence for the effects of CME on ADL independence and caregiver burden. Overall, outcomes of ADL independence and caregiver burden were neutral, with no evidence of either benefit or harm when compared with control conditions, i.e. usual care, other intervention or no intervention. However, sensitivity analyses demonstrated significant positive effects on basic ADL independence postintervention. The analysis distinguished between 'CME-core' interventions and trials in which the effects of CME could not be separated from the effects of other rehabilitation approaches, e.g. caregiver-mediated Constraint-Induced Movement Therapy (CIMT) versus therapist-delivered Neuro Developmental Treatment (NDT). Importantly, ADL independence is mainly determined by lower limb functions, and the 'CME-core analysis' only included trials focused on the lower extremity. The findings further suggested that CME may improve standing balance, walking distance and health-related quality of life as measured with the self-reported mobility, physical functioning, and general recovery domains of the Stroke Impact Scale (SIS). In contrast, no beneficial effects were observed for upper limb outcomes. The limited number of studies, substantial clinical heterogeneity and inconclusive results indicated the need for further well-designed trials to establish the effectiveness of CME interventions after stroke.

Subsequently, the effects of CME combined with e-health support were investigated in two identically protocolized RCTs conducted in parallel in the Netherlands and Australia. In **chapter 4**, we combined individual patient data from both trials (N=129) and identified important clinical differences across countries. Cross-cultural differences in patient casemix, with a younger age ($p = 0.005$) and lower functional status ($p = 0.001$) observed among Dutch patients, could result in a different potential for recovery. In addition, Australian patients were recruited earlier poststroke, spent less time in exercise therapy, had a shorter LOS, and suffered less from contamination when compared to Dutch controls. Both trials showed neutral effects on self-reported mobility, but consistent positive effects were observed on caregiver-related psychological outcomes, including fatigue, self-efficacy, and mood. Despite clear differences across countries, study setting did not moderate the trial outcomes. This suggests that contextual differences between healthcare systems may influence implementation processes, but do not necessarily alter the overall effects and we can proceed faster to evaluating CME interventions in international pragmatic trials.

Because informal caregivers play a central role in stroke rehabilitation, especially after discharge, **chapter 5** focused on family functioning after acquired brain injury (ABI). The central objective of this study was to investigate agreement and differences in the perception of family functioning between patients with ABI and their partners. Baseline data from 77 patient-partner dyads (87% stroke) recruited from the CARE4Patient and CARE4Carer trials, revealed that discrepancies may exist between patient and partner perceptions of family functioning. Within-dyad agreement was poor, with partners reporting significantly worse family functioning compared to the patients (32.5% versus 18.2%). Partners who perceived ineffective family functioning also reported higher caregiver burden and more symptoms of anxiety and depression, underscoring the need for systematic monitoring of caregiver wellbeing. These findings also emphasize the importance of addressing the experiences of both members of the patient-caregiver dyad when implementing and designing family-centred rehabilitation interventions.

Actively involving caregivers in stroke rehabilitation while considering their perspectives, goals and support needs may address the current gap between intensive multidisciplinary support during inpatient care and self-management and informal care after discharge to the community. In addition, combining telerehabilitation and face-to-face support may empower

patient-caregiver dyads and smoothen the transition from professional support to self-management at home.

Chapter 6 describes the study design of the ARMed4Stroke trial, a multicentre, observer-blinded RCT. The primary aim was to investigate the effects of an 8-week CME program using a blended care approach in addition to usual care, on recovery of mobility after subacute stroke. Patient-caregiver dyads were recruited from four rehabilitation centres in the Netherlands during in- or outpatient rehabilitation. The primary endpoint was the self-reported mobility domain of the SIS. Secondary endpoints included outcomes of self-efficacy, psychological wellbeing, fatigue, family functioning, LOS, care transition preparedness, walking capacity, paretic leg strength, balance, extended ADL, quality of life and caregiver burden. Outcomes were assessed at enrolment, end of treatment and six months follow-up. We calculated a required sample size of 72 dyads based on an expected improvement of 10 points on the SIS mobility domain. The ARMed4Stroke program focused on joint goal setting and was specifically developed to heighten motivation and stimulate self-management during the transition from inpatient care to the community. Participants in the intervention group received a tailor-made training program aimed at improving gait, balance, physical activity and outdoor activities. Dyads were asked to perform the CME program for 2.5 hours per week, supported by four face-to-face sessions and a web-based telerehabilitation system with a messaging environment and individualized goals and exercises to achieve important milestones for community ambulation.

The results of the ARMed4Stroke trial were reported in **chapter 7**. In total, 41 patient-caregiver dyads (21 intervention, 20 control) were randomized, and 37 dyads were analysed following intention-to-treat. No significant between-group differences were found for the primary outcome of SIS mobility (B 0.8, 95% CI -6.8–8.5, p = 0.826). However, significant beneficial effects were observed for the secondary endpoints of caregiver quality of life (p = 0.013) and depressive symptoms (p = 0.025) postintervention, as well as extended ADL independence in leisure activities (p = 0.024) after six months. A significant difference in favour of the control group was observed for self-reported muscle strength (p = 0.002) after 6 months. We concluded that CME combined with telerehabilitation yielded no significant beneficial effect in terms of mobility recovery. Although the study was insufficiently powered to draw precise conclusions, we did report an added value on psychological wellbeing of caregivers consistent with previous trials.

In the general discussion presented in **chapter 8**, the main findings of chapters 2 through 7 are summarized and discussed within the broader context of stroke rehabilitation. Taken together, the studies in this thesis demonstrate that augmenting stroke rehabilitation through enhanced caregiver involvement during CME combined with telerehabilitation support is a promising strategy that deserves a large phase III trial with a health-economic evaluation, to address the gap between recommended and delivered therapy intensity after stroke.

This thesis shows that recovery of mobility after stroke is strongly influenced by both walking capacity and the organization of stroke rehabilitation. Gait speed emerged as a robust and key prognostic factor for long-term community ambulation outcome using a cut-off value of 0.5 m/s. Acknowledging that community ambulation is not precisely defined and is probably dependent on varying personal and environmental characteristics, future research should combine self-reported measures, monitoring data and psychological information to gain more insight into the complex nature of community ambulation poststroke. In addition, recovery of mobility is dose-dependent and with that negatively influenced by insufficient rehabilitation services, particularly after discharge to the home setting. The results of this thesis provide no evidence for a beneficial effect of CME combined with telerehabilitation on mobility recovery poststroke, which is probably explained by contamination resulting into insufficient treatment contrast between experimental and control groups at the end of the intervention period. Future trials should consider cluster randomization to prevent contamination. Actively involving informal caregivers during inpatient care and providing remote support may improve psychological wellbeing and quality of life. Future studies should focus on identifying which caregiver profiles benefit most from structured involvement and how care systems can remain inclusive for patients without informal support. In addition, successful implementation requires careful consideration and monitoring of family dynamics and contextual factors. Given the neutral mobility outcomes in relatively small phase II trials, future research should move towards larger pragmatic phase III and IV trials, preferably with health-economic evaluations, to assess whether a high-dose home-based CME program can be a cost-effective alternative or complements to existing ESD services poststroke.

Samenvatting

Het aantal mensen met een beroerte neemt wereldwijd toe door de vergrijzing en een toename van risicofactoren, zoals te weinig bewegen of een ongezond dieet. Een beroerte ontstaat wanneer de bloedvoorziening naar een deel van de hersenen plotseling wordt onderbroken, waardoor het hersenweefsel tijdelijk geen zuurstof krijgt. Hierbij wordt onderscheid gemaakt tussen een hersenbloeding en een herseninfarct. Bij een hersenbloeding scheurt een bloedvat in de hersenen, terwijl een herseninfarct ontstaat doordat een bloedprop een bloedvat afsluit. Beide vormen van beroerte kunnen leiden tot sterfte of langdurige problemen met bewegen, spreken, denken en het uitvoeren van dagelijkse activiteiten. Hierdoor verliezen mensen met een beroerte vaak een deel van hun zelfstandigheid en wordt hun deelname aan het sociaal-maatschappelijk leven beperkt. De terugkeer van zelfstandige mobiliteit in de eigen leefomgeving wordt beschouwd als een belangrijk doel van revalidatie na een beroerte.

Intensieve oefentherapie kan leiden tot een verbetering van mobiliteit en een grotere zelfstandigheid in het dagelijks leven. Hoewel intensieve oefentherapie wordt aanbevolen in richtlijnen voor revalidatie na een beroerte, blijft de hoeveelheid daadwerkelijk geleverde therapie-uren vaak achter bij de aanbevolen oefenintensiteit, met name na het ontslag naar huis. Door de toenemende zorgvraag en een tekort aan zorgpersoneel in de revalidatie, worden patiënten steeds sneller naar huis ontslagen en moeten daar vaker een beroep doen op hun sociale netwerk. Een vervroegd ondersteund ontslag naar huis, ook wel early supported discharge (ESD) genoemd, kan positief bijdragen aan het functioneel herstel als intensieve oefentherapie wordt voortgezet in de thuissituatie. Daarom zijn betaalbare alternatieven nodig om de oefentijd te verhogen en de overgang naar de thuissituatie te ondersteunen.
Een mogelijke oplossing om meer te oefenen is het actief betrekken van naasten in de revalidatie door middel van caregiver-mediated exercises (CME), waarbij de patiënt taak-specifieke oefeningen uitvoert met een partner, familielid of andere naastbetrokkene. Deze vorm van oefenen kan de overgang naar de thuissituatie mogelijk ondersteunen door inzicht te vergroten in het functioneren van de patiënt en doordat naasten ook na het ontslag ondersteuning kunnen blijven bieden. Een innovatieve manier om patiënten en mantelzorgers hierin te trainen en ondersteunen is door traditionele face-to-face zorg af te wisselen met telerevalidatie, ook wel bekend als hybride of gemengde zorg. Deze vorm van ondersteuning biedt meer flexibiliteit aan patiënten, mantelzorgers en zorgprofessionals, omdat de ondersteuning op een eigen gekozen plaats en moment geboden kan worden. Ook is meer maatwerk mogelijk, zoals het geleidelijk afbouwen van intensieve face-to-face begeleiding om de overgang naar zelfmanagement thuis te faciliteren.

Het hoofddoel van dit proefschrift was om te onderzoeken of CME gecombineerd met telerevalidatie na een beroerte, de huidige intensiteit van oefentherapie kan verhogen en de overgang van klinische revalidatie naar informele zorg in de thuissituatie kan verbeteren. De studies in dit proefschrift belichten verschillende, maar complementaire aspecten van herstel en revalidatie na een beroerte. Meer specifiek richt dit proefschrift zich op (1) identificeren van prognostische factoren voor mobiliteit in de eigen omgeving, (2) samenvatten van beschikbaar bewijs voor de effectiviteit van CME-interventies, (3) vergelijken van internationale implementaties van CME met e-health ondersteuning, (4) onderzoeken van familie functioneren binnen patiënt-partner relaties, en (5) evalueren van een CME-programma gecombineerd met telerevalidatie (ARMed4Stroke) in een multicenter, gerandomiseerde en gecontroleerde trial (RCT).

In **hoofdstuk 2** werden patiënten met een beroerte in klinisch relevante subgroepen ingedeeld op basis van gemeenschappelijke kenmerken bij ontslag uit de klinische revalidatie, om mobiliteit na zes maanden in de eigen omgeving te voorspellen. Hiervoor werden gegevens van 243 patiënten geanalyseerd via een beslisboom voor classificatie en regressie. In deze studie kwam naar voren dat de comfortabele loopsnelheid bij ontslag een belangrijke voorspeller is voor mobiliteit in de eigen omgeving. Een loopsnelheid van 0,5 meter per seconde bleek een belangrijke grenswaarde. Patiënten met een loopsnelheid boven deze grens hadden een grote waarschijnlijkheid (94%) op terugkeer van zelfstandige mobiliteit na zes maanden. Deze bevindingen benadrukken het belang van vroege beoordeling van de loopvaardigheid en ondersteunen het gebruik van loopsnelheid als een eenvoudige voorspellende factor bij het organiseren van revalidatie en ondersteuning thuis.

Een CME-programma kan een efficiënte en betaalbare strategie zijn om de oefentijd te verhogen en tegelijkertijd de zelfredzaamheid van patiënten en mantelzorgers stimuleren tijdens de overgang van klinische revalidatie naar huis. In **hoofdstuk 3** werd het beschikbare bewijs voor de effectiviteit van CME-interventies tot 2015 samengevat in een systematisch literatuuronderzoek. Het doel was om vast te stellen of CME de zelfstandigheid in het dagelijks functioneren verbetert, leidt tot een hogere kwaliteit van leven, en om te bepalen wat het effect is op de belasting van mantelzorgers. De resultaten zijn gebaseerd op negen studies, waarvan zes studies met in totaal 333 koppels geschikt waren voor meta-analyse. Hoewel de resultaten niet eenduidig waren, werden er geen significante effecten gevonden voor zelfstandigheid in het dagelijks functioneren. Wel werden er aanwijzingen gevonden voor een positief effect op

stabalans, loopafstand en kwaliteit van leven, met name op de domeinen mobiliteit, fysiek functioneren en algemeen herstel. Er werden geen gunstige effecten gevonden voor herstel van arm- en handfunctie. Tenslotte werd geen significant voordeel of nadeel van CME gevonden op de ervaren belasting van mantelzorgers. Het beperkte aantal studies, grote verschillen tussen de studies en inconsistente resultaten wijzen op het belang van goed opgezette vervolgstudies naar de effectiviteit van CME na een beroerte. Met name CME-interventies gericht op het verbeteren van mobiliteit en functioneren van de onderste lichaamshelft, verdiend aanvullend onderzoek.

Hoofdstuk 4 vergelijkt de toepassing van identieke onderzoeksprotocollen in Nederland en Australië in studies om de meerwaarde van CME met e-health ondersteuning te onderzoeken. Er werden duidelijke verschillen gevonden tussen beide zorgsystemen en in patiëntkenmerken. De Nederlandse deelnemers waren significant jonger en hadden een grotere functionele beperking. De patiënten in Australië kregen minder therapie, gingen sneller terug naar huis en in de controlegroep (reguliere zorg) werd minder vaak met een naaste geoefend. Ondanks duidelijke verschillen in de populatie en context van implementatie, werden er vergelijkbare resultaten gevonden. Beide studies lieten geen duidelijke verbetering zien in zelf-gerapporteerde mobiliteit. Wel werden positieve effecten gevonden voor wat betreft het psychologisch welbevinden van mantelzorgers, waaronder minder vermoeidheid, een betere stemming en meer vertrouwen in zorgtaken, ook wel zelfeffectiviteit genoemd. Deze bevindingen suggereren dat CME met e-health ondersteuning in verschillende zorgsystemen toepasbaar lijkt. Hoewel cross-culturele verschillen de implementatie kunnen beïnvloeden, veranderen de algemene effecten van CME waarschijnlijk niet. Concluderend kan in de toekomst sneller worden overgegaan tot evaluatie van de effectiviteit van CME-interventies in grote internationale, pragmatische trials.

Omdat mantelzorgers steeds vaker een belangrijke rol hebben binnen de revalidatie na een beroerte, met name na het ontslag, richtte **hoofdstuk 5** zich op het familie functioneren na niet-aangeboren hersenletsel (NAH). In deze studie werden overeenkomsten en verschillen onderzocht in de perceptie van het familie functioneren tussen 77 patiënten met NAH (87% beroerte) en hun partners. Uit deze studie bleek dat de beleving van patiënten en partners op dit vlak relatief vaak verschilt. Partners ervaren significant vaker problemen in het familie functioneren dan patiënten (32,5% versus 18,2%). De partners die het familie functioneren als problematisch ervaren, rapporteren ook meer gevoelens van overbelasting, angst en depressieve

klachten. Deze resultaten benadrukken dat niet alleen het welzijn van de patiënt, maar ook het welzijn van de mantelzorger goed gemonitord moet worden. Bij het ontwikkelen van familiegerichte interventies moeten zowel ervaringen van patiënten als van mantelzorgers betrokken worden.

Gebruikmakend van de opgedane kennis in voorgaande hoofdstukken is het ARMed4Stroke-programma ontwikkeld waarin meer nadruk werd gelegd op samenwerking tussen patiënten, naasten en zorgprofessionals bij het stellen van doelen en op zelfstandige mobiliteit in de eigen omgeving, ondersteund door een online telerevalidatiesysteem. **Hoofdstuk 6** beschrijft de opzet van een multicenter gerandomiseerd onderzoek waarin de effectiviteit van het ARMed4Stroke-programma, CME gecombineerd met telerevalidatie aanvullend op de gebruikelijke zorg, werd onderzocht. Aan deze studie deden patiënten en mantelzorgers mee die klinisch of poliklinisch revalideerden in een deelnemend revalidatiecentrum. De interventiegroep kreeg een op maat gemaakt oefenprogramma van acht weken gericht op het verbeteren van lopen, balans, fysiek bewegen en activiteiten buitenshuis. De koppels oefenden 2,5 uur per week samen en werden getraind tijdens 4 face-to-face sessies met een fysiotherapeut. Daarnaast kregen zij toegang tot een online telerevalidatiesysteem met een berichtenfunctie, persoonlijke doelen, oefenvideo's en mijlpalen voor zelfstandige mobiliteit in de eigen omgeving. De primaire uitkomstmaat van het onderzoek was gericht op herstel van zelf gerapporteerde mobiliteit, gemeten met de Stroke Impact Scale (SIS). Bovendien werden de effecten op zelfeffectiviteit, psychologisch welbevinden, vermoeidheid, familie functioneren, kwaliteit van leven en voorbereiding op ontslag van patiënten en naasten onderzocht. Ook werd gekeken naar de loopvaardigheid, spierkracht, balans en zelfstandigheid in dagelijkse activiteiten bij patiënten, naar de opnameduur en de belasting van mantelzorgers. De uitkomsten werden gemeten voorafgaand aan de randomisatie, direct na de interventie en na zes maanden. De benodigde steekproefgrootte werd geschat op 72 koppels.

De resultaten van de ARMed4Stroke-trial werden beschreven in **hoofdstuk 7**. In totaal namen 41 koppels deel aan het onderzoek. Deelnemers in de interventiegroep oefenden gemiddeld ruim 2,5 uur per week samen, zoals beoogd in het protocol. Er werden geen significante verschillen gevonden in de zelf gerapporteerde mobiliteit van patiënten die het ARMed4Stroke-programma volgden in vergelijking met alleen gebruikelijke zorg in de controlegroep. De neutrale uitkomst van deze trial kan worden verklaard uit een gebrek aan behandelcontrast tussen beide groepen. De totale oefentijd was niet significant verschillend, omdat er meer

oefentijd met een zorgprofessional werd gerapporteerd in de controlegroep. Ondanks de neutrale uitkomst, werden er wel veelbelovende positieve effecten gevonden na de interventie op het welbevinden van mantelzorgers, namelijk een hogere kwaliteit van leven en een minder depressieve stemming. Ook waren patiënten na zes maanden significant zelfstandiger in hun vrijetijdsactiviteiten. Hoewel de steekproef te klein was om definitieve conclusies te trekken, sluiten deze bevindingen aan bij resultaten uit eerder onderzoek waarin ook voordelen werden gevonden op het psychologisch welbevinden van mantelzorgers.

In de algemene discussie in **hoofdstuk 8** werden de belangrijkste bevindingen van dit proefschrift samengevat en besproken binnen de bredere context van actuele uitdagingen in de revalidatie na een beroerte. Tot slot werden aanbevelingen gedaan voor vervolgonderzoek. De resultaten van dit proefschrift laten zien dat het actief betrekken van mantelzorgers tijdens CME, gecombineerd met telerevalidatie, een veelbelovende manier kan zijn om de overgang naar huis te verbeteren. Hoewel voorgaand onderzoek wees op een mogelijk gunstig effect van CME op herstel van mobiliteit, was de uitkomst van het ARMed4Stroke onderzoek neutraal. De bevindingen suggereren dat het effect mogelijk wordt beperkt door onvoldoende behandelcontrast tussen de interventie- en controlegroep als gevolg van contaminatie, waarbij gedurende het onderzoek de controlegroep meer is gaan oefenen met zorgprofessionals, zowel in therapie als met verpleging.

Toekomstige studies zouden alternatieve studiedesigns, zoals een ‘stepped wedge’ clustergerandomiseerd onderzoek, moeten overwegen om contaminatie te beperken en implementatie van CME te bevorderen. Dit proefschrift laat zien dat herstel van mobiliteit in de eigen leefomgeving niet precies gedefinieerd is en afhankelijk van zowel lichamelijke functies zoals loopsnelheid als van persoonlijke en omgevingsfactoren. Bij de keuze van een uitkomstmaat zouden zelf gerapporteerde uitkomsten gecombineerd moeten worden met objectieve monitor gegevens en psychologische informatie, zoals zelfeffectiviteit.

Ten aanzien van het actief betrekken van mantelzorgers, werden robuuste gunstige effecten gevonden op het psychologisch welbevinden van mantelzorgers. Er is echter meer onderzoek nodig om te bepalen welke koppels het meeste baat hebben bij het gestructureerd betrekken van mantelzorgers en hoe revalidatiezorg toegankelijk kan blijven voor patiënten zonder informele ondersteuning. Succesvolle implementatie van familie-gerichte interventies vereist daarnaast

aandacht voor het familie functioneren, welzijn van mantelzorgers en contextuele factoren binnen zorgsystemen.

De potentie van CME gecombineerd met telerevalidatie om de kloof te dichten tussen aanbevolen en daadwerkelijk geleverde therapie-uren, evenals de positieve effecten op het psychologisch welbevinden, rechtvaardigen vervolgonderzoek in een grote fase III of IV-trial met een gezondheids-economische evaluatie om te bepalen of hoog-intensieve CME in de thuissituatie een kosteneffectief alternatief is voor reguliere zorg of een aanvulling kan vormen op bestaande ESD-programma's na een beroerte.

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Tijdens een revalidatietraject maken mensen een enorme ontwikkeling door, soms met onverwachte omwegen of momenten van stilstand, waarbij de steun en bijsturing van professionals, familie en naasten onmisbaar zijn. Dit geldt ook voor de leerzame en uitdagende reis die ik heb afgelegd tijdens mijn promotietraject. Op deze plek wil ik dan ook graag iedereen bedanken die heeft bijgedragen aan de totstandkoming van dit proefschrift.

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About the author

ABOUT THE AUTHOR

Marijn Mulder was born on September 23rd, 1986, in Amersfoort, the Netherlands. In 2008, she graduated as a physical therapist at Hogeschool Utrecht. During her work as a physical therapist, she developed a particular interest for the transition from inpatient rehabilitation care to the community setting and informal care support at home. In 2013, she obtained her master's degree in health sciences at the Vrije Universiteit Amsterdam with a specialization in international public health. Since 2014, she has been involved in scientific research at the department of rehabilitation medicine at the Amsterdam UMC, location VUmc. Marijn collaborated with Gert Kwakkel and his research group in the CARE4STROKE trial and CARE4BRAIN project, and in 2019 they started the ARMED4STROKE trial. From 2023 to 2025, Marijn worked as a senior researcher at the department of neurorehabilitation at Reade, centre for rehabilitation and rheumatology.

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