2015•2016

FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN

master in de revalidatiewetenschappen en de kinesitherapie

Masterproef deel 1

What is the effect of rehabilitation interventions on the actual performance of upper limbs, in neurological patients, taken the parameters of the accelerometer into account?

Promotor :
Prof. dr. Peter FEYS

Copromotor :
dr. Ilse LAMERS

Jessie Hollandts

Eerste deel van het scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

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Effects of rehabilitation approaches on actual performance in neurological patients

A high prevalence of various upper limb impairments and disabilities are common in patients with neurological disorders. Dysfunctions of upper extremities often compromise pain, spasticity, tremor, paresis, somatosensory disruptions and less fractionation of movements. All these impairments obstruct a coordinated bilateral movement pattern and consistently a high quality performance of daily tasks. Different evidence-based rehabilitation approaches mostly aimed to restore motor function and to regain motor capacity, but does not address the actual performance of the upper limb in home environment. Yet most goals of rehabilitation are associated with the daily execution of real-life tasks. Furthermore, accelerometers are highly recommended for an accurate assessment of actual performance, but this sensor device still suffer from limitations and flaws.

The main research questions in this paper focuses on:

1) What are the effects of different rehabilitation interventions on the actual upper limb performance in neurological patients?

In complement to the main research question, a secondary underlying question focuses on:

2) In what extent can the effects on actual performance be explained through the parameters of the accelerometer?

The most important findings of this literature review are illustrated:

- Only 2 of the 10 included RCT's managed to report significant results on actual performance. Apart from methodological weaknesses, the type and dose of intervention were determined for the significance of results. In contrast to the 'gold standard' RCT, four of the five included observational cohort studies did succeed to find significant results on actual performance. Here, the content and dose of the interventions are not described in detail, thus high variability in inpatient health care setting can be suspected. In total, 8 included studies demonstrate significant improvements on actual performance.
- In general, three profiles can be distinguished based on clinical outcome measures
  All studies with significant actual performance demonstrate significant body function, capacity and/or perceived performance (n=8)
  No significant increase of actual performance is contradictory with significant body function, capacity and/or perceived performance (n=4)
  No significant improvement on actual performance is similar to lacking of significance on body function, capacity and/or perceived performance (n=3)
- Parameters of accelerometer are highly variables in clinical evidence.
- Actual performance is influenced through many factors, not only the amount of daily use, but also the quality of the UE movements

Student: Hollandts Jessie
Promotor: Prof. dr. Feys Peter
Co-promotor: dr. Lamers Ilse

CONTEXT OF MASTER THESIS

This master thesis fits into the field of neurological rehabilitation. Severe damage to the Central Nervous System is the primary cause for common upper motor disorders, like stroke, Multiple Sclerosis (MS), Parkinson's disease, Spinal cord injury (SCI) and Traumatic Brain injury (TBI). Central Nervous System is responsible for various life-saving human functioning. The consequences of these disorders expand beyond the motor disabilities. Sensorimotor deficits are often characterized by pain, decreased muscle force, increased muscle tone, dysesthesia, balance disorders, coordination problems etc. Additional non-motor functions, like speech, vision, cognition, autonomous regulation and even behavior and personality, can be affected. Through these long-term impairments, patients experience difficulty performing daily tasks in home environment. The decrease of real-life use of the impaired upper limb arises from sensorimotor impairments at first, but this phenome is maintained through learned non-use. Eventually patients will use their upper limb substantially less for performing functional motor skills. Furthermore, improvements of various ADL tasks are aimed during rehabilitation.

Evidence-based practice addressed amelioration of these upper extremity impairments and disabilities, in order to re-acquire basic motor skills during real-life performance. Though different rehabilitation approaches often fail to incorporate actual performance direct into the intervention. Often a substantially enhancement of motor abilities has to occur first, before actual performance will begin to grow. That is why effects on actual performance may be delayed compared to improvements of motor function. Moreover, interventions should aim more on the functional practice of relevant daily tasks. According to principles of motor learning, like 'The more, the better' and 'Massed practice', repetitive, high-intensity interventions are preferred. In order to evaluate task-related goals during rehabilitation, an accurate assessment of the effectiveness of rehabilitation on actual performance is necessary.

Accelerometer has recently becoming more popular in different fields of rehabilitation. The major strength of this technological device is the opportunity to measure upper limb movements in home environments. Preliminary evidence proves good promising results of the accelerometer. Yet the correct applications of this device to assure an accurate assessment, are still unknown. Few clinical studies used the accelerometer to measure the effects of interventions on actual performance. Further development of the sensor to trigger the use of the accelerometer in intervention studies is necessary. This paper is designed for every researcher who wants to enhance the effect of rehabilitation intervention, and for every clinician who wants to use the accelerometer in the clinical practice.

In the second part of this master thesis, an explorative pilot Randomized Controlled Trial will be conducted to investigate the intensity-dependent clinical effects of task-related practice in persons with Multiple Sclerosis (PwMS). Under supervision of Prof dr. Feys Peter and dr. Lamers Ilse, this study is performed at the 'Revalidatie & MS Centrum Overpelt'. These preliminary findings are part of a larger research project on the upper limb rehabilitation in Multiple Sclerosis. In collaboration with two other fellow students (JS and MM), clinical and neural effects of task-oriented upper limb rehabilitation in Multiple Sclerosis will be reported. The pilot study is approved by the Medical Ethics Committee of 'Universiteit Hasselt', 'Katholieke Universiteit Leuven' and 'Mariaziekenhuis Noord-Limburg', and is

registered at clinicaltrials.gov (NCT02688231). In January 2016, the first task-oriented interventions were conducted. By the end of August 2016, the first results are expected. Further data analysis and interpretation of the results will be discussed in the second master year.

The research protocol for this pilot study has been edit by Prof dr. Feys Peter and dr. Lamers Ilse. For the purpose of this master thesis, the original research protocol has been adjusted according to the obtained results in the literature review. The corresponding research question in the adjusted protocol focuses on the intensity-dependent clinical effects of task-related practice on actual and perceived performance in PwMS. It should be clear that this research protocol will not be conducted.

This thesis was a single master research project. Central format was applied for the literature review and research protocol. For the literature review, research question and search strategy was selected with the assistance of dr. Lamers Ilse. Final description of the results and interpretation of the literature review was supervised by Prof dr. Feys Peter.

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Part 1 – Literature review

Part 2 – Research protocol

Part 1 – Literature review

1 Abstract

Background. Many stroke patients show a decreased daily function of the affected upper limb in home environment. Rehabilitation mainly focuses on function and capacity level to eventually improve daily activities. Accelerometer shows promising results for measuring actual performance, but still show important flaws. It is unclear how accelerometers should be used in order to obtain a meaningful description of upper extremity usage in real-world environment.

Objective. This literature review investigates the effect of different rehabilitation interventions on actual performance in neurological patients, taken the parameters into account.

Methods. A systematic search was conducted in PubMed and Web of Science by one examiner. In total, 19 studies were included; 10 randomized controlled trials (RCT); 3 non-randomized controlled trials; 4 observational cohort studies and one case serie.

Results. In total, 8 studies could report significant improvement of actual performance; 2 RCT's, 2 non-RCT's and 4 cohort studies. In general, quality of clinical studies was high, but large sample size and high power was lacking. In all interventions, a task-oriented component was present. The precise content and dose of the treatments were very different. In all 8 studies that found significant results of actual performance, these improvements were similar in function and capacity measurements. However, in four studies motor function and capacity of the affected arm did improved, but contradictory no significant increase of actual performance was observed. The parameters of the accelerometer were quite variable in all included studies.

Conclusion. The majority of the rehabilitation approaches failed to improve actual performance of the paretic arm. In some studies, these findings were contradictory to upper limb motor function and capacity. Recommendations regarding the correct parameters of the accelerometer are necessary.

2 Introduction

Upper limb disabilities, caused by sensory and motor impairments, are quite common among various neurological disorders. In a non-selected population with first ever stroke, 48% of the patients experienced disabled arm and hand function (Persson, Parziali et al. 2012)[1]. Loss of arm function is mostly perceived as a major problem. Patients suffer from pain, spasticity, paresis and loss of somatosensation of the impaired arm. In PwMS, both uni- and bilateral upper extremity abnormalities were reported. Bilateral disorders were apparent in sensation (68%), strength (44%) and manual dexterity (75%) (Bertoni, Lamers et al. 2015)[2]. All these deficits have a significant impact on the capacity of the arm to performance Activities of Daily Living (ADL). Because of a higher difficulty to accomplish simple and complex daily tasks, upper limb use during daily life substantially decreases. All these restrictions are associated with a lack of self-efficacy and satisfaction, which leads to depressive mood and affect (Mayo, Wood-Dauphinee et al. 2012)[3] Hartman-Maeir, Soroker et al. (2007)[4] (Jonkman, De Weerd et al. (1998)[5]. The loss of independency contributes to a worsening of motor function and health-status, which eventually results in a lower quality of life in neurological patients (Kauhanen, Korpelainen et al. 2000)[6] (Yozbatiran, Baskurt et al. 2006)[7]. Carod-Artal, Egido et al. (2000)[8] confirmed that functional status (eg. housewife, female, unemployed and diminished social activity) and depression are predictors of quality of life. Another study by Suenkeler, Nowak et al. (2002)[9] indicates that quality of life still gradually declines over a longer period, although neurologic function and disability remain stable.

The phenomena of learned non-use explains that a certain motor deficit is not only the result of damage to the Central Nervous System, but also due to learned nonuse (Taub, Uswatte et al. 2006) [10]. This concept indicates that a patient does not use their affected arm, even though motor function and impairments of the upper limb significantly improved. Apparently motor deficits and daily upper limb use are two separate aspects, so rehabilitation and measurements should discriminate these components. It is not enough to solely focus on dysfunctions and impairments of the upper limb during rehabilitation to achieve a better daily use the affected arm. According to the International Classification of Functioning, disability and health (ICF), various health-related domains exists (figure 1). A spectrum of functioning and disabilities affected by neurological disorders, can be described widely at three different levels (Holper, Coenen et al. 2010)[11] (Nichols-Larsen, Clark et al. 2005)[12]. It is possible to determine the complex and multidimensional character of the arm more widely, and understand the impact of deficits and impairments on capacity and performance of the upper extremity.

Measuring activity is an important item, since most neurological disorders cause difficulty carrying out a specific task or action. At capacity level, several valid and reliable measurement exists. The most popular measurements are Wolf Motor Function test, Fugel-Meyer Assessment (FMA), Nine Hole Peg Test (NHPT) en Arm Reach Action test (ArAT). All these measurements evaluate a specific task administered with standard protocols, at just one moment in time. Although these scales are good for monitoring disease severity and evaluating treatment effects, they don't give any information about the daily use of the arm in the home environment. The use of both arms during daily tasks at home is quite different, with more variability of the tasks, objects and context, at a longer duration and higher intensity.

So performance is added to the classification to evaluate the execution of daily actions or specific tasks in his or her current environment. To capture the perspective of the patient, perceived performance focuses on the subjective experiences of the patient to use the impaired arm in daily life. In order to achieve subjective information, self-reports and questionnaires are frequently used, like Motor Activity Log, ABILHAND and Manual Ability Measure. For an objective evaluation of performance, there is a lack of direct measures to determine the full range of hemiparetic arm use in real-life environments (Chen and Winstein 2009)[13] (Ashford, Slade et al. 2008)[14]. Yet goals of rehabilitation often focus on the improvement of actual performance of the impaired upper limb in home environments. So to determine the best rehabilitation intervention, it is necessary for outcome measurement to determine all the different aspects of upper extremity, including the objective daily use of the impaired arm. Therefore, there is an urgent need for a valid and reliable measurement tool, that can easily measure upper limb use in the home environment.

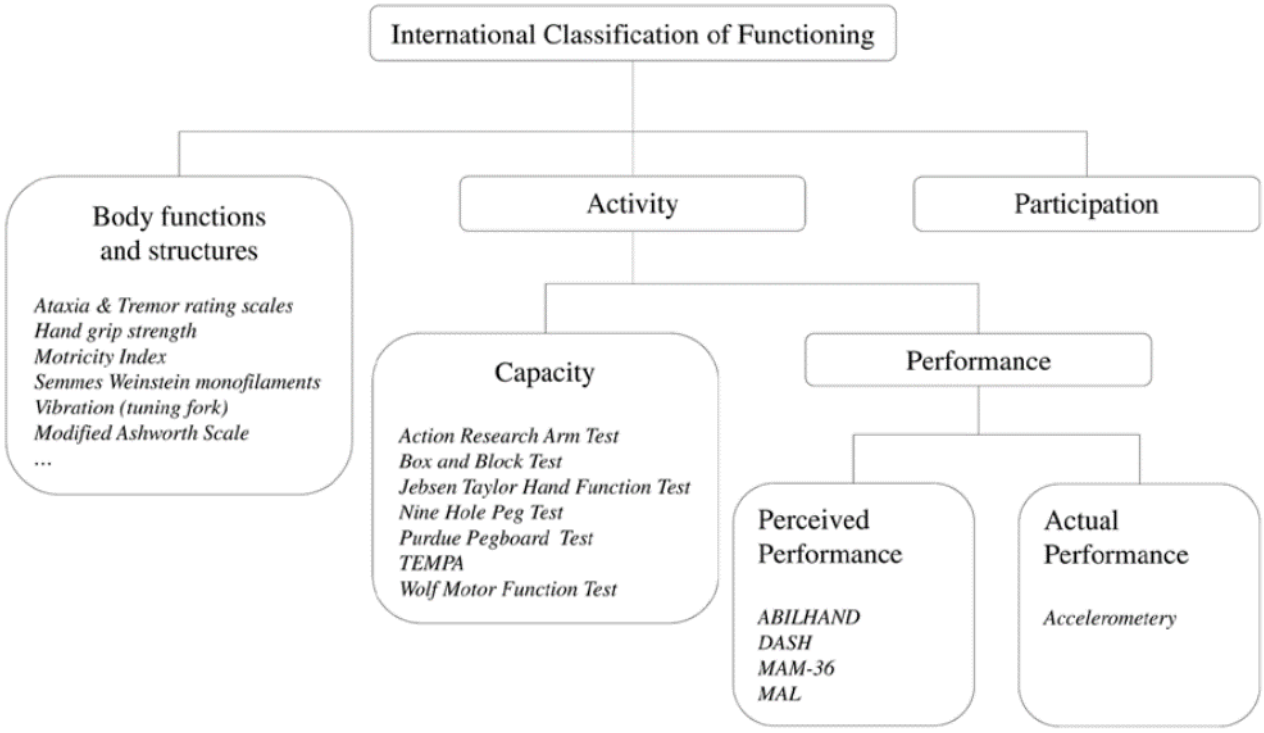

Figure 1: ICF Classification [15]

Accelerometer is a non-invasive, wearable wristwatch-sized device, that registers acceleration of arm movements. The change of speed is converted into a digital signal, known as ‘activity count’, which forms the direct outcome of the sensor. To be able to measure complex and variable upper limb movements, the accelerometer has the capacity to record movements in three orthogonally axes. To attain a relevant and interpretable outcome, several activity counts are integrated over a certain timespan, called ‘epoch length’. This timeframe can vary from one minute to one second, and will be defined beforehand by the clinical. The most common type of accelerometer is the piezoelectric device, which measures acceleration by means of a voltage generation of a precision piezoelectric bimorph-ceramic cantilevered beam. Due to the compactness, user-friendly and low power of the device, the

accelerometer has the ability to register objective upper limb use during daily activities in the home environment. Several studies signify the high accuracy of the sensor measurement, thus proving validity and reliability of the accelerometer (Uswatte, Giuliani et al. 2006)[16] (Reiterer, Sauter et al. 2008)[17] (van der Pas, Verbunt et al. 2011)[18] (Shim, Kim et al. 2014)[19] (Gebruers, Truijen et al. 2008)[20] (Urbin, Waddell et al. 2015)[21] (Thrane, Emaus et al. 2011)[22].

The applications of accelerometers expand towards different fields, from sports to sleep studies. In the rehabilitation of neurologic patients, the accelerometer can be easily used to monitor upper limb behavior of the paretic and non-paretic arm during activities in daily living (ADL) at home. Several observational cross-sectional studies describe the use of the affected and non-affected paretic limb of neurological patients and healthy controls. Lang, Wagner et al. (2007)[23] compared the amount of upper limb use of mild-to-moderate acute stroke patients with control subjects. Hemiparetic stroke patients used their affected and unaffected arm respectively 3,3 and 6 hours per day, which is significantly lower than the 8 till 9 hours per day of the control subjects. Another study by Seitz, Hildebold et al. (2011)[24] also reported that movement activity of the non-affected upper limb ranged from less than 10 hours till more than 16 hours a day in acute stroke patients. Bailey, Birkenmeier et al. (2015)[25] stated that amount of unaffected and affected arm activity was strongly correlated (r=0,78). In this study, mean hours of affected and unaffected upper limb use were 5.0 ± 2.2 and 7.6 ± 2.1 hours respectively in chronic stroke patients. Michielsen, Selles et al. (2012)[26] suggest that chronic stroke patients used their affected limb less than unaffected limb, 5.3h and 2.4h respectively, while the amount of both arms was more equal in controls (5.4 and 5.1 hours). Rand and Eng (2015) [27] indicated that the daily use of the non-affected arm was three times higher than the affected arm. Lamers, Kerkhofs et al. (2013)[28]reported a significant lower score on all the outcome measures for both arms in PwMS compared to healthy controls, including accelerometer. All these clinical studies confirm the decreased actual performance of both upper limbs after neurologic disorder.

Despite the promising clinical implications, few studies have used accelerometry to measure the effect of the intervention during clinical trials. Like said before, it is important to determine all the multidimensional aspects of upper extremity to decide the best rehabilitation intervention. Especially the objective upper limb use in daily activities is of interest, because actual performance is often related with global rehabilitation goals. The accelerometer is the only measurement, that collects objective arm behavior during daily tasks in the home environment.

To stimulate the use of the accelerometer during intervention studies, a clear guideline of the parameters of the accelerometer is necessary. Up to now, clinical studies just choose certain settings of the accelerometer, based on their own theories and expertise. There is no evidence of clear recommendations about certain settings of the sensor, concerning the type of accelerometer, the number of accelerometers, the placement of the watches, the wearing time of sensors, sampling rate, epoch length and data collection. These parameters are important for the sensor to have the sensitive capacity to measure a change of upper limb use after intervention. With correct settings of the accelerometer, it would be much easier to compare multiple clinical trials for the effect of the intervention on daily upper extremity use.

3 Methodology

3.1 Research question

The aim of this paper is to figure out the effects of different rehabilitation interventions on the actual performance of upper limbs, measured by accelerometers. Further the relationship between the effects on actual performance and the used parameters of the accelerometer are discussed in detail. To determine the sensitivity of the sensor in capturing an objective change on actual performance of the upper limbs after rehabilitation, correct settings of these measurement tools are crucial. Depending on the parameters of the accelerometer, upper limb activity values might be different. Thus, these parameters are essential to accurate determine the effects of rehabilitation interventions on actual performance of the upper limbs.

The main question of this paper is as follows *"What is the effect of rehabilitation interventions on actual upper limb performance in neurological patients, taken the parameters of the accelerometer into account?*

Under this literature topic, two major subquestions are drawn from this main question:

1) Does the intervention have an effect on daily arm use, measured with accelerometer?
2) What are the technical parameters and settings of the accelerometer, especially the type, number, placement, wearing time, sampling rate, epoch length and data collection? Do these parameters determine the effect of the intervention on actual performance of upper limb?

To clarify this research question, PICO will provide more details about the topic of this paper.

Patient: All neurological patients, especially stroke, PwMS, SCI, Parkinson's disease, TBI,…

Intervention: General rehabilitation interventions of the upper limb

Comparison: No control therapy, sham therapy or any other rehabilitation interventions

Outcome: Actual performance of upper limb, measured by accelerometry

3.2 Literature search

To construct a comprehensive search, two data bases were used to search for relevant articles. In PubMed and Web of Science, several relevant keywords were combined with boolean operatiors. A detailed description of the keywords is presented in table 1. By reading title and abstract, studies were screened for eligibility through strict inclusion and exclusion criteria. During the first search, all studies that did not used an accelerometer type or not incorporated an intervention, were excluded. Afterwards, the remaining studies were throughout screened to include only accelerometer measurement in daily life, thus accelerometer recordings during task specific performance was excluded. If necessary, full texts were searched. At least, characteristics of the remaining studies were looked at to exclude other irrelevant studies. From the included articles, a second search was carried out. Out of the reference lists of the included articles, additional studies were selected for inclusion based on the same previously used inclusion and exclusion criteria. To explore the field of accelerometry, some systematic reviews were obtained through manual search. The reference list of these systematic reviews were also screened for inclusion. Finally, other relevant publications of authors of included articles were also screened for admission. Through these three pathways, all included articles were obtained.

3.3 Selection criteria

To systematically include relevant articles during database search, criteria were composed to screen the title and abstract for eligibility: (a) upper limb use in real life is measured through accelerometry (b) stand-alone accelerometer, without any influence of the outcome of accelerometer by other sensors (gyroscope or magnetometer) (c) some form of intervention was implemented, with repeated measurements of accelerometry (d) intervention has to be performed for minimal 2 weeks or 10 sessions, this is the required time to achieve a significant intervention effect (e) minimal sample size of 5 participants (f) articles were written in English or Dutch. Apart from inclusion criteria, some criteria were formed to exclude studies: (a) no medication, Deep Brain Stimulation or other surgical interventions (b) only wearable watch-sized accelerometers, that is not fixed to a robotic or rehabilitation system (c) actual upper limb performance is not restricted to the performance of specific tasks during rehabilitation or clinical test. All these criteria provide a fundamental basic for the selection of inclusion studies. Regarding the type of included studies, cross-sectional studies were excluded because of a lack of repeated measures.

3.4 Quality assessment

Before data extraction, quality of each included study is assessed. Quality assessment tools were identified from a search in PubMed database and an Internet search using Google. Detailed descriptions of the used key words and terms are presented in table 2.

From the 536 results on PubMed, 10 relevant full texts were selected. Guidelines for reporting a good quality study, were not primarily of interest. Thus, articles concerning CONSENT guidelines for Randomized Controlled Trials or STROBE guidelines for observational cohort studies were excluded. Most studies reported evidence of the 'best' quality assessment tools in a single type of study. Only one Systematic review collected most popular quality assessment tools of several types of study, and provided recommendations for a certain checklist or scale for every type of study (Zeng, Zhang et al. 2015)[29]. Because of good quality of this recent review, recommendations to choice a certain quality assessment tools were followed. For Randomized Controlled Trials (RCT), 6 possible quality assessment tools were identified, namely the Cochrane collaboration tool, PEDro scale, Jadad scale, Delphi list, CASP and NICE checklists. From these 6 tools, Cochrane collaboration tool and PEDro scale were typically preferred. When comparing these two tools, eight items described the same characteristics. While the PEDro scale added an item of the eligibility criteria, the Cochrane collaboration tool included an item regarding an equal management, apart from the test intervention. Also an item which exclude the unwanted influence of sponsors in the study was included in the Cochrane. This Systematic review preferred the Cochrane collaboration tool, since both internal and external valididty are evaluated. Because of a great similarity between Cochrane collaboration tool and PEDro checklist, both quality assessment tools are combined in a revised checklist. Non-randomized trials typically lack a randomized allocation process of the participants. For this type of study, only two assessment tools were described. MINOR checklist was clearly recommended, because this checklist can be used for both comparative and non-comparative studies. For cohort and case-control studies, three possible tools were found. Despite good quality of the CASP and SIGN checklist, Newcastle-Ottawath scale was

recommended. For case series, only the 18-items modified Delphi checklist was found. Cross-sectional studies were excluded from the literature search. Further diagnostic accuracy test studies, animal studies, systematic reviews and clinical practice guidelines are not expected to be relevant for the paper purpose.

Often quality assessment tools lack certain items that are also relevant for the quality of the study. These items were collected through a manual search, and added on the quality assessment items. Mostly these quality checklists and scales focus on the internal validity of the study, causing a limited discussion of the external validity of the study. Cochrane collaboration tool is the only quality checklists that involved external validity. Here, three items were reported to evaluate the generalisability of the results of the study, namely the agreement of participants in the study and the targeted population, the feasibility of intervention in the clinical practice and the benefits and disadvantages of the tested intervention for the patients. Additionally, a match between the study and other evidence completed the quality checklists and scales.

PubMed search	
((((((("Quality of Health Care"[Mesh]) OR Quality[Title/Abstract]) OR Clinical study[Title/Abstract])) AND (("Bias (Epidemiology)"[Mesh]) OR Bias[Title/Abstract])) AND ((Checklist"[Mesh]) OR Checklist[Title/Abstract])) AND (("Randomized Controlled Trial" [Publication Type]) OR Randomized controlled trial[Title/Abstract])	746 results Systematic review: 265 results
((((((("Quality of Health Care"[Mesh]) OR Quality[Title/Abstract]) OR Clinical study[Title/Abstract])) AND (("Bias (Epidemiology)"[Mesh]) OR Bias[Title/Abstract])) AND (("Checklist"[Mesh]) OR Checklist[Title/Abstract])) AND (("Non-Randomized Controlled Trials as Topic"[Mesh]) OR Non-Randomized controlled trials[Title/Abstract])	2 results
((((((("Quality of Health Care"[Mesh]) OR Quality[Title/Abstract]) OR Clinical study[Title/Abstract])) AND (("Bias (Epidemiology)"[Mesh]) OR Bias[Title/Abstract])) AND (("Checklist"[Mesh]) OR Checklist[Title/Abstract])) AND ((("Controlled Clinical Trial" [Publication Type]) OR Controlled intervention[Title/Abstract]) OR Controlled clinical trial[Title/Abstract])	29 results
(((((((("Quality of Health Care"[Mesh]) OR Quality[Title/Abstract]) OR Clinical study[Title/Abstract]))) AND ((("Bias (Epidemiology)"[Mesh]) OR Bias[Title/Abstract]))) AND ((("Checklist"[Mesh]) OR Checklist[Title/Abstract]))) AND Before-After study[Title/Abstract]	1 result
(((((((("Quality of Health Care"[Mesh]) OR Quality[Title/Abstract]) OR Clinical study[Title/Abstract]))) AND ((("Bias (Epidemiology)"[Mesh]) OR Bias[Title/Abstract]))) AND ((("Checklist"[Mesh]) OR Checklist[Title/Abstract]))) AND (("Clinical Trial" [Publication Type]) OR Clinical trial[Title/Abstract])	62 results
((((((("Quality of Health Care"[Mesh]) OR Quality[Title/Abstract]) OR Clinical study[Title/Abstract])) AND (("Bias (Epidemiology)"[Mesh]) OR Bias[Title/Abstract])) AND (("Checklist"[Mesh]) OR Checklist[Title/Abstract])) AND ((((("Epidemiologic Studies"[Mesh]) OR Epidemiologic study[Title/Abstract]) OR "Observational Study" [Publication Type]) OR Observational study[Title/Abstract])	169 results
(((((((("Quality of Health Care"[Mesh]) OR Quality[Title/Abstract]) OR Clinical study[Title/Abstract]))) AND ((("Bias (Epidemiology)"[Mesh]) OR Bias[Title/Abstract]))) AND ((("Checklist"[Mesh]) OR Checklist[Title/Abstract]))) AND Case series[Title/Abstract]	8 results

3.5 Data extraction

From all included studies, relevant data are distracted. After assessing the quality of each study, a comprehensive reading was performed to select information to answer the two main questions. First of

all, the effects of the concerned interventions on different outcome measures on the ICF are collected and discussed. In function of these results, the technical parameters and settings of the accelerometer were added to elucidate the effects on actual upper limb performance. Particularly the type of accelerometry, the number and placement of the sensors, the wearing time during assessment, the specific sampling rate and epoch lengthy, and the method for data collection and statistical analysis are discussed. Further the relationship between these parameters of the accelerometer and the change in actual upper limb performance is illustrated. To completely review the results on outcome measures, other certifying factors were involved in this discussion: (1) the population, especially time since stroke and upper limb disabilities (2) type and dose of intervention, with a possible additional therapy (3) quality and power of the study. Based on these analysis, significant and non-significant results, along with a possible discrepancy between different outcome measures on several levels of the ICF, can be explained. Finally, any problems with patient compliance were also reported.

4 Results

4.1 Study selection

After comprehensive literature search, 19 studies were included. Randomised Controlled trials were the most appropriate study type to include, but also non-randomized controlled trials and observational cohorts were obtained. At least, one case series was also included. The majority of the studies were obtained through search in two databases. From two Systematic reviews by Noorkoiv, Rodgers et al. (2014)[30] and Lang, Bland et al. (2013)[31], 4 additional clinical studies could be included that were not found in the databases. None additional studies were found through looking at other publications of authors of included studies. For more details about the literature search, a flowchart is drawn according to the PRISMA guidelines (figure 2).

4.2 Quality assessment

In Table 3, more details on the quality assessment of the included studies are presented. At first, the type of study was determined to select an appropriate checklist. Considering the purpose of this study, Randomized Controlled Trials are primarily of interest. Ten Randomized Controlled Trials (RCT) were found in databases. Seven of these RCT's were individual studies, while three studies were part of another RCT. Six of these 7 individual RCT's had an excellent to high quality of methodology on the quality checklist. Hsieh, Wu et al. (2016)[32] implicate a high dose of robotic priming and task-oriented training (90 min/day, 4 days/week), but some participants quite during study (4 in intervention and 6 in control). An even higher drop-out was observed after a period of 3 months, thus follow-up data was lacking. Because the minimal sample size of 31 participants per group for a high power was not reached, the study is underpowered to detect a significant difference. Another study of Hsieh, Lin et al. (2014)[33] used the same robotic intervention, but this time in a sequential combination with CIT. Here, the required sample size was precisely calculated. An estimated minimal required sample size of 15 participants in each group was attained, so power was high enough to detect a significant difference. No drop-out was reported, except for accelerometer assessments (41%). The study by Thrane, Askim et al. (2015)[34] is the first to evaluate the effects of CIMT. Sample size is moderate (n=47), but yet lacks a high power, which may explain the small effects sizes of treatment. Drop-out rate in both groups is statistically acceptable. Control group did not follow a predefined protocol, so there is no reliable data about the actual time spent in active upper limb training. Lemmens, Timmermans et al. (2014)[35] engaged a robot-supported upper limb training with a moderate dose of 2x30min/day. In the chronic stages of stroke, intervention mostly become less intensively compared to acute or subacute stages. Due to a low sample size, this study lacks statistical significance to detect changes. Timmermans, Verbunt et al. (2013)[36] is the only clinical study to investigate mental practice approaches. After calculations of sample size, 160 participants were thought to be necessary, but this high amount was not reached by far (n=42). This means that the study was underpowered for recording a clinical difference. Further there is no evidence regarding the optimal training duration or intensity of mental practice, so it may be possible that the dose of the intervention is not optimal. At least, the high drop-out indicates some concerns. The drop-out in the control group is quite high (33%), but surprisingly the rate in the experimental group is relatively low, which is an acceptable value. At the end, the study by Liao, Wu et

al. (2012)[37] also describes the application of robot-assisted upper limb training. The focus on bimanual movement of the forearm and wrist, makes this robotic system a good choice to improve object manipulation and ADL. The high dose of training (90-105min/day, 5 days/week) results in 2700 to 3600 repetitions during each session. The low sample size (n=20) results in a lack of significance for between-group differences.

The remaining individual RCT by Shim and Jung (2015)[38] had a moderate to low score on the quality checklist. Because of a lack of reported information in the methodology, this score does not necessarily mean that the quality of the methodology was not good. If the data of the checklist is not reported in the study, the items cannot be scores correctly. Characteristics of subjects are present in a table, but were not compared to each other at baseline, so it is not clear whether the participants were similar at baseline. There is no flow chart of the participants drawn, so rate of drop-out is unknown. Sample size is moderate (n=40), but it lacks calculations to indicate the required sample size in this study. There is also no information about the specific content of interventions.

A similar problem arises in the three studies. All three RCT's had a moderate to low score on the quality checklist. Due to a lack of reported information, items can't be scored correctly. Concealed allocation was not reported in two studies (Lang, Edwards et al. 2008)[39] (Uswatte, Giuliani et al. 2006)[16]. Flow chart was lacking in all three studies, along with a clearly reported intention-to-treat analysis.

Apart from the RCT's, non-randomized controlled trials without a random allocation of participants to the different groups, were also included. From the three non-RCT controlled studies, the study by Wang, Lin et al. (2011)[40] had high to moderate quality with a score of 17 on 24 on the comparative non-RTC's checklist. Flow chart was not presented, thus drop-out was not reported. Sample size calculations and power estimated in advance to the study was also lacking. Next, the study by Uswatte, Foo et al. (2005)[41] also reported moderate quality methodology with a score of 14 on 24. As in the previous non-RCT, drop-out and sample size calculations were not reported. Additionally, blinding of the outcome assessors was also lacking. At last, the study by Uswatte, Taub et al. (2005) [42] had moderate to low quality assessment with a score of 11 on 24. Comparable with previous studies, drop-out, sample size calculations and blinding of the assessor were not identified. An additional item concerning the timing of treatment and assessments was not applied, since control group was treated and measured previously.

Only one case serie was included in the literature review. Quality of this study was rated as high, considering the lack of reported drop-out in a flow chart and blinding of the assessors.

Five observational cohort studies with repeated measures of the outcome measurements were included. Two of these observational cohort studies reported excellent to high quality with a score of 8 stars (Doman, Waddell et al. 2016)[43] (Waddell, Birkenmeier et al. 2014)[44]. Further Rand and Eng (2012)[45] also indicate high quality assessment with 7 stars. Than Urbin, Waddell et al. (2015)[21] followed with a score of 6 stars, which represents a high to moderate quality score. At last, Reiterer, Sauter et al. (2008)[17] had moderate quality assessment with 5 stars out of 9.

4.3 Data extraction

In this section, more relevant data in function of the research questions are described for each type of study separate. Data will be described from highest to lowest level of evidence, so randomized controlled trials are described at onset. First the effects of intervention on actual performance of upper extremity are discussed, and in addition the parameters of the accelerometer are illustrated in detail. Characteristics of the included studies are presented in Table 3.

4.3.1 Type of studies

From the 19 included articles, most studies were Randomized Controlled Trials (n=10). Additionally, three Non-randomized controlled trials, one Case serie and five observational cohort studies were included. Despite the inclusion of different neurological diseases, all included studies investigated stroke patients. Moreover, only four studies included stroke patient in an acute setting, while seven studies involved subacute stroke patient and six studies investigated chronic stroke survivors. Striking, the definition of these stroke stages varied among the studies. Looking at the level of upper limb disabilities, most studies included moderate to low impairments of the upper limb. Regarding the chosen intervention, all included RCT's applied some form of task-oriented training, mostly in combinations with traditional UE rehabilitation approaches. Along with a high variability in evidence-based rehabilitation interventions, a variety in the dosage and intensity of the training is noticed.

4.3.2 The effects on actual performance, related to other outcome measures

4.3.2.1 Randomized Controlled Trials (RCT)

Ten Randomized Controlled Trials (RCT's) were included. From all ten RCT's, only two studies reported a significant effect of intervention on actual performance of the upper limb. Shim and Jung (2015)[38] evaluates the difference between functional bilateral and unilateral training on the real life performance of the upper extremities. Although the quality of the study was moderate due to a lack of reported data, the study did succeed to indicate a significant increase on accelerometry. For quantitative amount of affected arm-hand use, pre and post measurement in bilateral training was significant for movement around axis y and axis total ($p<0,01$). Movements in the sagittal plane represent the ability to locate the upper limb in space, necessary for reaching function of the affected arm. Although in sitting position, movement in transversal plane are mainly necessary, but since this movement is still impaired, reaching function of the affected upper extremity is also limited. For the intensity of arm-hand use, bilateral training of the affected arm resulted in a decrease of sedentary level ($p<0,01$) and increase of moderate level of arm activity ($p<0,01$). Thus, stroke patients show a high time spent on high intensity movement after bilateral training of functional upper limb tasks. These progression is coupled with an increase on measurements of body function and capacity. For body function, Manual Function test (MFT) significant increased on the affected arm-hand ($p<0,01$). For capacity of upper extremity, Functional Independence Measure (FIM) prove in a significant increase ($p<0,01$). In Liao, Wu et al. (2012)[37] hemiplegic arm activity increased significantly after robot-assisted therapy ($p=0,026$). This study included 20 subacute stroke patients, but the initial motor criteria of hemiparetic arm was not reported. Experimental intervention exists out of training of functional tasks with both hands together simultaneously, such as

opening and closing drawers, table cleaning and moving objects. With a moderate dosage of 30 min per session and 5 sessions per week, the intensity of the training is sufficiently high to obtain a significant effect on actual performance. The experimental group provoked significantly more daily tasks and use of impaired arm during daily life, than control group. This improvement on actual performance can also be extended to measurement on body function, capacity and perceived performance of the paretic upper limbs. On body function, Fugel-Meyer Assessment (FMA) significantly increased after robot-assisted therapy (p=0,002). On perceived performance, both Motor Activity Log (MAL) and ABILHAND questionnaire indicate a significant change (MAL/AOU p=0,007; MAL/QOM p=0,002; ABILHAND p=0,043). Nevertheless, no significant increase could be established on the capacity level, indicated by a high p-value (p=0,88) on Functional Independence Measure (FIM). Lang, Edwards et al. (2008)[39] was part of the VECTOR trials, which is a Randomized Controlled Trial of Constraint-Induced Movement Therapy (CIMT). The aim was to estimate Minimally Clinically Important Difference (MCID) of several upper extremity measures. This study reported an increase of summed variables from accelerometry, that represented the duration of upper extremity movements. Despite a mean change of 1,2±1.4 hours on daily use of the paretic arm, no p-value was available within or between the experimental and control group. All other measurements (grip strength, composite strength, ARAT, WMFT and MAL) also demonstrate a promising increase of mean change score, but p-value was lacking. Thus no distinctive conclusions can be drawn out of these results.

The most prominent from these RCT's were the six studies, where no significant p-value was found in favour for an improvement on actual performance of upper limbs. This outcome is mostly associated with measurements of body function and capacity. Hsieh, Wu et al. (2016)[32] reported a high p-value on actigraphy (p=0,438), along with a no significant changes on body function, capacity and quality of life. For body function, FMA (p=0,812) and grip strength (p=0,548) were used. For capacity, Box & Block test (p=0,383) and FIM (p=0,647) did not measure a change between experimental and control groups, except for modified Rankin Scale (p=0,065). For quality of life, scores for every subscales of Stroke Impact Scale were determined. All scores did not report any significant changes, except for the strength subscale (p=0,012). In Thrane, Askim et al. (2015)[34], arm use ratio did not change after intervention (p=0,301) or after 6 months' follow-up (p=0,215). These same results could be observed in measurements of body function, capacity and quality of life. For body function, upper extremity subscale of the FMA was used (p=0,116 posttreatment; p=0,296 6 months). For capacity, several subscale of Wolf Motor Function Test reported high p-value, except for log time of WMFT posttreatment (p=0,018). Nine Hole Peg Test also established significant changes posttreatment (p=0,035), but not after 6 months (p=0,635). For quality of life, several subscale of Stroke Impact Scale reached high p-values after 6 months.

Despite a lack of significance on accelerometry variables, some studies did attain an amelioration on measurements of body function and capacity of the upper limb. This finding suggest that improvement on body function and capacity has to be very high before stroke patients use their paretic upper limb during daily life. Hsieh, Lin et al. (2014)[33] indicated this inconsistency between actual performance, capacity and body function. Although significant changes on FMA (p<0,01) and WMFT Functional assessment (p=0,01) were found, high p-values were reported on the accelerometers (p=0,33). Though

the time component of WMFT was also just not significant (p=0,028). Similar to actual performance, perceived performance on MAL did also not changed significantly after treatment (p=0,20 for AOU; p=0,54 for QOM). In Timmermans, Verbunt et al. (2013)[36], motor impairments clearly changed significantly after treatment for both control and experimental group, but actual performance did not reach a significant increase. For body function, both FMA (p<0,05) and Frenchary arm test (p<0,05) increased significantly in the experimental group. For capacity, several subscales of WFMT were used. In the experimental group, only significant changes between posttreatment and one year follow-up were found for all subscales of WMFT. Only the Functional Assessment subscale of WMFT did change significantly between pre- and posttreatment.

In two studies by Lemmens, Timmermans et al. (2014)[35] and Uswatte, Giuliani et al. (2006)[16], the outcome measurement solely focused on accelerometer. No other clinical scales or self-reports for body function, capacity or perceived performance were used in these studies. The remaining study by Uswatte, Taub et al. (2006)[46] aimed to evaluate the reliability and validity of Motor Activity Log, so no within or between group changes in the experimental group for actual performance was determined.

4.3.2.2 Non-Randomized controlled intervention studies

Three non-randomized controlled intervention studies were selected out of the 19 included articles. These type of studies have a separate experimental and control group, which are not randomized divided over the interventions. All three studies are primarily validity and clinimetric studies, thus were not direct aimed to investigate the effect of intervention on the actual performance of upper limb. Wang, Lin et al. (2011)[40] did not report any within or between group changes before and after intervention in the control or experimental group. Uswatte, Taub et al. (2005)[42] assessed the correlations between AOU and QOM subscales of the Motor Activity Log and accelerometry. No changes of actual performance before and after intervention were determined. Beside the MAL questionnaire and accelerometer, no other measurements were incorporated in this study. Thus, only one study has reported the change on actual performance before and after rehabilitation intervention. Uswatte, Foo et al. (2005)[41] aimed to evaluate the reliability and validity of accelerometer as an adequate measurement tool to register changes during rehabilitation intervention. In the experimental CIMT group, a significant increase of the arm use ratio was reported (p<0,05). The effect size of the improvement was large (d'=0,9) compared to control group, which demonstrates the superior effect of CIMT. Hereby the responsiveness of accelerometer to change during rehabilitation can be established. No other outcomes on body function, capacity or perceived performance were measures.

4.3.2.3 Case series

Taub, Uswatte et al. (2013)[47] investigated the effects of a combined CIMT protocol with conventional Neurodevelopment techniques (NDT) in a 6 chronic stroke patients. The significance on actual performance is consistent with other measurement of body function and perceived performance. A similar pattern of gains was observed for accelerometer and grade 4/5 Motor Activity Log with large and significant changes in both phases of the intervention (p=0,012; d'=1,2 for accelerometry and p<0,001; d'=3,4 for Grade 4/5 MAL). Improvements on body function were also strongly marked on the FMA (p<0,05) and active Range of Motion.

4.3.2.4 Observational cohort studies

From the five observational cohort studies, four succeeded to report significant improvements on actual performance. In the pilot study of Doman, Waddell et al. (2016)[43], every participant was analyzed separately, because the individual pathways of change during rehabilitation were primarily of interest in this study. Thereby all participants were placed under a specific profile, according to significant scores on upper limb capacity (measured by ARAT) and actual performance (measured by accelerometry). The first profile described a significant change on ARAT, along with an increase on accelerometer. Only 2 out of the 15 participants were assigned to this category, and showed clearly significant change on ARAT and accelerometer in favor for treatment. The next profile indicated a significant increase on capacity measurement of ARAT, but no significant change on accelerometer. Only 4 participants fitted into this profile type, which showed inconsistent results between capacity and actual performance. The last profile characterizes non-significant results on both ARAT and accelerometry. This profile was applicable in most of the participant (7 out of 15), thus half of the participants did not improved on any aspect after intervention. In general, a high variability between the effects of an outpatient intervention on capacity and actual performance, can be established. A before-after observational study by Urbin, Waddell et al. (2015)[21] also evaluates the responsiveness of the accelerometer to change of upper limb characteristics. Five variables, derived from accelerometer, increased significant after intervention; use ratio ($p<0,01$), magnitude ratio ($p=0,01$), variation ratio ($p=0,03$), median paretic upper limb magnitude ($p=0,03$) and paretic upper limb variability ($p=0,03$). Along with an improvement on actual performance, capacity of paretic upper extremity, measured by ARAT, also registers a significant change after intervention ($p<0,01$). Waddell, Birkenmeier et al. (2014)[44] evaluated the potential of implementing high-repetition task-specific training of upper extremity. Thereby a significant increase of the arm use ratio ($p=0,05$) from baseline to discharge was found, but this improvement was not retained after 1-month follow-up. Two outcome measures at impairment level also changed significantly after discharge and after 1-month follow-up: grip strength, measured by JAMAR dynamometer ($p=0,007$ after discharge and $p=0,052$ after 1 month) and pinch strength, measured by three-jaw-chuck pinch ($p=0,001$ at discharge and $p=0,02$ after 1 month). On capacity level, Functional Independence Measure ($p=0,000$ at discharge and $p=0,009$ after 1 month) and ARAT ($p=0,000$ at discharge and $p=0,018$ after 1 month) were used. All these significant outcome measures indicate the promising opportunity of high-repetition task-specific training protocol of the upper extremity after stroke. At last, Reiterer, Sauter et al. (2008)[17] incorporated actigraph as an objective tool to monitor progression during stroke recovery. At four different time points during rehabilitation course, actual upper limb performance was measured: after 24-36 hours (T1), after 5-7 days (T2), after 3 months (T3) and after 6 month (T4). Total Activity Score was assessed for the impaired arm (TASi) and non-impaired arm (TASni) separately. At the non-impaired upper limb, TASni only increased from T1 to T4 measurement. From 5-7 days till 3 and 6 months, the activity at the impaired side (TASi) changed significantly, but in this period TASni remained similar with no change. Thus, TASi and TASni both improved significantly after 24-36 hours and 5-7 days, but this was no longer obvious after 3 and 6 months post stroke. Other measurements were administered to determine the extent of correlation between actigraph and Scandian Stroke Scale,

Barthel Index, Rankin Scale and Motricity Index. Though no change of these measurements between various time points during the course of rehabilitation were calculated.

However, one observational cohort study did not report any significant improvements on actual performance. Rand and Eng (2012)[45] compared the changes of upper limb activity during general rehabilitation among subacute stroke patients with community dwelling older adults. Three variables were determined from the accelerometer recordings: mean daily use for an entire day, mean daily use for three consecutive days including physical and occupational therapy and upper limb activity counts outside physical and occupational therapy session. From the purpose of this paper, the latter outcome variables are mainly of interest. Daily use of upper limb at baseline was quite similar to the accelerometer recordings three weeks later on discharge. Although daily use of both impaired and non-impaired arms did show an increase after 3 weeks, these changes were not found significant (d=5861 activity counts for paretic arm; d=15110 activity counts for non-paretic arm; p-values were not significant). In comparison to actual performance, conflicting evidence of a significant improvement on impairment and capacity of the upper limbs was found. On disability level, FMA increased significantly (p=0,005) after 3-weeks rehabilitation. For capacity of the hemiparetic arm, both ARAT and FIM (p<0,001) changed significantly in favor for rehabilitation. Thus despite improvement on upper limb function and capacity, subacute stroke patients did increase daily activity amount of the upper limb.

4.3.2.5 Conclusions

In total, eight studies did report significant improvement on actual performance, which were similar findings on motor function and capacity of the affected arm. In this case, the effectiveness of the rehabilitation can be clearly stated.

Significant effects on accelerometer	
STUDY	*Similar improvement on clinical outcome scales*
Shim and Jung (2015)	– Capacity (MFT p<0,01) – Actual performance (amount of activity is significant)
Liao, Wu et al (2012)	– Body function (FMA p=0,002) – Perceived performance (MAL/AOU p=0,007; MAL/QOU p=0,002; ABILHAND p=0,043)
Uswatte, Foo et al (2005)	– No other clinical outcome measures
Taub, Uswatte et al (2013)	– Body function (FMA p=0,005) – Perceived performance (Grade 4/5 MAL p<0,001)
Doman, Waddell et al (2016)	– Change in ARAT score and a change in the accelerometry profile (n=2) – Increase in ARAT score, but no change in the accelerometry profile (n=4) – No change in ARAT score and no change in the accelerometry profile (n=7)
Urbin, Waddell et al (2015)	– Capacity (ARAT p<0,01)
Waddell, Birkenmeier et al (2014)	– Body function (JAMAR p=0,052; Pinch p=0,02) – Capacity (ARAT p=0,018)
Reiterer, Sauter et al (2008)	– Body function (MI p=0,01 on TI; p=0,01 on T2)

However, four studies could not find any increase on actual performance. Though, assessment tools for motor function and capacity did reveal significant improvements. This contradictory can be explained through a possible delayed occurrence of effects on actual performance. It is suspected that a certain threshold of capacity of the affected arm has to be reached in order for patient to use their affected arm more in daily life. Although, these hypothesis has not been confirmed yet.

No significant effects on accelerometer	
STUDY	*Conflicting improvement on clinical outcome scales*
Hsieh, Lin et al. (2014)	– Body function (FMA total p<0,01; FMA distal p=0,01) – Capacity (WMFT-FAS p=0,01; WMFT-time p=,028) – Perceived performance (MAL-AOU p=0,20; MAL-QOU p=0,54)
Lemmens, Timmermans et al. (2014)	– Body function (FMA no significant p-value) – Capacity (ARAT p= 0,008) – Perceived performance (MAL p=0,013)
Timmermans, Verbunt et al. (2013)	– Body function (FMA p<0,01; WMFT/lift p<0,05; WMFT/GS T1-T4 p<0,01) – Capacity (FAT p<0,05; WMFT/FAS p<0,01; WMFT/time p<0,01)
Rand and Eng (2012)	– Body function (FMA p=0,005) – Capacity and disabilities (ARAT p<0,001)

4.3.3 The parameters and settings of accelerometers, that are responsive to change

4.3.3.1 Randomized Controlled Trials (RCT)

Out of the ten RCT's, five studies used a tri-axial accelerometer as outcome measure for actual performance of upper limb (Hsieh, Wu et al. 2016)[32] (Shim and Jung 2015)[38] (Thrane, Askim et al. 2015)[34] (Hsieh, Lin et al. 2014)[33] (Liao, Wu et al. 2012)[37]. When looking at the specific type of triaxial accelerometer, Motionlogger was reported in two RCT's (Hsieh, Wu et al. 2016)[32] (Liao, Wu et al. 2012)[37], while actigraphy (GT3X) was mentioned in three RCT's (Shim and Jung 2015)[38] (Thrane, Askim et al. 2015)[34] (Hsieh, Lin et al. 2014)[33]. Moreover two remaining studies regarded a biaxial type of accelerometer to be the required outcome measure (Uswatte, Taub et al. 2006)[46] (Uswatte, Taub et al. 2005)[42], while three studies incorporated a uniaxiale accelerometer as measurement tool (Lemmens, Timmermans et al. 2014)[35] (Timmermans, Verbunt et al. 2013)[36] (Lang, Edwards et al. 2008)[39]. Apart from the use of a triaxial accelerometer, Thrane, Askim et al. (2015)[34] also offered a uniaxial actigraph (GT1M) for the participants, but no further explanation was reported in the study.

Consistency about the number and placement of the accelerometer is considered, because all RCT's integrated two accelerometers, which were worn on both wrists. Although this parameter was not clearly described in Shim and Jung (2015)[38], it is possible to indirect derive the use of two accelerometer distal to each wrist of both upper limbs.

Seven out of ten RCT's reported a timing period of three consecutive days or 72 hours (Hsieh, Wu et al. 2016)[32] (Hsieh, Lin et al. 2014)[33] (Lemmens, Timmermans et al. 2014)[35] (Timmermans, Verbunt et al. 2013)[36] (Liao, Wu et al. 2012)[37] (Uswatte, Taub et al. 2006)[46] (Uswatte, Taub et al. 2005)[42], while only two studies measures actual performance over 24 hours (Thrane, Askim et al. 2015)[34]

(Lang, Edwards et al. 2008)[39]. The study by Shim and Jung (2015)[38] did not mentioned the wearing time of accelerometer.

In general, specific settings of the accelerometer regarding the sample size and epoch length are mostly not reported in detail. In three studies, only the sample frequency was found (Shim and Jung 2015)[38] (Lemmens, Timmermans et al. 2014)[35] (Timmermans, Verbunt et al. 2013)[36], while one study solely mentioned the epoch length (Lang, Edwards et al. 2008)[39]. Two other studies did not report anything about the precise settings of the accelerometer (Hsieh, Wu et al. 2016)[32] (Hsieh, Lin et al. 2014)[33]. When comparing the settings between RCT's, a large variation between sample frequencies and epochs were noticed. Epoch length can range from 1 second to 1 minute, while sampling rate varies from 10 to 60 Hz. In the remaining four studies, the combinations of settings are far apart from each other. In the study by Thrane, Askim et al. (2015)[34] a sampling rate of 60 Hz is combined with an epoch of 1 sec, while the study by Liao, Wu et al. (2012)[37] sets the accelerometer on a sampling frequency of 10 Hz with a one-minute epoch. Other studies by Uswatte, Taub et al. (2006)[46] and Uswatte, Taub et al. (2005)[42] both are comparable with Thrane et al. and sampled data at 10 Hz within a 2 second-epoch. This discrepancy showed the widely variations between the settings of accelerometry.

Description of data collection is quite rare. Generally speaking, three possible outcomes can be derived from accelerometer raw values. First, the intensity of the arm movements can be determined. Next the amount of arm movement during the observation period is a possible outcome value. At last, the ratio of more-impaired to less-impaired arm use can be calculated.
Two RCT's that are both conducted by the same researchers, Lemmens, Timmermans et al. (2014)[35] and Timmermans, Verbunt et al. (2013)[36], managed to discuss the data collection in detail. Maximal signal intensity per second ($I_{MAX/sec}$), derived from the accelerometer signal, is identified as the highest peak within each second. Amplitudes of two peaks in every 2 consecutive seconds were summed, and is expressed as a 'unit of activity counts'. Thus the intensity of use, indicated by the sum of activity counts (signal intensity per data point) within a given epoch length, was the first direct outcome. Furthermore, the time period between the first activity count in the morning and the last activity count in the evening, identified as uptime, was registered. First and last arm activity of each day was detected through a minimal threshold of signal amplitude. These metrics from both arms were summed, using the resultant accelerometer signal. Duration of use was identified as the hours of upper limb use, relative to the uptime. Thus, these two studies mainly focus on the intensity and amount of arm-hand use. As a third outcome of interest, the ratio between the total intensity of paretic and non-paretic upper limb was also determined.

Table 1. Variables used to calculate the actual amount of arm-hand use.

Abbreviation (unit)	Definition
T_{up} (hour)	Time span between first arm activity detected in the morning and last arm activity detected in the evening/night, displayed in hours
$D_{aff\text{-}uni}$ (%)	(Hours with only activity of the affected arm-hand)/(T_{up}) * 100%
D_{bi} (%)	(Hours with bimanual arm-hand use)/(T_{up}) * 100%
$I_{tot\text{-}aff}$ (activity/hour)	(Sum of acceleration counts of the affected arm-hand during unimanual activity of the affected arm-hand and during bimanual activity)/(hours with only activity of the affected arm-hand + hours with only bimanual activity)
$I_{tot\text{-}unaff}$ (activity/hour)	(Sum of acceleration counts of the unaffected arm-hand during unimanual activity of the unaffected arm-hand and during bimanual activity)/(hours with only activity of the unaffected arm-hand + hours with only bimanual activity)
$I_{aff\text{-}uni}$ (activity/hour)	(Sum of acceleration counts of the affected arm-hand during unimanual activity of the affected arm-hand)/(hours with only activity of the affected arm-hand)
$I_{aff\text{-}bi}$ (activity/hour)	(Sum of acceleration counts of the affected arm-hand during bimanual activity)/(hours with only bimanual activity)
$R_{tot\text{-}aff/tot\text{-}unaff}$	Ratio of $I_{tot\ aff}$ divided by $I_{tot\ unaff}$

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Table. Lemmens, Timmermans et al (2013)

Comparable to these two studies, Uswatte, Taub et al. (2006)[46] and Uswatte, Taub et al. (2005)[42] also published two similar articles with a detailed description of the data collection. Here the accelerometer recordings where the subjects were thought to have the accelerometers off, were removed from data analysis. Due to wearing the impaired upper limb unit on the less-impaired arm and vice versa, incorrect recordings exists and need to be corrected. Invalid accelerometer recordings were eliminated from data collection, if the length of recordings was insufficient to produce reliable data, or if the summary variables go beyond benchmarks (more than 3 standard deviations). If these steps are executed, the raw counts were divided for each epoch around a low threshold. These transformed accelerometer recordings are summed to determine a summary variable for each arm. thus two direct outcomes were calculated for the duration of upper limb use; impaired and unimpaired arm summary variable. Further a threshold filter was applied for a more accurate measure of duration of arm-had usage. As last outcome, a ratio of unaffected-to-affected arm use was indirect calculated, and expressed as ratio summary variable.

Other studies briefly mentioned the mode of measures. Shim and Jung (2015)[38] measured the intensity of arm activity through summations of activity counts, in addition to the amount of mean upper limb motion around x, y, z and total axis. The study by Lang, Edwards et al. (2008)[39] exclusively reported the duration of upper limb use through a summation of epochs, where an arm activity was recorded. Two studies by Thrane, Askim et al. (2015)[34] and Hsieh, Lin et al. (2014)[33] suggested the arm use ratio of the more and least affected arm by measuring the duration of arm activity of both upper extremities separately.

4.3.3.2 Non-Randomized controlled intervention studies – case series

Two out of the four studies incorporated different types of accelerometers. Wang, Lin et al. (2011)[40] mentioned a specific type of activity monitors, which is among a biaxial accelerometer. Uswatte, Foo et al. (2005)[41] reported the use of the Stroke Upper Limb Activity Monitor, which are a two-accelerometer system. Other two studies by Uswatte, Taub et al. (2005)[42] and Taub, Uswatte et al. (2013)[47] did not reported the specific type of accelerometers. Although all previous RCT's reported the placement of two accelerometers distal to both wrists, Uswatte et al. increased the number of accelerometers with an additive accelerometer on the chest and on the ankle of the more affected leg. This adjustment allows for a distinguish of gait related movements from purposeful arm movements. The other three studies

were consistent with the RCT's and placed two accelerometers on both wrists. Though Wang, Lin et al. (2011) did not report the used time period for accelerometer recordings, the other three studies were consentient about a measurement time of three consecutive days, except when washing. Further the specific settings of the accelerometer were not reported in three of the four studies. Uswatte, Foo et al. (2005) choose for a sampling rate of 10 Hz along with a 2 second epoch length. In data collection, two out of the four studies reported the ratio of less to more impaired arm activity. Apart from the ratio summary variable, Uswatte, Foo et al. (2005) also reported the summed variable of duration of movement in each accelerometer. Uswatte, Taub et al. (2005)[42] did not reported outcome measures of data analysis of accelerometer recordings.

4.3.3.3 Observational cohort studies

All five observational cohort studies were agreed to incorporate a triaxial type of accelerometer. Doman, Waddell et al. (2016)[43] and Waddell, Birkenmeier et al. (2014)[44] both reported the Actigraph (GT3X) type, while Reiterer, Sauter et al. (2008)[17] mentioned an Actiwatch system. Because Rand and Eng (2012)[45] investigated both the change in upper and lower extremities, an accelerometer type that is mostly used for the lower extremities was implemented for the upper extremity. For the placement of the accelerometer, consistency was also reached among all five observational cohorts. Although Rand and Eng (2012) added an extra accelerometer on the ankle of the affected leg, these recordings were only used for the outcome of the lower extremity. For the time period for accelerometer measurement, high variability among all five studies were noticed. Three studies preferred a 24-hour measurement period, while Rand and Eng (2012) choose for three consecutive days. A remarkable choice was made in the study by Urbin, Waddell et al. (2015) to register accelerometer recordings over 22 hours. Up to now, no other study reported this time period for accelerometer recordings. For the sampling rate, three studies managed to report similar settings of the accelerometer. In Doman, Waddell et al. (2016) and Urbin, Waddell et al. (2015) data was equal sampled at 30 Hz within a 1 second epoch, while Rand and Eng (2012) reported a sampling rate of 32 Hz within a 15 second epoch. Two remaining studies did not report sampling frequency clearly. For data collection, use ratio between affected and non-affected upper limb was favored in three studies. Apart from this variable, duration of affected and non-affected upper limb activity was also reported in four studies. As a third outcome variables, intensity of arm activity was also determined in one study.

4.3.3.4 General parameters of accelerometer, sensitive to change

To evaluate the sensitivity of the accelerometer to capture a change of arm activity after intervention, the correct parameters of the accelerometer are critical. From all 19 included articles, only 8 studies accomplish significant results on actual upper limb performance. Only two RCT's could report significant improvements on actual performance. Additionally, one controlled intervention study and one case series found significant improvement on accelerometer. Of the five observational cohort studies, four studies managed to report significant results on actual performance. When looking deeper how the accelerometers precisely were implemented in these intervention studies, large variations among the parameters is noticed. Both RCT's incorporated a triaxial type of accelerometer, which was similar to the four observational cohort studies. While the controlled intervention preferred a biaxial accelerometer,

the case series did not report the type of accelerometer. To conclude, 6 out of 8 studies preferred the use of an triaxial accelerometer. Although a triaxial accelerometer is considered most reliable and accurate, some studies prove the accuracy of other types of accelerometer, which is also demonstrated in the controlled intervention study. Apart from the Motionlogger and Actigraph type of accelerometer, Actisleep and Actiwatch was also reported. All studies reported a number of two accelerometers, placed distal from both wrists, except for Uswatte, Foo et al. (2005)[41]. This controlled intervention study increased the complexity of the accelerometry system with an additional accelerometer on the chest and ankle of the affected leg. Further clarification or additional benefits of this choice were not provided. The measurement time of accelerometer is difficult to compare because of a clear distinction between observational cohort studies and the remainders. Three observational cohort studies reported a 24-hour recordings of accelerometer, with a 22-hours wearing time as exception in Urbin, Waddell et al. (2005)[21]. Three other studies by Liao, Wu et al. (2012)[37], Uswatte, Foo et al. (2005)[41] and Taub, Uswatte et al. (2013)[47] consider a recording time of three consecutive days as a more appropriate measurement time. The remaining RCT by Shim and Jung (2015) did not report the time period, in which participants wear the accelerometers. Since an equal part of the significant studies are divided over two possible accelerometer recordings, it is hard to make profound conclusions. Along with the varied accelerometer recordings, high variability is also marked for sampling rate and epoch length. In three studies, no information or explanation about the sampling rate of epoch was provided. First, a sample rate of 30 Hz was reported in three studies, while an another sample rate of 10 Hz was mentioned in two studies. Thus again, studies are quit equally divided over two possible frequencies. Second, the epoch length was quite small in three studies, ranged from 1 second in Doman, Waddell et al. (2016) and Urbin, Waddell et al (2015) to 2 seconds in Uswatte, Foo et al. (2005). At the same time, large epoch length of one minute was indicated in Liao, Wu et al. (2012) Based on these findings, one may prefer a small epoch length to capture a change of actual performance during intervention.

Parameters of significant included studies	
STUDY	*Specific parameters of the accelerometer*
Shim and Jung (2015)	– Sample rate = 30 Hz – Epoch length = unknown
Liao, Wu et al (2012)	– Sample rate = 10 Hz – Epoch length = 1 min
Uswatte, Foo et al (2005)	– Sample rate = 10 Hz – Epoch length = 2 sec
Taub, Uswatte et al (2013)	– Sample rate = unknown – Epoch length = unknown
Doman, Waddell et al (2016)	– Sample rate = 30 Hz – Epoch length = 1 sec
Urbin, Waddell et al (2015)	– Sample rate = 30 Hz – Epoch length = 1 sec
Waddell, Birkenmeier et al (2014)	– Sample rate = unknown – Epoch length = unknown
Reiterer, Sauter et al (2008)	– Sample rate = 40 Hz – Epoch length = unknown

At last, variables of interest during data collection were quite distinct among several studies. Because of the complexity of actual upper limb performance, most studies focused their interest over multiple variables. One study discussed actual performance comprehensive, by means of three outcome variables from accelerometer recordings. Only three studies reported solely one accelerometer variable, which is mostly the ratio of affected to non-affected arm use in two out of three studies. This ratio variable is quite popular among all the studies, what appears from the 6 intervention studies that provided this arm use ratio. Apart from this variable, duration of paretic and non-paretic arm activity also appeared in five out of the 8 studies. As a third outcome variable of interest, intensity of arm activity was also indicated in three out of 8 studies. A further discussion of the possible outcomes, reflecting both quantitative and qualitative characteristics of daily upper limb use is addressed in discussion.

5 Discussion

5.1 Quality of included studies

In general, quality of the included studies is quite high, causing a reinforcement of the results and conclusions of the studies. Although good quality is reached, improvements can be made. There is an overall lack of large-scale studies with a high number of participants. Due to low sample size, power estimates can be too low to gain significant results in the studies. Therefore, it is important to calculate the precise sample size to establish sufficient power in advance of the study.

Randomized controlled trials (RCT) are considered as a gold standard in scientific research. Despite a good internal quality of methodology, generalizability of the results is mostly limited due to specific and detailed eligibility criteria. Significant results of the included RCT's are restricted, in contrast to the other included studies. In complementary to the results of the RCT's, observational cohorts are increasingly recommended. Because these studies provide more 'real-life' data in rehabilitation, respect to observational cohort studies is growing. Although much variability is noticed in the involved intervention due to differences in health care services, this type of study offers an opportunity to address effectiveness in a real-life and more naturalistic context. Disadvantages of observational cohort studies are the possibility for a selection bias, in which the characteristics of the treatment group are likely different from the other comparison or control group. Other than selection bias, observer bias can also cause a limited validity and deviating results. Thus, it is crucial to interpret the results of all the included studies as one whole, with an increased focus for the results in RCT's and observational cohort studies.

First of all, the type of study reveals a clear distinction, in relation to the effects on actual performance. While only 2 out of 10 RCT's could find significant results on accelerometer, this was the case in 6 out of 9 other studies that were not RCT's. This corresponds to 20% in the RCT's, compared to 67% in the other 'non RCT' studies. Though Randomized Controlled Trials are assumed to have a high quality, yet they do not seem to find significant results on actual performance.

In general, most RCT's lack high power due to small sample sizes. Sample size ranged from 20 to 52 participants, which does not reach the required number of participants from calculations of sample size. The only exception is het EXCITE trial, which recruited 222 subacute stroke patients, from which accelerometer recordings were available from 169 out of 222 participants. But yet these RCT's did not achieved significant effects.

5.2 Findings in function of research question

In this section, the interpretation of the results above is discussed in detail to establish a response on the main research question. First, the effects on actual performance will be debated. In function of the results of the included studies, several determining factors will be highlighted. First, the basic fundaments and underlying principles of the rehabilitation interventions are illustrated. One may look at previous evidence to compare results on different outcome measurements of the ICF with the included study. Second, the quality of the study with regard to the sample size and power estimates will influence the results. Underpowered studies have a much lower chance to find significant results. As a third factor,

time since stroke and initial upper limb disabilities of the participants could also contaminate the results. Depending on the recovery stage of stroke and the levels of upper limb disabilities, the predicted extent of motor improvement will vary.

In general, the time course of stroke recovery turns out to be fairly predictable. According to Jorgenson, Nakayama et al. (1995) [48], in the first 10 to 12 weeks after stroke attack, motor function and daily performance will enhance the most. Stroke patients with mild disabilities recover more completely. Because of an initial high level of motor function, stroke recovery remained constant with a light increment (Mirbagheri and Rymer 2008)[49]. Within three to six weeks, best outcomes in neurological recovery can be reached in this population. However, stroke patients with more severe disabilities and low level of motor function recover more quickly at the start, but will gradually tapering off. This motor threshold is mostly reached after 3 to 6 months. After this plateau, slightly progression is possible, but recovery becomes progressively more difficult (Kwakkel and Kollen 2013)[50]. Within 13 to 14 weeks, best outcomes in neurological recovery can be obtained in this stroke group. Eventually, these severe stroke patients will still have some residual deficits in the end of the treatment. Apart from general prediction courses, the recovery of an individual patient can deviate from the guidelines. Looking at initial upper limb deficits, early severity of paresis is the best predictor of motor improvements in the future (Kwakkel, Kollen et al. 2003)[51] (Hendricks, Van Limbeek et al. 2002)[52] (Olsen 1990)[53]. Additional predictors include the active Range of Motion (Bland, Beede et al. 2008)[54], grip and pinch strength (Heller, Wade et al. 1987)[55] and voluntary finger extension and shoulder abduction (Stinear 2010)[56]. Furthermore, a proximal arm control is also considered as an important predictor for regaining hand dexterity (Houwink, Nijland et al. 2013)[57]. Non-motor symptoms, like somatosensory deficits and hemianopsia, also influence stroke recovery (Kwakkel, Kollen et al. 2003)[51] (Patel, Duncan et al. 2000)[58]. At last, an early and rapid improvement of upper limb deficits is linked to a more likelihood to reach higher level of functional performance and independence (Jorgenson, Nakayama et al. 1995)[48]. While motor and somatosensory dysfunctions will not excessively increase during intervention, high intensity practice is required to diminish limitation of daily activities and functional performance. Apart from the intensity of practice, large improvement of motor function and upper limb capacity needs to be obtained before daily performance will follow this increment. Thus, it could be expected that the recovery of actual performance will be much later than the mostly predicted motor function and disabilities.

As a fourth factor, the type and dose of the intervention is addressed to evaluate the correct implementation of evidence-based interventions. Like stated before, the optimal dose of specific rehabilitation approach needs to be determined with regard to significant effects of upper limb function. According to Lang, Macdonald et al. (2009)[59], current doses of task-specific training are not sufficiently high to activate neural reorganization in the brains. Since evidence for the optimal dose is lacking, high variability is found in clinical studies. In general, the higher the intensity of a rehabilitation approach, the more improvement on outcome measures are suspected (Sehatzadeh 2015)[60] (Lohse, Lang et al. 2014)[61] (Han, Wang et al. 2013)[62] (Kwakkel, Wagenaar et al. 1999)[63]. However, this hypothesis had not been established yet (Cooke, Mares et al. 2010)[64]. Especially for an increase of actual performance in daily life, a high-intensity rehabilitation program is necessary. If spontaneous arm use sufficiently increases after training, this increased ADL performance will reinforce the motor function of

the upper limbs and vice versa (Han, Arbib et al. 2008)[65]. This vicious circle can break through a possible developed learned non-use of the impaired arm. But if the spontaneous arm use does not exceed the threshold, compensatory movement strategies of the upper limb will develop further. The increased dose of treatment can be achieved by combining traditional upper limb interventions with new technologies (Reinkensmeyer and Boninger 2012)[66]. Although, a high intensity of a treatment often is associated with a high drop-out rate, increased pain, discomfort or injuries. In the first few hours, days and/or weeks, a longer duration of therapy sessions may not be always beneficial for the patients (Lang, Lohse et al. 2015)[67]. In Hayward and Brauer (2015)[68], dose of activity-based arm training after stroke is often quite low, thus effectiveness of the treatment is limited. These findings are similar with Connell, McMahon et al. (2014)[69], in which stroke patients did not sufficiently engaged in one third of each active exercise session. Thus, it is important to balance between the optimal dose of intervention to obtain significant effects, and the motivation and severity of the impairments of the patient. Further examinations of the dose-response relationship of different rehabilitation approaches is urgent needed

After analyzing these factors, a correct implementation of parameters of the accelerometer will determine the accuracy of the measurement tool. At last, the aspect of actual performance will be expanded if none of these factors can really point out the conflicting results in the included articles. For every included study, these factors will be discussed in detail to provide an in-depth explanation of the results.

5.2.1 The effects on actual performance, related to other outcome measures

Of the fifteen included studies that reported repeated measures before, during or after a rehabilitation intervention, 8 studies found significant effects on actual upper limb performance. Other studies were primarily validity and clinimetric studies, that don't purpose to compare accelerometer recordings before and after intervention. Results on the accelerometer are discussed according to the specific type of rehabilitation practice.

5.2.1.1 Bilateral training of functional tasks

Bilateral training involves the execution of daily tasks with both arms simultaneously. Most stroke patients have major difficulty with performing bilateral activities, because the precise coordination between the two upper limbs is affected through paresis, spasticity, somatosensory deficits and lack of fractionate movements. Though, bilateral coordination is a key component of various arm skills. Thus, smoothed coordination of both arms is required for ADL performance. Since most functional activity in real-world are performed with both hands, this type of rehabilitation approach could ease the transfer between clinical practice and daily environment. By performing both upper limbs symmetrically and simultaneously, the non-affected arm is thought to enhance relearning of motor tasks. By dragging the less-impaired arm into the training, the loading of this upper limb benefits the performance of bimanual tasks (Cunningham, Stoykov et al. 2002)[70]. Facilitation of cortical plasticity occurs through a disinhibition of the motor cortex, an increased recovery of the ipsilateral neural pathways from the contralesional hemisphere and an upregulation of descending premotorneurons commands (Cauraugh and Summers 2005)[71]. Thereby, hand dexterity also demonstrates promising effects. The spatiotemporal control of the paretic arm improves (Lin, Chen et al. 2010)[72], along with an enhanced

temporal coupling between both upper limbs (McCombe Waller, Harris-Love et al. 2006)[73]. Basic principles of motor learning, like task specificity and intensity, are applied to adjust the precise content of the training. Previous studies indicate the fluctuation of the effectiveness of this type of rehabilitation approach. According to a Cochrane systematic review, opposing evidence could not support the superior effects of bilateral training. There is a lack of good quality studies to establish the effectiveness of simultaneous bilateral arm training compared to placebo, no intervention or usual care (Coupar, Pollock et al. 2010)[74]. Few studies show increased motor function and dexterity in favor of bilateral training (Stoykov and Stinear 2010)[75]. However, other studies failed to prove the clinical effects of bilateral training (Desrosiers, Bourbonnais et al. 2005)[76] (Whitall, Waller et al. 2011)[77] (Wu, Chuang et al 2011)[78] (Morris, van Wijck et al. 2008)[79]. According to McCombe Waller and Whitall (2008)[80], intervention has to be adjusted on the baseline characteristics of the patients.

Shim and Jung (2015) [38] investigates the recovery of upper extremity impairments after bilateral task-oriented training in subacute stroke patients. The amount of paretic upper limb use was significant increased after bilateral training ($p<0,01$), along with a significant increase of the moderate intensity level of arm-hand use ($p<0,01$). These improvements are associated with an increase on upper limb function and capacity on the Manual Function test (MFT) and Functional Independence measure (FIM) ($p<0,01$). Thus, all outcome measure consistently improved in favor of bilateral arm training. Like stated in the review of Coupar, Pollock et al. (2010), the quality of the RCT is substantially lower compared to the other RCT's. The reported internal validity of the study was constrained, because items couldn't be scored correctly due to a lack of reporting data. Further, a small sample of 20 subacute stroke patients does not satisfy the required sample size for a power of 80%. This is a major drawback in RCT's evaluating effectiveness of intervention. As a dose-matched usual care control group was not incorporated, the additional effects could not be compared to usual care. However, the unilateral task-oriented practice could be considered as a form of control therapy. Nevertheless, the study did manage to found significant results. From the subacute stroke participants, moderate upper limb disabilities are reported. Compared to baseline tests of other studies, initial accelerometer activity counts can be considered as quite low. Although moderate disabilities and low clinical scores, these subacute stroke patients could still benefit from bilateral arm training after 6 months. Although mostly a motor threshold is reached after 6 months, innovative rehabilitation approach could result in more progression. Although the required dose of bilateral arm training is not clearly identified, a dose of 150 min per week is substantially lower than other comparable studies. Although significant results on actual performance were obtained the applied dose of bilateral arm training can be assumed to be too low for significant improvements. To conclude, low sample size, lack of dose-matched control group and insufficient dose of arm training are major methodologically drawbacks. The recruitment of moderate disabilities is highly responsible for the significant results in this RCT, considering low level of arm hand function might benefit more. Bilateral training could give the opportunity for additional progression after 6 months due to different underlying mechanisms.

5.2.1.2 Robot-assisted arm therapy

Robot-assisted therapy is a new technology-based rehabilitation approach, that is mostly combined with traditional interventions. To enhance recovery, massive and intensive practice in a combination of different interventions is important. A large amount of repetitions and practice of motor skills could be trained in a consistent manner. Thereby, the system could adapt the degree of difficulty by increasing the resistance or actively help with the patient. The active movements of the less impaired arm regulate the passive movement of the impaired arm without any active exertion. Robotics can be precisely programmed according to individual needs and goals. Based on principles of motor learning, a large variety of sensorimotor feedback could reinforce motor function. However, it is important for the robot system to focus on a task-oriented practice of motor skills in order to increase functional performance. Though a natural environment of the patient is often lacking, resulting in a lesser extent of motor learning. The transfer of practice setting to the home environment is also hindered. Thereby, confounding factors of the robotic system are possible intruders for the effectiveness of robotics. Because of these restrictions, robot therapy by itself might not be enough practice to improve motor function and ADL performance. Therefore, four included studies combined robot-assisted therapy with a supplementary rehabilitation approach to give the stroke patient more opportunities to learn more specific motor skills. Even so, robot-assisted therapy is a save and interactive intervention. Because of rare adverse effects, drop-out rate in clinical studies is not excessively reported.

In general, robotic systems mainly focus on motor functions, but less on capacities and daily activities. A systematic review by Mehrholz, Pohl et al. (2015)[81] reveled the lack of high quality studies, resulting in great variations between the trials regarding the intensity, duration and amount of robot practice. Future research should focus on revealing a unified methodology in robot-assisted therapy trials (Peter, Fazekas et al. 2011)[82]. Therefore, significant improvements were only observed on body functions, like muscle strength, but increase of ADL performance and clinical capacity tests were rarely found [83] [84] [85]. Norouzi-Gheidari, Archambault et al. (2012)[86] found no superior effects of a high-intensity robot-assisted arm therapy, compared to a dose-matched conventional therapy, on motor function and functional performance. Similar to these findings, Kwakkel, Kollen et al. (2008)[87] reported no overall significant results for the effectiveness of robot-assisted therapy, especially not for daily arm function. Prange, Jannink et al. (2006)[88] stated short- and long-term improvements of motor function of the affected shoulder and elbow in subacute and chronic stroke patients. However, daily capacity of the upper limbs did not change after robot-aided therapy. However, Brochard, Robertson et al. (2010)[89] undermined the effectiveness of robot-assisted therapy, considering only the clinical benefits of this rehabilitation approach is an intensive and repetitive practice of arm movements.

Recently, the development of robotics has been excessively increased. Up to now, more types of robot system are becoming functional and adjusted to the needs and capabilities of the patients. Chang and Kim (2013)[90] supports the effect of either an end-effector and exoskeleton as an adequate additional arm rehabilitation training, supplementary to conventional interventions, in chronic stroke. Furthermore, the effectiveness of MIT-MANUS and MIME robot system, which practice more the proximal shoulder and elbow movements, has been established (Lum, Burgar et al. 2002)[91] (Fasoli, Krebs et al. 2003)[92] (Masiero, Celia et al. 2007)[93].

The Bi-Manu-Tack is a robotic system, that enables an active pronation and supination of the forearm with wrist flexion and extension. Like states before, the non-affected arm works as a mirror to the affected arm, and thereby promotes motor recovery through symmetrical and simultaneous movements of both limbs. Training of the distal components of the arm represents more functional ADL movements and object manipulation. Another advantage of training the wrist and hand is the larger cortical representation of the hand, compared to the shoulder. As a result, increased activity in more cortical brain areas will be provoked. Like other robot-assisted therapies, they provide the opportunity to increase the duration and intensity of traditional interventions. Despite the distinct qualities of this robot system, previous studies failed to show significant improvements, due to study design, sample size, patient criteria, motor severity of included patients, content of robotic protocol and intensity of robot arm training. However, the precise dose of robot-aided therapy to reveal significant improvements is not identified.

Liao et al. [37] explored the superior effects of robot-assisted upper limb training, compared to dose-matched active control therapy on the functional recovery of the arm. Activity of the paretic arm increased significantly (p=0,026), together with motor impairments on FMA (p=0,002) and perceived performance on MAL (p0,002-0,007) and ABILHAND (p=0,043). Moreover, scores of FMA exceeded minimal clinically difference. Quality of this RCT is regarded as a high methodology. However, sample size (n=n=20) is quite small, thus study is underpowered to detect significant effects. Like reported in the study, a lack of an adequate sample size is a major limitation of the study. Despite low power, a significant improvement on actual performance was rated. Furthermore, capacity outcome measures that evaluate hand dexterity, like WMFT or ARAT, are not administered. Time since stroke is set to more than 6 months after stroke onset, with an average of 22-24 months after stroke. At baseline, upper limb disabilities can be categorized as mild upper limb disabilities. Like said before, recovery course in mild impairments does not substantially increases. Similar to UE deficits, initial accelerometer recordings are lower than normative reference values, but are still quite high compared to other stroke population. Furthermore, chronic stroke patients usually have reached a motor plateau. But new technology-based interventions are based on different underlying principles, thus progression is still possible. Further, the type of robot-assisted upper extremity therapy is discussed above. Although Bi-Manu-Track has lots of promising advantages, effectiveness is still not clear. Moreover, dose of robot-aided intervention is uncertain due to lack of convincing evidence. Compared to other intervention, a weekly dose of 450 to 525 min can be considered as a moderate intensity. Since the study resulted in a significant increase, it can be assumed that the used dosage is sufficient. Despite a lack of high power, significant effects were found on most outcome measures. Although the effects of the intervention on hand dexterity is unknown, improvement could be suspected considering an increase daily use of the paretic arm. Furthermore, predictive recovery in chronic stroke patients with mild deficits is not good. The mean reason of these significant effects is probably the good choice of robot system with an applied high dose of bilateral arm training.

However, three included RCT studies were lacking significance effects on actual performance in robot-assisted therapy. Two studies by Hsieh [32] [33] evaluates the additional effects of a combination of robot-assisted training with other rehabilitation techniques, compared to the intervention alone. The first

study analysed a sequential combination of robot-assisted therapy with a distributed form of CIMT, compared to robot-assisted therapy and conventional rehabilitation (Hsieh, Lin et al. 2014)[33]. Although significant effects of Constraint-induced therapy (CIT) has been established, the additional effects of this combined therapy approach is unknown. CIT mainly addressed the functional performance of the more paretic upper limb. According to the standard protocols by Uswatte, Foo et al. (2005)[41] and Uswatte, Giuliani (2006)[16], Constraint-Induces movement therapy consist of restraining the less impaired upper limb for up to 90% of waking hours, with an additional intensive training of the more impaired arm for up to 6 hours each day. However, this high intensity program cannot be applied in all stroke severities, leading to the development of modified or distributed forms of CIMT (Page, Levine et al. 2008)[94] (Smania, Gandolfi et al. 2012)[95] (Wu, Chen et al. 2007)[96]. In these adjusted CIMT program, the daily hours of constraint times of the less impaired arm and the training of the more impaired arm were either or both reduced, but were more divided over a longer intervention of more than 2 weeks. Although effectiveness of the traditional protocol has been established, these modified CIMT forms also show beneficial effects on motor capacity of the hand and performance of the more impaired arm in real-life (Lin, Wu et al. 2009)[97] (Wolf, Winstein et al. 2006)[98] (Page, Levine et al. 2008)[94] (Smania, Gandolfi et al. 2012)[95] (Wu, Chen et al. 2007)[96]. Recently, more advanced results have been noticed in the application of combined rehabilitation approaches.

In this RCT, a modified CIMT program was applied in supplement with robot-aided therapy of the Bi-Manu-Track. Conflicting results on different outcome measures of various ICF levels were observed. Upper extremity function and capacity changed significantly on the FMA ($p<0,01$) and WMFT Functional assessment ($p=0,01$), while actual performance ($p=0,33$ on accelerometer) and perceived performance ($p=0,20$ for MAL AOU; $p=0,54$ for MAL QOM) did not improved. However, MAL and accelerometers did show gains after treatment, but the changes between the experimental and robot-aided group were not sufficiently high. These findings confirm a previous statement, that a high increase of impairment and disabilities has to be reached, before any improvements on performance of the upper limbs can be reached. Although it is suspected that the transfer of improvement on motor capacity to a more daily use of activities of the upper limb might occur at follow-up. This delayed effect on actual performance is just a hypothesis, and has not been determined so far. Despite high to excellent quality of this RCT, no significant effect could be found. By adding the control group, effects of robot-assisted therapy and the combination with CIMT can be compared to usual care. Also superior effects can be evaluated when comparing effects of both interventions of interest. To correct determine sample size, the effect size, significant levels and power estimates of previous studies were used. With a large sample of 48 subacute stroke patients, power will be high to discover significant effects. Adults of 20 to 28 months post stroke reported moderate upper limb deficits. However, these UL disabilities are required for a successful execution of the modified CIMT program. Baseline characteristics indicate an initial accelerometer arm use ratio of 0.65 – 0.69, which is significant lower than normative value. Again, these scores point out the moderate UE disabilities of this stroke sample. Dose of the robot-assisted therapy is similar to Liao, Wu et al. (2012). A weekly dose of 450 to 525 min of arm training can be considered as a moderate intensity. Although Liao, Wu et al. (2012) did report significant effects on actual performance, Hsieh, Lin et al. (2014) could not. It could be assumed that this high intensity dose is

adequate to achieve a significant change after treatment. Bringing all factors together, disappointing results are not suspected considering the adequate power and the implication of a good high-intensive robot therapy. Although the choice of this intervention was stated to be the main reason for significant effects in Liao, Wu et al. (2012), no improved actual performance was found here. The main difference between both studies is the lack of a dose-matched control therapy in this RCT.

In a more recent study by Hsieh, Wu et al. (2016)[32], robot-aided therapy with the Bi-Manu-Track was executed, in combination with a task-oriented training. In clinical evidence, task-oriented training is considered as an excellent rehabilitation approach to increase the daily use of arm and hand in stroke patients. The high-intensity, real-world practice of motor skills in a familiar environment with real objects enlarged the re-acquisition of actual performance, instead of using compensatory strategies in daily activities (Bosch, O'Donnell et al. 2014)[99] (Rensink, Schuurmans et al. 2009)[100]. Additional to clinical improvements, neural reorganization of brain areas can be triggered. Regarding basic principles of motor learning, varied mass and repetitive practice of functional ADL tasks is mostly emphasized. Thereby, complexity of tasks can be easily increased with other settings, tasks and objects, along with precise and timed feedback in different forms. Task-oriented training is mostly applied in supplement with other traditional intervention. Since there is no standard protocol on the precise implementation or dose of task-oriented training, high variability of the arm therapy is observed in clinical studies.

In this RCT, robot-aided therapy is adjusted into a bilateral priming form. Priming is defined as a change in motor behavior, that is triggered by previous stimuli. This rising rehabilitation approach is suspected to enhance motor learning (Stoykov and Madhavan 2015) [101]. Various types of motor priming have been developed, but in this RCT the motor priming consist of a bilateral robot-assisted arm training. Like stated before, simultaneously and symmetrical movement of the less impaired arm facilitates the motor function of the more affected arm. Current evidence already supports the effectiveness of bilateral priming, combined with additional conventional therapy in chronic stroke (Stinear, Barber et al. 2008)[102] and subacute stroke (Stoykov and Stinear 2010)[75]. Yet, the additional benefits of a priming treatment, compared to unprimed intervention, is not known.

The latest study by Hsieh, Wu et al. (2016)[32] assessed the additional benefits of bilateral robot priming in advance to task-oriented training (priming group) compared to task-oriented training alone (unpriming group). However, this RCT fails to gain significant effects on actigraphy (p=0,438), FMA (p=0,812), grip strength (9=p=0,548), Box & Block test (p=0,383), FIM (0,647) and modified Rankin Scale (p=0,065). Except for the strength subscale of the Stroke Impact scale, significant effects were reported (p=0,012), despite no improvements on the grip strength measurement were found. Like the previous study of Hsieh, Lin et al. (2014), quality of this RCT was also rated as high till excellent. High drop-out during treatment resulted in a failed follow-up period of 3 months, but no clear reasons for this high rates were provided. According to sample size, power estimates, significance level and effect sizes of previous studies, accurate sample calculations could be made. Though, the recommended sample size of 31 participants in every single experimental and control group lead to a total of 62 subacute stroke patients. This high number of participants was too ambiguous and could not be recruited. Thus, study is underpowered to find significant results. Apart from a small sample, the RCT lacks a control group to

assess the effects of both experimental therapies with conventional rehabilitation. Included patients with stroke onset of average 2,4 months demonstrate moderate UE deficits, that is associated with the minimal requested hand function to successful follow a task-oriented training programme. Compared to Liao, Wu et al. (2012), baseline characteristics revealed a slightly worse severity of upper limb impairments in this RCT. Like noticed on the initial accelerometer activity counts, upper limb of this sample is moderately affected. The strengths of the robotic system have been discussed above. The intensity of applied robot-assisted therapy is slight decreased here, though a weekly dose of 450 min of arm training can still be considered as a moderately dosage. Compared to previous study by Hsieh, Lin et al. (2014), the dose is slightly diminished. Due to lacking of evidence, no clear statements can be made about the intensity of the training. Compared to Hsieh, Lu et al. (2012) and Liao, Wu et al. (2012), recruited participants were more subacute with still moderate disabilities. In subacute stroke patient, more improvement could be achieved in a more accelerated time course, but progression is gradually slowed after some time. The implementation of the robot-assisted therapy is quite similar in Hsieh, Lu et al. (2012) and Liao, Wu et al. (2012), except for a slight decreased intensity. The main reasons for the non-significance effects includes the low sample size and the lack of a dose-matched control group.

In the last study that investigated robot-assisted therapy, another robot system was preferred. The haptic master is a prominent end-effector robot that emphasize functional ADL tasks, like reaching, grasping and object transportation. Through the use of a gimbal, all 6 possible degrees of freedom are set for the patient to move free in the environment. The major advantage of this robotic system is the use of haptic feedback. Preliminary evidence supports increase of motor function (Prange, Jannink et al. 2006)[88] (Kwakkel, Kollen et al. 2008)[87], but in combination with task-oriented training, quality of motor skills and arm-hand performance might be more addressed (Liao, Wu et al. 2012)[37] (Hsieh, Wu et al. 2011)[103] (Housman, Scott et al. 2009)[104].

Lemmens, Timmermans et al. (2014)[35] addressed the superior effects of robot-assisted task-oriented training, compared to task-oriented training alone, on objective actual performance. Both duration and intensity of the affected upper limb activity were not significantly different between bimanual task-oriented training in the robot-assisted training and unimanual task-oriented practice without support. Even though the study could not find significant difference between these two types of studies, the quality of this RCT was rated as high till excellent. Sample size calculations were made, but the required sample size to have a high power of 80% could not be attained. Thus, the study is likely underpowered to find significant effects. Apart from the small sample size, the RCT's lacks a control therapy. Here, one may not know the benefits of both interventions on usual care. These two factors operate as the major drawback in this study. Perhaps a significant effect was obtained if the effects of both interventions were compared with a control therapy. Now, all we know is that bimanual robot-assisted task-oriented practice has no superior effects compared with traditional unimanual task-oriented training. Chronic stroke patients with 12,5 to 25,5 months after stroke with moderate to low UE disabilities were recruited. Progression achieved after one year of stroke and the rate of recovery in moderate to low disabled stroke patient is less favourable. Like stated before, robot therapy demonstrates a lot of promising opportunities to increase duration and intensity of therapy, in complement to traditional conventional treatment. Here, the robotics were used during task-oriented training, but no other additional treatments

were provided for the participants. There is still no distinctness about the required dose of robot-assisted therapy. Though a weekly dose of 240 min per week is considered as a low intensity intervention, in comparison to other RCT's. Compared to the dose used in Liao, Wu et al. (2012), a high intensity robot training of 450-525 min a week is not reached in this RCT. Although the type of robotic system has promising strengths, the practice of solely unilateral functional tasks is a major disadvantage. Considering that the paretic arm is mostly used in bimanual tasks, these type of tasks should be incorporated into the treatment. Thereby, a higher intensity of robot-aided therapy is preferred. Together with a low dosage of treatment, the lack of high power and dose-matched control group describe the main explanatory factors for disappointing results.

5.2.1.3 Constraint-induced movement therapy

According to the standard protocols by Uswatte, Foo et al. (2005)[41], Uswatte, Giuliani (2006)[16] and Morris , Constraint-Induces movement therapy consist of restraining the less impaired upper limb for up to 90% of waking hours, with an additional intensive training of the more impaired arm for up to 6 hours each day. Some studies also incorporate adherence-enhancing behavioral strategies (transfer package). According to the protocols, CIMT sessions are usually programmed on 10 consecutive workdays, spread over two weeks. Regarding the primary purpose of CIMT, a high intensity task-specific training was developed in the early stages of stroke. The first weeks after stroke are considered as a critical window for neuroplasticity. Effectiveness of an early CIMT program shows a significant worsening of the experimental group, while the low intensity CIMT training did improved significantly on short term. (Dromerick, Lang et al. 2009)[105] (Boake, Noser et al. 2007)[106]. These findings indicate that this high intensity program cannot be applied in early stroke patient or highly severe patients, leading to the development of modified or distributed forms of CIMT (Page, Levine et al. 2008)[94] (Smania, Gandolfi et al. 2012)[95] (Wu, Chen et al. 2007)[96] . In these adjusted CIMT program, the daily hours of constraint times of the less impaired arm and the training of the more impaired arm were either or both reduced, but were more divided over a longer intervention of more than 2 weeks. The major strength of CIMT is the high intensity of arm training, together with the practice of functional real-life tasks. Therefore, the main outcome of interest is the daily use of the paretic arm in performing ADL. However, a major disadvantage of CIMT is the selection of eligible participants though strict inclusion criteria. Severely impaired stroke participants are excluded for this purpose. Furthermore, CIMT is often associated with safety issues and patient discomfort.

From three non-Randomized controlled interventions, only one study found significant results on actual performance. Although the first aim of Uswatte et al. [41] is to evaluate the reliability and validity of the accelerometer, the study did also compare actual performance before and after intervention. The ratio of paretic to non-paretic arm use significantly increased after Constraint-Induced Movement Therapy ($p<0,05$) with a large effect size ($d'=0,9$). No other outcome measures were used. On the MINOR quality checklist, this RCT achieved a moderate score of 14 on 24. Although this quality assessment highlighted some flaws, obtained data and results should still be reported in this paper. With a small sample size of 20 chronic stroke participants, it can be assumed that the study is underpowered considering the lack

of concrete calculations of power and sample size. The study incorporated a chronic stroke population with mild to moderate motor impairments of the hemiparetic upper limb.

though specific inclusion criteria were missing. Baseline accelerometer recordings are not reported. Previous evidence also supports the effect of Constraint-induced movement therapy within this population.

At last, a Case serie by Taub et al. [47] examines the effects of Constraint Induced therapy, combined with conventional Neurodevelopmental rehabilitation techniques on motor recovery in severe chronic stroke patients. Significant improvements on actual performance are large for both stages of the intervention ($p=0,012$; $d'=1,2$). Similar results are observed on the grade 4/5 Motor Activity Log with even more excessive effect sizes ($p<0,001$; $d'=3,4$). Likewise, this progression is established on body functions with a significant increase on active Range of Motion and FMA ($p<0,05$). A small sample of six is suitable for this type of study. However, power is often decreased with a smaller sample size, thus study is probable underpowered to detect significant effects. Further, The Newcastle Ottowah Scale reported excellent to high quality of the case series, but an illustrated flow-chart with drop-out and blinding of the assessors was lacking. Community residents with more than 1 year post stroke and initially fisted hands were recruited. The severity of the upper limb impairments and spasticity improved in the year after stroke onset, thus participants met the strict inclusion criteria for CIMT. Accelerometer recordings at baseline demonstrate an activity use of $0,46 \pm 0,07$ hours at baseline, which is much lower compared to normative data ($9,1 \pm 1,9$ hours). The desired quantity and quality of ADL performance is still not reached. Previous evidence also supports the effect of Constraint-induced movement therapy within this population.

However, two other studies could not report significant results in favor of Constraint Induced Movement Therapy. Thrane et al. [34] looked into the effects of a modified CIMT protocol in acute stroke patients. All outcome measures were similar before and after CIMT without any significant changes. High p-values were detected for arm use ratio ($p=0,301$ posttreatment; $p=0,215$ after 6 months), FMA ($p=0,116$ posttreatment; $p=0,296$ after 6 months), several subscales of WMFT and Stroke Impact Scale. Except for two upper extremity capacity test, significant effects were found on NHPT ($p=0,035$ posttreatment) and log time of WMFT ($p=0,018$ posttreatment). Like most other RCT's, methodological quality of this study is rated as high to excellent. A major drawback however was the high drop-out in the experimental (17%) and control group (13%), which may lead to an effect-dependent bias. Apart from the criteria on the checklist, sample size was rated as moderate to large in this RCT. 47 acute stroke patients were recruited, but specific calculations that prove that the required sample size is attained were not reported. Thus, it can be assumed that the number of participants is sufficient for a high power estimate, but still objective calculations are lacking to prove that the recommended sample size is satisfied. Thrane et al. choose to engage stroke patients at more than 5 and less than 26 days after stroke. Further, the modified Rankin Scale was used to evaluate the level of functional independence in daily life. Acute stroke patients with a score between 0 and 2 were included, which represents stroke patients with a very low to low functional independence in daily life. On average, a score of 2,6 on mRS was obtained from all participants, along with an average score of 1,7 on the NIHSS. Apart from the used inclusion criteria,

extra strict criteria for participation on a CIMT programme were added. Baseline assessment on the arm use ratio amounts 0,73 in the experimental group, which is much lower compared to reference values (0,95 ± 0,06 arm use ratio). Although 10 therapy sessions on two weeks is considered as a minimal dose of intervention, participants were excepted to train for 3 hours daily, with additionally wearing a splint on more than 90% of the waking hours. The duration of the treatment is quite short, but this compensate with a high daily dose of 3 hours intensive training. Previous study proves the effectiveness of a modified CIMT protocol in acute stroke patients.

Uswatte et al. [16] considered the accelerometer as an objective tool to examine real-world arm activity, and aimed to assess the psychometric properties of the accelerometer in subacute stroke patients. This RCT is part of large scale EXCITE trial (Extremity Constraint Induced Therapy Evaluation), which evaluates the effectiveness in upper extremity function and impairments in chronic stroke patients. Yet no significant changes in the outcome variables, derived from the accelerometer were found ($p>0,48$). Other outcome measures were not used. Contradictory to the other RCT's, methodology of Uswatte et al. was rated as moderate, because of a lack of reported data. Although the large scale (n=169) indicates a high power to detect differences, no significant differences were found. The study recruited a high number of participants 3 to 9 months after stroke onset, with mild to moderate motor impairments of the upper extremities. Initial assessments incorporated mean duration of paretic arm movements (22,1 ± 10,3) and mean arm use ratio (0,56 ± 0,16), which are both significantly lower than normative values (9,1 ± 1,9 hours of arm activity; 0,95 ± 0,06 arm use ratio). Other baseline characteristics were mean MAL points (1,4 ± 0,9) and mean AAUT (0,9 ± 0,8), which also indicates mild to moderate arm disabilities. Because of the aim to explore psychometrics, no baseline accelerometer recordings were reported. Apart from these baseline features, other strict criteria were provided to warrant a good performance during CIMT. Similar to the other study of Thrane et al., the minimal duration of therapy was preferred due to the high intensity of practice every day. Previous studies indicate that even in chronic stroke patient, progression of upper limb disabilities can be made through high intense and new treatment approaches.

5.2.1.4 Mental practice

Recently mental practice and motor imagery has given a lot of attention, that resulted in great controversy on the effectiveness of this newly rehabilitation approach. Timmermans et al. [36] is the single study that estimated the effects on upper limb disabilities with recommendations for clinical implications. This RCT explored the potential benefits of adding a task-oriented mental practice therapy to traditional upper limb training (NDT) in subacute stroke patients. Despite significant changes on motor impairments, actual performance did not significantly improved. Thus, significant increases on the FMA ($p<0,05$), Frechary arm test ($p<0,05$) and Functional Assessment subscale of WMFT did not lead to ameliorate on arm-hand use. Similar to other RCT's, quality of this RCT was equally high to excellent. Though, drop-out ratio was very high, with 14% in the experimental and 33% in the control group. Further, sample size was precisely calculated from effect sizes, significant level, power estimates and expected drop-out from previous studies. Based on these calculations, a sample size of 160 subacute stroke patients was recommended. This number of participants was very high, so is very difficult to

reach. Only 42 participants could be recruited, which is substantially lower than the calculated recommendations. Apart from the required 2 to 6 weeks since stroke onset, no specific criteria were composed to include a certain level of upper limb disabilities. The recruited subacute stroke patients showed high functional independence during ADL with low to moderate upper limb disabilities, what can be extracted from high scores on baseline characteristics; 72.35/100 on Barthel index, 56.4/60 on Frenchary activity index, 43.5/66 on FMA, 3.4/5 on Frenchary arm test, 3.055/5 on Functional ability of WMFT and 5.45 on Performance time of WMFT. When comparing initial accelerometer measurements with normative values, the subacute stroke population (arm use ratio of 0,35) clearly scored lower than healthy older adults (arm use ratio of 0,95 ± 0,06). As quoted by Timmermans et al. the minimal dose of mental practice to obtain significant effects is not quite identified, so it is very difficult to choose an adequate intensity and dose.

5.2.1.5 General inpatient rehabilitation

Five observational cohort studies were included. These type of studies typically pronounce the effectiveness of regular rehabilitation courses in stroke patients. As a result, more variety in the rehabilitation courses is suspected, because of high variability in health care services. Though, the intervention and population is not strictly determined in advance of the study, thus generalizability of the results can be expanded to a broader field of population and stroke intervention. Because methodology is not strict delineated, significant results of observational studies are difficult to convert in profound statements. Four of these studies managed to find significant effects on actual performance.

Urbin et al. [21] aimed to monitor the changes on upper limb impairments and daily activity during an outpatient occupational intervention in stroke patients. Every participant in the study is separately analyzed, because group means were not primarily of interest. The study aimed to track the individual evolutions throughout a traditional occupational therapy. Three patterns were observed; a change in ARAT and accelerometry (n=2); a significant increase in ARAT, but yet no change on accelerometry (n=4); no change in ARAT and accelerometry (n=7). Since this type of study is a pilot observational cohort, previous or comparable studies are lacking. Although quality of observational cohort study is not comparable with RCT, this observational cohort study managed to achieve a moderate to high score on the Newcastle-Ottowah scale. Other confounding factors were not incorporated, and a non-exposed control sample was lacking. Apart from the quality checklist, sample size and power estimates are also important for high quality studies. Considering the purpose of this pilot observational cohort, a recruited sample of 15 participants is satisfying. Though, large scale studies are still desirable for future research. As to the participants, a broad stroke population with hemiparesis and some retained motor function (score between 29 and 91 on Motricity Index) were targeted. These criteria represented stroke patients with low to moderate upper limb disabilities. Time since stroke was not reported, thus all stages of stroke recovery could be included. Average group scores on initial values of FMA and accelerometer were lacking. Occupational therapy compromise different rehabilitation approaches that all addressed individual goals and challenges. With this wide description, several therapeutic activities and exercises could be included. Together with the content of the occupational therapy services, the dose and intensity of the therapy sessions is different for every participant.

Waddell et al. [44] evaluated the practical potentials of implementing an inpatient high-repetition task-oriented arm training protocol in stroke patients. Significant changes were found on arm use ratio (p=0,05), JAMAR hand-held dynamometer (p=0,007 at discharge and p=0,052 after 1 month), pinch strength (p=0,001 at discharge and p=0,02 after 1 month), FIM (p=0,000 at discharge and p=0,009 after 1 month) and ARAT (p=0,000 at discharge and p=0,018 after 1 month). Comparable to Doman et al., this cohort study also obtained a high to moderate to high score of 6 stars on the NOS quality checklist. Confounding factors and a non-exposed control treatment is lacking. Like in Doman et al. a small sample of 15 stroke patients was recruited. Often a low sample size is associated with a low power to detect significant results, thus a larger sample would be preferred. To select an adequate sample, stroke patient with unilateral hemiparesis were selected. Thereby moderate to high preserved motor function, indicated by a score between 42 and 93 on the Motricity Index, is an important criterion for successful task-specific training. Contradictory baseline ARAT score of 25,47/57 signify stroke moderate to severe upper limb disabilities. No inclusion criteria of time since stroke was formed, but the average number of days since stroke of all the participants was 20 days, which indicates a sample in the acute stage of the stroke recovery. Initial affected arm-hand use was measured at 0.47 ± 0,14 on the use ratio, which is significantly lower than reference values of 0.95 ± 0.06. Further, the rehabilitation approach in this cohort study is mainly focused on task-related practice during occupational therapy. To achieve a high-repetition intervention, a minimal of 300 repetitions of various daily tasks has to be obtained after each session. With a dose of 240 min therapy every week, significant results were elicited. Though, the minimal dose of task-oriented training to capture significant results has not been established yet.

Reiterer et al. [17] intended to enhance the capacity of the accelerometer to objective motor recovery and the functional performance during stroke rehabilitation. For the non-paretic upper limb, TASni changed from T1 (24-36h) to T4 (6 months), but no increase was found for the measurement points in between. For the paretic upper limb, change occurred between T2 (5-7 days) and T3 (3 months) till T4 (6 months). Thus, both upper extremities improved significantly in the first two measurement points, but this increase could no longer be retained after 3 and 6 months. Quality of this cohort was substantially lower, due to a lack of a descripted recruitment of participants, a non-exposed control group and an illustrated flowchart with clear drop-out rates. Thereby, there was no clear prove that the outcome of interest was not extant at baseline measures. A recruited sample of 38 stroke patient is the largest reported number of participants in all four significant cohort studies. Thus, it can be assumed that the sample size is sufficient, but precise calculations of the sample size are not provided. Regarding the participants, stroke patients are assumed that stroke onset was longer than 24-36 hours before the first actigraphic monitoring. Further, a minimal motor deficit of the upper limbs was requested, but full paralysis was excluded. From the baseline characteristics were not reported, an initial score of 99.8 ± 1.2/100 on the Barthel Index and 0.4 ± 0.6 on Rankin scale. Time since stroke are not reported, thus all stage in the stroke recovery are included. Apart from a general rehabilitation course in stroke patients, no other descriptions of the intervention are provided. Thus, the content of the therapy sessions can be very wide. This is similar with the dose of therapy, that can be quite variable.

Rand et al. [45] is the only observational cohort study that could not find significant results on daily arm use. The purpose is to compare the recovery of daily performance of the upper limbs during stroke

rehabilitation with daily performance of older, healthy adults. The small increase of paretic and non-paretic arm activity was not found significant. However, conflicting results indicate an improvement on FMA (p=0,005), ARAT (p<0,001) and FIM (p<0,001) after 3-week treatment. Again, these findings affirm the high requested improvements in arm function and capacity, before quantity and quality of performance of ADL starts to improve. Quality of this cohort study was moderate, due to absence of a described recruitment of participants and an adequate non-exposed control group. This cohort managed to recruit a quite excessive sample of 60 stroke patient, who sustained a stroke within 60 days. Apart from the subacute timing of the stroke, no further criteria of upper limbs disabilities were formed. Thus, this cohort incorporates a large subacute stroke sample with widespread upper extremity impairments. In baseline characteristics, days since stroke are amounted at 33.4 days after stroke onset. Apart from an initial score on the FIM of 91.4/126, no further baseline scores on clinical tests are reported. Thus, subacute stroke patients with a high functional independence are discussed in this cohort. When looking at the intervention, no specific details are reported a general subacute stroke rehabilitation. Similar to the content of the therapy sessions, the duration and intensity of the rehabilitation program is unknown.

5.2.1.6 General outpatient rehabilitation

Doman et al. [43] is the only observational cohort study that took place in an outpatient rehabilitation setting. This pilot cohort explored the alternations of upper limb capacity and daily use during outpatient rehabilitation in stroke patients. Because of more emphasis on the individualized monitored progression, participants were not analyzed as a whole group. Based on individual scores on ARAT and accelerometer, three observed profiles represented the change in functional capacity and daily performance. Though most participants fitted to no change in ARAT score and accelerometer (7 out of 15 participants), two participants did show a significant improvement on ARAT score and accelerometer. In the remaining participants (4 out of 15), upper limb capacity increased significant without any change in accelerometer. These findings affirm the high improvements on upper limbs function and capacity, that are needed for daily use of the upper limbs to increase. In general, half of the recruited stroke participants did not improve after general rehabilitation. Because of a lacking group variables, no mean baseline characteristics of all participants were provided. Time since stroke and initial upper limb disabilities are unknown in this stroke sample. The rehabilitation consisted mainly out of occupational therapy sessions, which included different therapeutic approaches and exercises. All therapy activities were precisely chosen in function of the individual goals and needs of the participants. Although the content of the therapy session is well established, no average number of therapy sessions or duration of each session is provided. Only individual values were provided.

5.2.2 The parameters and settings of accelerometers, that are responsive to change

As seen from the table above, great variability in the parameters of the accelerometer is observed. Across all included studies that reported significant effects of actual performance for effectiveness of the involved treatment approach, large fluctuations of sample rate and epoch length can be noticed. Range of sample frequency is situated between 10 and 30 Hz. While a low sample frequency of 10 Hz is reported in two studies [37] [41], three studies set up a sample frequency of 30 Hz [38] [43] [21]. As stated in the results, no clear statements about the best parameters to capture significant effects of

accelerometer, can be made. Thus, it is difficult to drawn some profound conclusions about the sensitivity of the accelerometer to capture a minimal change of actual performance after intervention. Because of a lack of evidence-based guidelines, most studies select accelerometer parameters based on their own knowledge, preferences and experience. Additional studies are needed to compare actual performance, measured by different sample rates and epoch lengths. There is an urgent need for clear recommendations about the correct implementations of the accelerometer in intervention studies.

Two studies did report some preferences of certain parameters of the accelerometer. First, the type of accelerometer is discussed. During the interpretation of the results, Lemmens, Timmermans et al [35] clearly stated that the use of a uniaxial accelerometer could possibly explain the disappointing results. This verdict is based on a comparable study of Liao et al. that managed to found significant results on actual performance during a similar type of intervention. However, Lang, Bland et al [31] showed evidence, which proves that the type of accelerometer does not necessarily influence results on actual performance. A systematic review by Noorkoiv et al. also prefers a multi-axes accelerometer, because of higher validity results. However, evidence regarding the best accelerometer type mostly is implemented for the lower limbs. Despite several validity studies of a certain accelerometer type for the lower limbs, little knowledge is available about validity of upper limb accelerometers. According to the review, it is impossible to calculate a minimal clinical difference of daily use of the paretic arm with a uniaxial accelerometer. However, conflicting evidence shows no great differences between an applied tri- or uniaxial accelerometer. In an explorative study concerning the role of accelerometers to measure real-world activity [107], several practical barriers and obstacles are discussed. According to this study, multiple axes accelerometer types should be used whenever it is possible.

Next, the number and placement of the accelerometers are discussed. Consistency of this parameter across all studies can be viewed. All studies placed two accelerometers on both wrists, except for Uswatte, Foo et al (2005) [41]. This non-randomized controlled trial preferred to add an extra accelerometer on the chest and the more-affected leg, which resulted in significant effects on actual performance. Though a higher accuracy of placing two additional accelerometers on the chest and on the affected leg is also reported on other studies, the increased complexity of the accelerometers is often associated with faults in correct wearing the accelerometer or lower patient adherence. Some studies report a possible existing cueing effect, when one accelerometer is solely placed on the hemiparetic upper limb. By adding an accelerometer placed on the non-paretic upper limb, this type of bias would be ruled out. In het explorative study by Hayward, Eng et al (2016), clearly recommended to apply two accelerometer on both wrists of the upper limbs. Though, an additional accelerometer on the paretic leg could be beneficial to control for lower limb movements during functional use of the upper extremities.

As a third parameter, the time period for accelerometer recordings are discussed. This parameter is direct related to the patient compliance of the sensor. The longer the participants need to wear the accelerometer, the more chance that the accelerometer is put on incorrectly or forget to put on. In the end, more data measurement of accelerometer will be missing. Thus, in a careful consultation between therapist and patient, a balance between sufficient wearing time and the willingness of the participant to

wear the accelerometer is often very decisive to choose a certain period. The range of duration of accelerometer recordings can range from 24 hours till 7 days. When looking at the recording period of significant studies, three studies preferred a measure period of three consecutive days [37] [41] [47]. Despite three observational cohort studies choose for a period of 24 hours, which is representative of a regular daily activity value [43] [44] [17]. A deviating measurement period was observed in Urbin et al., which tracked daily arm activity during 22 hours [21]. No other study has ever reported this measurement period. According to Hayward et al, a longer duration is often associated with a purposeful exploration of the variability of upper extremity use during several days. Multiple day assessment is often preferred to counterbalance this variability in daily arm use, so that collected data of accelerometer represents an average amount and intensity of arm activity over several days. Compared to lower limb accelerometer recordings, a 3-day measurement is clearly preferred over a 1 or 7-day assessment. To conclude, more days of monitoring are close to the ideal situation, but commitment and motivation are expected from the participants. Although, days of monitoring should try to cover a single week and weekday, because participants are often employed or executes different type of activities in week- and weekend days.

As a fourth parameter, the importance of a correct sample rate and epoch length are highlighted. The accuracy of an accelerometer measurement is strongly dependent on a correct implementation of the measurement tool with the exact parameters to make the accelerometer sensitive for small changes in arm activity. There is an urgent need for conclusive recommendations and guidelines about the requested sampling frequency and epoch length. None of the included studies managed to report any argumentations or reasoning for these choice of parameters. Thus, no conclusions can be made based on the included studies. The explorative study by Hayward et al [107] stated that the chosen parameters of the accelerometer need to reflect the underlying rate at which fast upper limb movements during daily activities can occur. While sample frequency can range from 1 to 60 Hz, epoch length can start at 0,03 sec and end with 60 seconds. Recommendations on the epoch length states that shorter epoch lengths should be considered for a more accurate recordings of functional performance of the upper extremities. But this can only be chosen if battery life and storage capacities are adapted for these parameters. Mostly an average value of 1 second is recommended for time-varying arm activities.

TABLE 2
Influence of Different Epoch Durations (1-second, 15-second, 60-second) Over a Selected 10-minute Period of Observation (Lakhani et al., 2015)

Epoch duration, seconds	1	15	60
Magnitude of upper-limb use, count	*696*	*696*	*696*
Total number of epochs	600	40	10
Total epochs with movement	100	25	4
Total epochs without movement	500	15	6
Duration of upper-limb use, minutes	*1.7*	*3.75*	*4*

Table. Hayward, Eng at al (2016)

At last, statistical analysis and data collection of accelerometer recordings are discussed. Liao et al. [37] provided argumentations for certain outcome variables. The ratio of mean activity between the affected and non-affected arm was preferred, because many other factors could easily influence the mean

activity value of the impaired arm. Like the duration of a walking pattern, where both arms are used simultaneously at the same intensity, can be excluded. For the intensity of arm-hand use, proportional integration measure was used. This metrics is a high resolution measurement of the area under absolute value of the accelerometer signal under the recti-field conditioned transducer signal. This mode of measurement is sensitive to detect subtle changes of arm-hand usage, compared to conventional zero crossing and time-above-threshold. According to Hayward, Eng et al (2016)[107], frequency and duration of arm activities should be reported in all studies reporting accelerometer recordings. Thereby, a ratio of more impaired to less impaired arm use is preferred. Up to now, this metric is the simplest and efficient manner to exclude lower limb movements from any upper limb activities.

5.2.3 The broad aspect of actual upper limb performance)

Bringing all factors together, sample size is the most important drawback that could possible explain the disappointing results in the included studies, especially in the 'golden standard' randomized controlled trials. Though, perhaps other 'blind' factors could point out possible explanations for the non-significance on upper limb function, capacity and performance. Some studies hypotheses that actual performance might be a broader and different aspect than what it is known up to now.

Actual performance is defined as the objectively detectable level of functioning of a person in a given domain at a given moment in his/her current environment (Lemmens, Timmermans et al. 2012)[108]. Through accelerometry, the amount of use and the intensity of the upper extremity movements are determined. However, those two parameters are just a small part of a much larger aspect, that is influenced by many other factors. In Lamers, Kerkhofs et al. (2013)[28], the dominant hand in PwMS scored significantly higher on clinical outcome measures of capacity, actual and perceived performance. These findings indicate that hand dominance might influence actual performance. According to Hayward, Eng et al. (2016)[107], other factors related to the performed task, the involved training and the context might also affect actual performance. Frist, factors related to the training undertaken are discussed. Like stated before, there appears to be a minimal threshold of capacity that needs to be reached for actual performance to change as a result of training. According to Lang, Wagner et al (2007)[23], the behavior of the affected upper limb within therapy is not consistent with performed movements outside the therapy. Secondly, factors related to the mood of the stroke survivor will also influence how much the upper limb is moved during a day. If the patients do not feel well, they will automatically use their affected upper limb less for daily activities. Here, motor fatigue will play an important role, especially during a rehabilitation intervention. As a third factor, the environment and the context will also influence actual performance. Not only thy physical adjustment at home to the handicap of the patients, but also the presence of mental support from a social network of family and friends. Sometimes, they can (over)protect the patients and help the patient in many ways they can. However, the behavior only results in a decreased activity of daily activities. As fourth factor, the period of monitoring during an entire week will affect actual performance. It is quite normal that upper extremity movement differ between weekdays and weekend days. However, a multiple day assessment of the accelerometer tries to exclude this variability. An average of the accelerometer recording over multiple days will be more representative for overall actual performance, and thus the accelerometer assessment

will be more accurate. At last, an important bias of the accelerometer could contaminate the accelerometer recording, and thus overestimate the real-life upper limb use. According to Noorkoiv, Rodgers et al. (2014)[30], the interpretation of the accelerometer is still very difficult. The recorded arm movements can be strongly influenced by other non-purposeful movement of the body, that are not related to the arm movement. Through these biases, upper extremity use can be overestimated. By wearing two accelerometers on both wrists, the device by itself cannot filter accelerometer data from only functional arm movements with a clear intention. Furthermore, accelerometer does not have the capacity to register quality of movement. Thus a greater amount of daily use of the affected arm may not necessarily reflect a better quality of performance.

Bailey, Birkenmeier et al. (2015)[25] tried to identify additional factors, other than motor function, that might influence daily upper limb activity. An increase severity of motor dysfunction and dependence in ADL's were important factors that could explain a decreased upper extremity use. No other factors, like time spent in sedentary activity, cognitive impairment, depressive symptomatology, number of comorbidities, age and living arrangement, were relevant for actual performance. Though, a strong positive correlation was found between the affected and unaffected upper limb use. Thus by triggering an increased activity of the unaffected upper limb, this will eventually lead to an improved daily performance of the affected arm. These findings have an important application for rehabilitation to enhance the strength of bilateral arm training.

5.3 Strengths and weakness of literature study

A strength of this literature study is the comprehensive literature search that was conducted. However, this single master thesis lacks an additional independent person to review the literature study. Moreover, an extensive overview of all studies that were reviewed for eligibility with clear reasons for exclusion is lacking. A second strength of this literature review was the use of evidence-based quality assessment tools. However, more experience with assessing quality of clinical studies is warranted for a more accurate quality analysis. At last, all results of the included studies are widely described. However, the discussion of the results could be more compact and to the point.

A possible flaw of the literature review is the lack of an additional independent examiner to conduct this master thesis. At last, conflicting results of in the included studies make it difficult to draw founded conclusions.

5.4 Recommendations for future studies

In the future, more high-quality clinical studies should be conducted. All discussed rehabilitation approaches clearly lack evidence of effectiveness in neurological disorders. Large-scale studies and systematic review on evidence-based approaches in neurorehabilitation are recommended.

Further, more intervention studies should use the accelerometer as an objective measurement tool for actual performance. Although the promising opportunities are established, the weaknesses of the device should be clearly identified with possible solutions for these barriers. First of all, the interpretation of the accelerometer should be more simple and easily conducted. There is an urgent need for differentiating between different types of arm movements. Discrimination between such activities would be very

interesting in order to detect what kind of activities the patient performs. Additionally, it is possible to decide whether or not patients changed or improved their activities or started to perform new activities (compensation or re-acquisition). In order to assess only purposeful arm movement with a clear intention, solutions have to be developed for excluding other general bod movements from the accelerometer recordings. Some preliminary studies propose a new device to discriminate non-purposeful arm movement from movements with a clear intention. However, these complex systems are lacking clear evidence and feasibility in patient populations. Future studies should focus on the development of new solutions, because this is essential to further elucidate performance.

In the future, valuable accelerometer output will be used to modify a therapeutic intervention. Feedback of accelerometer data to patient and clinicians might have a therapeutic role. Moreover, feasibility of a quality assessment through multiple accelerometers should be investigated. Quality of arm movement contains very important information for patients and clinicians.

6 Conclusion

First, the effectiveness of rehabilitation interventions is discussed. Only two of the 10 included RCT's could report significant results on actual performance. Apart from methodological weaknesses, the type and dose of intervention were determined for the significant results. In contrast to the 'gold standard' RCT, four of the five included observational cohort studies succeed to find significant results on actual performance. Here, the content of the intervention was not clearly delineated with a lack of reported dose of therapy sessions. Thus, inpatient rehabilitation approaches are high variably due to different health care services. Of the 15 studies that reported pre- and post-measurement of accelerometer, only 8 studies demonstrate significant improvements on actual performance. In general, three profiles can be distinguished based on clinical outcome measures. One group reported the studies with significant actual performance along with significant body function, capacity and/or perceived performance (n=8). A second group involved a lack of significant increase on actual performance, but conflicting results indicate significant body function, capacity and/or perceived performance (n=4). The last group reported no significant improvement on actual performance, that is similar to body function, capacity and/or perceived performance (n=3).

Measuring arm movement in neurological patients can be challenging, considering the high variability of the duration and amplitude of deviating arm movements. It is unclear how accelerometer data should be collected for in order to obtain a meaningful description of upper extremity usage in real-world environment. Parameters of the accelerometer, collected in this master thesis, are highly variable. Currently, there is a lack of clear recommendations and large-scale validity studies.

To conclude, actual performance is thought to represent a much bigger picture than it is identified till now.

- Actual performance is influenced through many factors, not only the amount of daily use, but also the quality of the UE movements
- Large-scale clinical trials with higher methodology quality is urgent

7 References

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8 APPENDIX

Table 1: Keywords, MeSh-termen en zoekstrategie

Keywords

	Keywords in PubMed	Hits in 4/2016	Hits in 8/2016
#1	((((((((((("Movement Disorders [Mesh]) OR "Nervous System Diseases"[Mesh]) OR "Stroke"[Mesh]) OR "Hemiplegia"[Mesh]) OR Stroke[Title/Abstract]) OR "Parkinson Disease"[Mesh]) OR Parkinson[Title/Abstract]) OR "Multiple Sclerosis"[Mesh]) OR Multiple Sclerosis[Title/Abstract]) OR "Spinal Cord Injuries"[Mesh]) OR Spinal cord injury[Title/Abstract]) OR "Brain Injuries"[Mesh]) OR Traumatic brain injury[Title/Abstract]	23 678 results	24 319 results
#2	((((((((((("Rehabilitation"[Mesh]) OR Rehabilitation[Title/Abstract]) OR "Exercise"[Mesh]) OR Exercise[Title/Abstract]) OR "Exercise Therapy"[Mesh]) OR Exercise therapy[Title/Abstract]) OR Exercise program[Title/Abstract]) OR "Physical Therapy Modalities"[Mesh]) OR Physical therapy modalities[Title/Abstract]) OR Physical therapy[Title/Abstract]) OR Physical training[Title/Abstract]) OR Training[Title/Abstract]	796 781 results	817 115 results
#3	((((("Upper Extremity"[Mesh]) OR Arm[Title/Abstract]) OR Hand[Title/Abstract]) OR Upper limb[Title/Abstract]) OR Upper extremity[Title/Abstract]	514 520 results	524 727 results
#4	((((((((("Psychomotor Performance"[Mesh]) OR Performance[Title/Abstract]) OR Actual performance[Title/Abstract]) OR "Activities of Daily Living"[Mesh]) OR Activities of daily living[Title/Abstract]) OR Motor function[Title/Abstract]) OR Motor task[Title/Abstract]) OR Real-world use[Title/Abstract]) OR Daily life activity[Title/Abstract]) OR Real-life use[Title/Abstract]) OR Daily motor activity[Title/Abstract]	776 158 results	799 477 results
#5	(((((((("Accelerometry"[Mesh]) OR Accelerometry[Title/Abstract]) OR Accelerometer[Title/Abstract]) OR "Actigraphy"[Mesh]) OR Actigraphy[Title/Abstract]) OR Activity monitor[Title/Abstract])) OR Arm use[Title/Abstract]) OR Arm activity[Title/Abstract]	53 040 results	12 700 results

	Keywords in Web of Science	Hits in 4/2016	
#1	TS=(Nervous system disease* OR Brain disease* OR Neurological disease* OR Neurological condition* OR Stroke* OR Hemiparesis* OR Hemiplegia* OR Cerebral infarction* OR Parkinson disease* OR Multiple Sclerosis* OR Spinal cord injury* OR Brain injury* OR Traumatic brain injury*)	762 644 results	784 396 results
#2	TS=(Rehabilitation* OR Exercise* OR Exercise therapy* OR Exercise program* OR Training* OR Physical training* OR Physical therapy* OR Neurological rehabilitation*)	863 736 results	889 787 results
#3	TS=(Upper extremity* OR Upper limb* OR Arm* OR Hand*)	1 256 324 results	1 287 767 results
#4	TS=(Motor performance* OR Actual performance* OR Activities of daily living* OR Motor function* OR Motor task* OR Motor recovery* OR Real-world use* OR Daily life activity* OR Real-life use* OR Daily motor activity*)	298 032 results	308 110 results
#5	TS=(Accelerometry* OR Accelerometer* OR Actigraphy* OR Activity monitor* OR Motion tracking* OR Action monitoring*)	189 239 results	193 952 results

Search strategy

PubMed

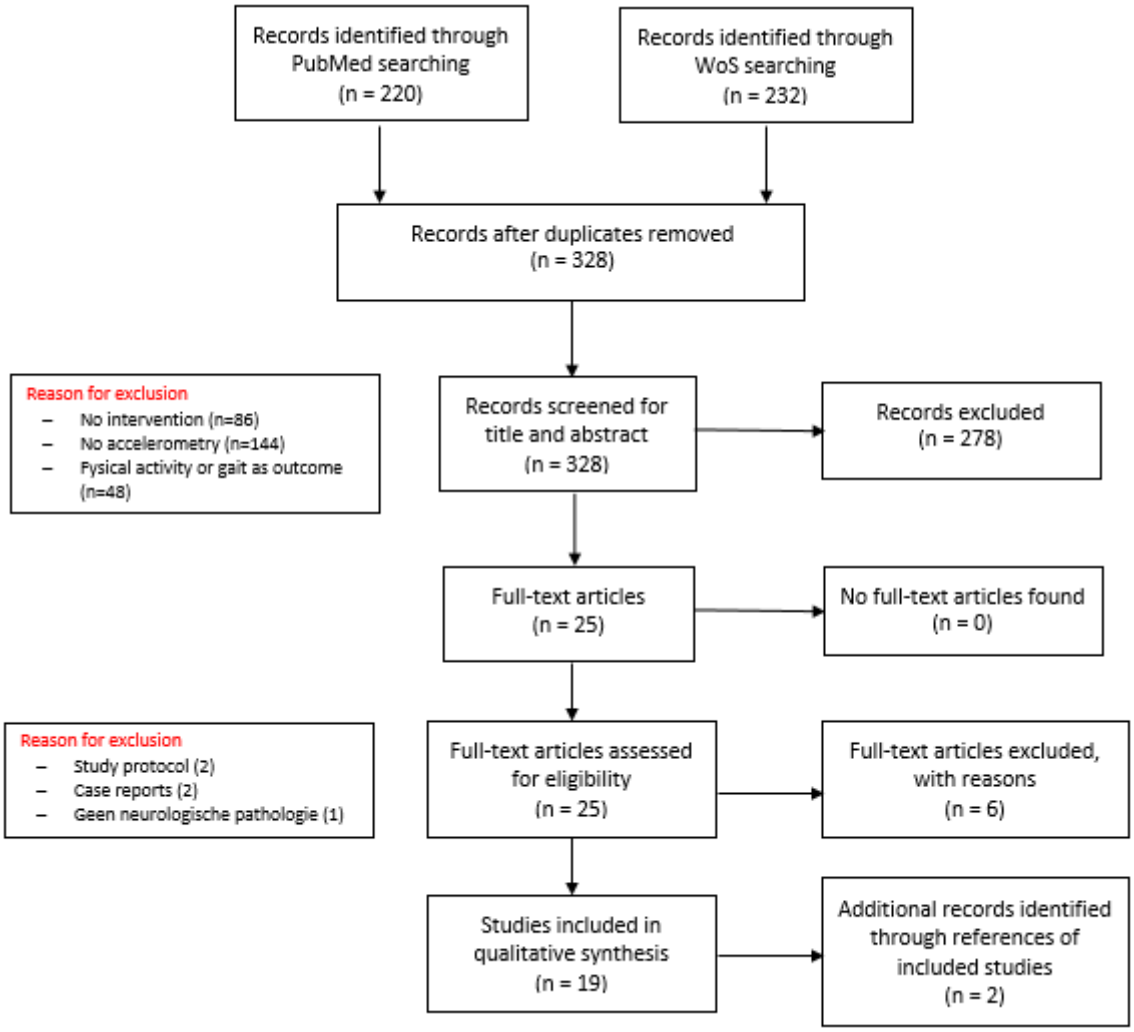
((((((((((((((("Movement Disorders"[Mesh]) OR "Nervous System Diseases"[Mesh]) OR "Stroke"[Mesh]) OR "Hemiplegia"[Mesh]) OR Stroke[Title/Abstract]) OR "Parkinson Disease"[Mesh]) OR Parkinson[Title/Abstract]) OR "Multiple Sclerosis"[Mesh]) OR Multiple Sclerosis[Title/Abstract]) OR "Spinal Cord Injuries"[Mesh]) OR Spinal cord injury[Title/Abstract]) OR "Brain Injuries"[Mesh]) OR Traumatic brain injury[Title/Abstract])))) AND ((((((((((("Rehabilitation"[Mesh]) OR Rehabilitation[Title/Abstract]) OR "Exercise"[Mesh]) OR Exercise[Title/Abstract]) OR "Exercise Therapy"[Mesh]) OR Exercise therapy[Title/Abstract]) OR Exercise program[Title/Abstract]) OR "Physical Therapy Modalities"[Mesh]) OR Physical therapy modalities[Title/Abstract]) OR Physical therapy[Title/Abstract]) OR Physical training[Title/Abstract]) OR Training[Title/Abstract])) AND (((((("Upper Extremity"[Mesh]) OR Arm[Title/Abstract]) OR Hand[Title/Abstract]) OR Upper limb[Title/Abstract]) OR Upper extremity[Title/Abstract])) AND ((((((((("Accelerometry"[Mesh]) OR Accelerometry[Title/Abstract]) OR Accelerometer[Title/Abstract]) OR "Actigraphy"[Mesh]) OR Actigraphy[Title/Abstract]) OR Activity monitor[Title/Abstract])) OR Arm use[Title/Abstract]) OR Arm activity[Title/Abstract]))

Web of Science

TS=(Nervous system disease* OR Brain disease* OR Neurological disease* OR Neurological condition* OR Stroke* OR Hemiparesis* OR Hemiplegia* OR Cerebral infarction* OR Parkinson disease* OR Multiple Sclerosis* OR Spinal cord injury* OR Brain injury* OR Traumatic brain injury*) AND

TS=(Rehabilitation* OR Exercise* OR Exercise therapy* OR Exercise program* OR Training* OR Physical training* OR Physical therapy* OR Neurological rehabilitation*) AND TS=(Upper extremity* OR Upper limb* OR Arm* OR Hand*) AND TS=(Motor performance* OR Actual performance* OR Activities of daily living* OR Motor function* OR Motor task* OR Motor recovery* OR Real-world use* OR Daily life activity* OR Real-life use* OR Daily motor activity*) AND TS=(Accelerometry* OR Accelerometer* OR Actigraphy* OR Activity monitor* OR Motion tracking* OR Action monitoring*)

Figure 2: Flowchart



TABEL 2: Quality assessment

Randomised Controlled Trials (RCT)					
STUDY	Hsieh, Wu et al. (2016)	Shim and Jung (2015)	Thrane, Askim et al. (2015)	Hsieh, Lin et al. (2014)	Lemmens, Timmermans et al. (2014)
Internal validity (PEDRO and Cochrane)					
Eligibility criteria	✓	✓	✓	✓	✓
Random allocation of subjects to groups	✓	✓	✓	✓	✓
Concealed allocation	✓	Not reported	✓	✓	✓
Groups were similar at baseline	✓	Not reported Baseline characteristics lacks p-value	✓	✓	✓
Blinding of all subjects	Not possible	Not possible	Not possible	Not possible	Not possible
Blinding of all therapists	Not possible	Not possible	Not possible	Not possible	Not possible
Blinding of all assessors	✓	Not reported	✓	✓	✓
Measures were obtained from more than 85% of subjects	No drop-out after intervention Drop-out after 3 months *Control group (n=6, 40%) *Experimental group (n=4, 25%) No follow-up after 3 months (average 323,3%)	Not reported Lack of drop-out and flow chart	In total, 7 participants dropped out *Experimental group (n=4, 17%) *Control group (n=3, 13%)	No drop-out after treatment 14 of 34 participants (41%) did not complete the accelerometer posttreatment assessment	No drop-out after intervention
Intention to treat analysis	✓	✓	✓	✓	✓
Equal management between groups, except for intervention	Unknown Patient recruitment from two different medical centers	Unknown	Unknown Patient recruitment from four different medical centers	Unknown	Unknown
Between group comparisons are reported for key outcomes	✓	✓	✓	✓	✓
Point measures and measures of variability for key outcomes	✓	✓	✓	✓	✓
Exclusion of unwanted influence of sponsors	✓	✓	✓	✓	✓

Randomised Controlled Trials (RCT)					
STUDY	Hsieh, Wu et al. (2016)	Shim and Jung (2015)	Thrane, Askim et al. (2015)	Hsieh, Lin et al. (2014)	Lemmens, Timmermans et al. (2014)
Internal validity (extra criteria)					
Sample size	Small sample size, because minimal number of participants per group (n=31) is not attained Study is underpowered	Calculations of sample size was not executed, but 21 stroke participants may be considered as a small sample size and thus low power	Sample size is moderate (n=47), but a high power of 0.8 would require 53 participants in each group The study was halted before 106 participants were included	Adequate sample size was calculated from significance level, power estimates and effect sizes from previous studies Recommendation of at least 15 patients in each intervention group is achieved, thus power is sufficient	Sample size was calculated from clinical effect sizes, standard deviation, significance level and power estimates, but the required sample size was not reached (n=20); thus study is underpowered
Type and dose of tested intervention	Dose of 450 min/week can be considered as a moderate intensity intervention	Dose of 150 min/week can be considered as a low intensity intervention	Dose of 1800 min/week, with additional wearing a constraining mitt on the less-affected arm for 90% of waking time, can be considered as a high intensity intervention (only 2 weeks)	Dose of 450-525min/ week can be considered as a moderate intensity intervention 4 weeks	Dose of 240min/week can be considered as a low intensity intervention 8 weeks
Accurate outcome measurements	Validity and reliability of all eight outcome measures was established	Manual Function test is not considered as a 'gold standard' measurement tool, but validity and reliability is established	WMFT, FMA, NHPT Stroke impact scale and accelerometer show evidence for validity and reliability	FMA, WMFT MAL and accelerometer have established good validity and reliability	No other outcome measures, except for accelerometer
Other comments	Lack of a dose-matched usual care control group Lack of neurophysiologic measurements (MRI)	Lack of a dose-matched usual care control group	Dose of the control therapy was not similar to the experimental group No training of examiners Trial was extended for 2,5 years, thus bias could influence results	Lack of follow-up	Lack of a dose-matched usual care control group (without robot) Lack of ad additional non-robotic intervention

Randomised Controlled Trials (RCT)					
STUDY	Timmermans, Verbunt et al. (2013)	Liao, Wu et al. (2012)	Lang, Edwards et al. (2008)	Uswatte, Taub et al (2006)	Uswatte, Guiliani et al. (2006)
Internal validity (PEDRO and Cochrane)					
Eligibility criteria	✓	✓	✓	✓	✓
Random allocation of subjects to groups	✓	✓	✓	✓	✓
Concealed allocation	✓	✓	Not reported	Not reported	Not reported
Groups were similar at baseline	✓	✓	✓	✓	✓
Blinding of all subjects	Not possible	Not possible	Not possible	Not possible	Not possible
Blinding of all therapists	Not possible	Not possible	Not possible	Not possible	Not possible
Blinding of all assessors	✓	✓	✓	✓	✓
Measures were obtained from more than 85% of subjects	Drop-out after intervention *Control group (n=3, 14%) *Experimental group (n=6, 28%) Drop-out after 12 months *Control group (n=0) *Experimental group (n=1, 4%) In total *Control group (n=3, 14%) *Experimental group (n=7, 33%)	Not reported Lack of drop-out and flow chart	Not reported Lack of drop-out and flow chart	Not reported Lack of drop-out and flow chart	Not reported Lack of drop-out and flow chart 23% missing data of accelerometer recordings
Intention to treat analysis	✓	✓	Not reported	Not reported	Not reported
Equal management between groups, except for intervention	Unknown	Unknown Patient recruitment from stroke units in three different medical centers	Unknown	Unknown	Unknown
Between group comparisons are reported for key outcomes	✓	✓	All data were pooled, regardless of group assignment in the previous trial	✓	✓
Point measures and measures of variability for key outcomes	✓	✓	All data were pooled, regardless of group assignment in the previous trial	✓	✓
Exclusion of unwanted influence of sponsors	✓	✓	✓	✓	✓

Randomised Controlled Trials (RCT)					
STUDY	Timmermans, Verbunt et al. (2013)	Liao, Wu et al. (2012)	Lang, Edwards et al. (2008)	Uswatte, Taub et al (2006)	Uswatte, Guiliani et al. (2006)
Internal validity (extra criteria)					
Sample size	Sample size was calculated from relevant effect sizes, standard deviation, significance level, power estimates and expected follow-up loss. In total, 145 participants would be required, but this wasn't reached (n=42), thus study is underpowered	Precise sample size calculations are lacking, but relatively sample size (n=20) is small It could be assumed that the study is underpowered	Number of subjects (n=52) used to calculate MCID values is similar to other studies It could be assumed that the power < 80%, thus study is underpowered	Precise sample size calculations are lacking, but relatively sample size (n=222) is large It could be assumed that a power estimate of more than 80% is achieved	Precise sample size calculations are lacking, but relatively sample size (n=222) is large It could be assumed that a power estimate of more than 80% is achieved
Type and dose of tested intervention	No evidence of optimal training duration, intensity and approach of Mental practice It could be assumed that the number of exercises were insufficient, with little challenge to keep patients motivated	Dose of 450-525 min/week can be considered as a moderate intensity intervention The high intensity is confirmed by the high number of repetitions (2700-3600 reps)	*Traditional CIMT: 600min/week with additional 6 hours mitt, can be considered as a moderate intensity intervention *High-intensity CIMT: 900min/week with additional 13-14 hours a mitt, can be considered as a high intensity intervention	Dose of 1800min/week with additional 13-14 hours a mitt, can be considered as a high intensity intervention 10 consecutive workdays	Dose of 1800min/week with additional 13-14 hours a mitt, can be considered as a high intensity intervention 10 consecutive workdays
Accurate outcome measurements	Reliability and validity of FMA, Frenchary arm test, WMFT and accelerometer has been established	FMA, FIM, MAL, ABILHAND and accelerometer have all good established reliability and validity	Grip strength, composite upper extremity strength, ARAT, WMFT, MAL and accelerometer have good to high reliability and validity	Reliability and validity of ABILHAND has been established	Reliability and validity of accelerometer has been established
Other comments	Difficulty in addressing cognitive screening, compliance and motivation in motor imagery	No measurement of hand dexterity (Wolf Motor function or ARAT) Lack of follow-up No exploration of motor control mechanisms (MRI)	No comments	Lack of pre- and posttreatment changes on the outcomes	No comments

Non-randomized controlled intervention studies (non-RCT)			
STUDY	Wang, Lin et al. (2011)	Uswatte, Foo et al. (2005)	Uswatte, Taub et al. (2005)
Internal validity (MINORS)			
Clearly stated aim	2	2	2
Inclusion of consecutive patients (inclusion criteria)	2	1 No inclusion criteria were reported, only exclusion criteria	2
Prospective collection of data (study protocol before the begin of the study)	2	2	2
Endpoints appropriate to the aim of the study (intention-to-treat)	2	2	2
Unbiased assessment of the study endpoint (blinding)	2	0	0
Follow-up period appropriate to the aim of the study	2	1 Intervention of 10 consecutive days or 2 weeks is minimal	1 Intervention of 10 consecutive days or 2 weeks is minimal
Loss to follow-up less than 5%	0	0	0
Prospective calculations of the study size (estimates of power)	0 It is assumed that the study is underpowered	0 It is assumed that the study is underpowered	0 It is assumed that the study is underpowered
Adequate control group	2	2	1
Contemporary groups (managed during the same time period, without any historical comparisons)	2	1	0 Control group was treated and tested previously
Baseline equivalents of groups (no confounders)	1	1	1

Adequate statistical analyses	2	2	2
Internal validity (extra criteria)			
Type and dose of tested intervention	A dose of 450min/week can be considered as a moderate intensity intervention	No precise dose of the intervention was reported	A dose of 900 min/week can be considered as a moderate to high intensity intervention
Accurate outcome measurements	ABILHAND, SIS, FIM, NEADL and accelerometer have established good reliability and validity	Reliability and validity of MAL and accelerometer have been established	Reliability and validity of MAL and accelerometer has been established
Other comments	No comments	Hotel residency of several participants could influence results	Both outcome measures are available for only a subsample of the participants

Observational cohort study					
STUDY	Doman, Waddell et al. (2016)	Urbin, Waddell et al. (2015)	Waddell, Birkenmeier et al. (2014)	Rand and Eng (2012)	Reiterer, Sauter et al. (2008)
Internal validity (NewCastle Ottawa scale)					
Selection					
1. Representative-ness to the exposed cohort	B* Consecutive referrals from the treating occupational therapist to research team (non-random sample)	D No description of the recruitment of the inpatient sample	B* Convenience sample of inpatient rehabilitation stay, recruitment occurred through informing inpatient staff occupational therapists about the study and criteria for participation	D No description of the recruitment of the inpatient sample of consecutive stroke patients	D No description of the recruitment of the participants
2. Selection of the non-exposed cohort	C No control or non-exposed cohort was selected	C No control or non-exposed cohort was selected	C No control or non-exposed cohort was selected	B Control sample existed out of community-dwelling, healthy older adults	C No control or non-exposed cohort was selected
3. Ascertainment of exposure	B* Accelerometer and ARAT are structured interviews	B* Only accelerometers were provided	B* ARAT, grip and pinch strength, FIM and accelerometers were provided	B* FMA, ARAT, FIM and accelerometers were provided	B* Motricity index, Scandinavian Stroke Scale, NIHSS, Barthel Index; Rankin scale and actigraphy were provided
4. Demonstration that the outcome of interest was not present at the start of the study	A* Initial use ratio was at least 2 Standard Deviation's below the normative mean	A* Upper limb use pretest was significant lower than post-test	A* Baseline score on arm use ratio is significantly lower than scores at discharge and after 1-month follow-up	A* Total amount of upper limb use per day was 30 525 for paretic and 134 180 activity counts for non-paretic arm	B Total activity score of the upper limbs before and at the time of admission was not presented
Comparability					
1. Comparability of cohorts on the basis of the design or analysis	Study did not control for additional factors	Study did not control for additional factors	Study did not control for additional factors	A* + B* Study controls for walking ability, hand function, depressive symptoms, visual neglect, cognitive ability, age, days since stroke, number of years of education, function of the non-paretic upper extremity	A* + B* Study controls for motor impairment of the upper extremity, severity of neurological deficit and the handicap (amount of assistance)
Outcome					
1. Assessment of outcome	B* No independent blind assessment is possible, because all participants received the same intervention	B* No independent blind assessment is possible, because all participants received the same intervention	B* No independent blind assessment is possible, because all participants received the same intervention	B* No independent blind assessment is possible, because all participants received the same intervention	B* No independent blind assessment is possible, because all participants received the same intervention

2. *Follow-up was long enough for outcomes to occur*	A* Number of occupational visits ranged from 10 to 78 visits	A* An average of 13 sessions of task-specific training exceeds the minimal dose of 10 therapy sessions	A* Treatment was given during inpatient stay, average 29 days till discharge, with 1-month follow-up	A* Post-treatment assessment was after three weeks of rehabilitation, close to discharge	A* Follow-up was provided after 24-36hours, 5-7 days, 3 and 6 months poststroke
3. *Adequacy of follow-up of cohorts*	A* No flowchart presented, but results show no drop-out, all participants completed outcome measurements	D No flowchart presented, follow-up or drop-out was not reported	A* No flowchart presented, but results reported no participants that withdrew or dropped out	B* Flowchart was presented, results reported 4 participants that dropped out of the study (7%)	D No flowchart presented, follow-up or drop-out was not reported
Internal validity (extra criteria)					
Type and dose of intervention	High degree of variability in UE functional capacity and performance in people receiving outpatient services Dose is not reported	Individualized, high-repetition, task-specific training shows less variability Dose of 13 sessions	Task-specific training during occupation therapy shows less variability *Dose of intervention:* 60 min, 4 days (240 min/week) is considered as a low intensity		
Accurate outcome measures	Accelerometer and ARAT have good validity and reliability	Accelerometer and ARAT have good validity and reliability	ARAT, JAMAR, three-jaw-chuck pinch, FIM and accelerometer have good reliability and validity	FMA, ARAT, FIM and accelerometer have establish validity and reliability	
Other comments					

Case series			
STUDY	Taub, Uswatte et al. (2013)		
Internal validity (modified Delphi scale)	*Yes*	*Partial/Unclear*	*No*
Study objective			
1. Clearly stated hypothesis/aim/objective of the study	✓		
Study design			
2. Prospectively conducted study	✓		
3. Cases were collected in more than one center		✓	
4. Patients were recruited consecutively	✓		
Study population			
5. Inclusion of the characteristics of the patients in the study	✓		
6. Clearly stated eligibility criteria (inclusion and exclusion) for entry into study	✓		
7. Patients enter the study at a similar point in the disease	✓		
Intervention and co-intervention			
8. Intervention of interest was clearly described	✓		
9. Additional interventions (cointerventions) were clearlt described	✓		
Outcome measures			
10. Relevant outcome measures established a priori	✓		
11. Outcome assessors were blinded to the intervention that patients received			✓ Blinding of assessors is not possible, because all participants received the same treatment
12. Relevant outcomes were measured using appropriate methods	✓		
13. Relevant outcome measures were made before and after intervention	✓		
Statistical analysis			
14. Statistical tests were used to assess relevant outcomes appropriate	✓		
Results and conclusions			
15. Follow-up was long enough for important events and outcomes to occur	✓ Follow-up after 4 weeks, 6 and 12 months		
16. Losses to follow-up were reported			✓ No flow chart presented or drop-out reported
17. Study provided estimates of random variability in the data analysis	✓		
18. Adverse events were reported			✓

19. Conclusions of the study were supported by the results	✓		
Competing interests and sources of support			
20. Both competing interests and sources of support were reported	✓		

TABEL 3: Characteristics of included studies

Randomised Controlled Trials (RCT)					
STUDY	Hsieh, Wu et al. (2016)	Shim and Jung (2015)	Thrane, Askim et al. (2015)	Hsieh, Lin et al. (2014)	Lemmens, Timmermans et al. (2014)
Aim of the study	To investigate the treatment effects of bilateral robotic priming, combined with the task-oriented approach on motor impairment, disability, daily function and quality of life in patient with subacute stroke	To investigate the recovery of arm function and the functional use of the affected arm in real life of stroke patients after bilateral arm training	To evaluate the effect of a modified CIMT within 4 weeks post stroke	To investigate the treatment effects of Robot-assisted therapy in sequential combination with a distributed form of Constraint-induced therapy (RT+dCIT) compared with RT alone and conventional rehabilitation, on motor and functional outcomes in stroke patients	To assess the extent to which accelerometers can be used to determine the effect of robot-supported task-oriented arm-hand training, relative to task-oriented arm-hand training alone, on the actual amount of arm-hand use of chronic stroke patient in their home situation
Study design	Pilot single-blinded Randomised Controlled Trial (RCT)	Randomised controlled trial (RCT)	Single blinded, multicentre, Randomised controlled trial (RCT)	Three-arm, single-blinded, Randomised controlled trail (RCT)	Single-blinded Randomised Controlled Trial (RCT) Sub-study of a larger (TEST-TRACS)
Participants	31 subacute stroke participants *Eligibility criteria* – Stroke of less than six months – Initial score on FMA > 10	20 subacute stroke participants *Eligibility criteria* – Stroke attack at least 6 months earlier	47 acute stroke participants *Eligibility criteria:* – Experience of a first-ever or recurrent stroke at >5 and <26 days – Modified Rankin scale between 0 and 2 before stroke – Persistent unilateral arm or hand paresis *Criteria for CIMT:* – Capacity to lift 2 fingers with the forearm pronated to the table – Capacity to extend the wrist at least 10° from a fully flexed position – No more than 2 cm deviation of the line bisection test	48 subacute stroke patients *Eligibility criteria:* – At least 6 months after stroke – Initial UL score of 20-50 on FMA-UE *Criteria for CIMT:* – Extension of the wrist ≥ 10° – Extension of at least 2 fingers >0° and <10° – Abduction of thumb ≥ 10°	16 chronic stroke patients *Eligibility criteria:* – Post-stroke time ≥ 12m
Intervention	*Type of intervention:* Bilateral priming with a bimanual robot-aided device (Bi-Manu-Track) combined with the task-oriented approach (priming group) 4 weeks *Control therapy:* Task-oriented approach alone (unprimed group) *Dose of intervention:* 90 min, 5 days (450 min/week) 4 weeks	*Type of intervention:* Bilateral training (BT) with functional tasks *Control therapy:* Unilateral training (UT) with functional tasks *Dose of intervention:* 30 min, 5 sessions (150 min/week) 6 weeks	*Type of intervention:* Constraint-induced movement therapy is a form of repetitive task oriented training, with adherence-enhancing behavioural strategies Constraining mitt on the affected arm for 90% of waking time *Control therapy:* Multidisciplinary usual care without a predefined protocol (no dose-matched control therapy) *Dose of intervention:*	*Type of intervention:* Robot-assisted therapy (RT) with Bi-Manu-Track, sequentially combined with CIT *Control therapy:* Robot-assisted therapy alone Conventional occupational rehabilitation *Dose of intervention:* 90-105 min, 5 days (450-525min/week) 4 weeks	*Type of intervention:* Task-oriented robot-supported arm-hand training with Haptic master according to (T)TOAT method, based on part practice *Control therapy:* Unsupported task-oriented arm-hand training according to (T)TOAT method, based on part practice *Dose of intervention:* 2x30min, 4 days (240min/week) 8 weeks

			180 min, 10 consecutive work days (1800 min/week) 2 weeks		
Setting	Inpatient occupational setting in two medical centers	Not reported	4 inpatient medical centers	Not reported	An inpatient rehabilitation centre (Adelante)
Accelerometer type	Mini-Motionlogger actigraph	Actisleep (GT3X) portable three-axis motion sensor	Actigraph GT1M or GT3X accelerometer	Actigraphy activity monitor (GT3X)	ActiWatch-AW7 device is a uniaxial piezoelectric accelerometer
Accelerometer placement	Both wrists	Not reported	Both wrists	Both wrists	Both wrists
Accelerometer wearing time	3 consecutive days	Not reported	24 hours	3 consecutive days	72 consecutive hours except during arm-hand training
Parameters of accelerometer	Not reported	*Sampling rate is 30 Hz *Epoch length is unknown	*Sample rate is 60 Hz *Epoch length is 1 sec	Not reported	*Sample rate is 32 Hz *Epoch length is unknown
Data collection and statistical analysis of accelerometer recordings	*Definition of unit of arm activity* Not reported *Method for data collection* Not reported	*Definition of unit of arm activity:* Arm activity is measured in counts, that is depending on duration of upper limb movements *Method for data collection:* *Mean motion of axis y, axis x and axis z, axis total, measures in number of counts *Intensity of activity is measured in count value	*Definition of unit of arm activity:* Not reported *Method for data collection:* *Ratio of affected-to-unaffected arm movements	*Definition of unit of arm activity:* Not reported *Method for data collection:* *Ratio of affected-to-unaffected arm movements	*Definition of unit of arm activity:* *The amplitudes of maximal signal intensity $I_{max/sec}$ (= the highest peak within each consecutive second) is summed for every 2 consecutive seconds, and expressed as an 'activity count' *Method for data collection:* *Duration of use = hours of arm-hand use relative to the uptime *Intensity of use = sum of counts, (signal intensity per data point) within a given time epoch *Ratio of affected-to-unaffected arm intensities
Effect on actual performance	*Actual performance:* Actigraphy *Between-group p=0,438 *No within-group values	*Actual performance:* <u>*Affected side*</u> Amount of arm activity Axis y *BT p<0,01 *UT no p-value Axis x * no significant p-value Axis z * no significant p-value Axis total *BT p is significant *UT no p-value Intensity of arm activity Sedentary *BT p is significant *UT no p-value Light	*Actual performance:* Arm use ratio *Post p=0,301 *6m p=0,215	*Actual performance:* Accelerometers *p=0,33	*Actual performance:* Duration and intensity of use of the affected arm-hand did not change significantly after training *No significant between-group differences for $D_{add-uni}$ and D_b between baseline and after 8 weeks of training (p=0,57 for $D_{add-uni}$; p=3,82 for D_b), or between the end of training and 6-month follow-up (p=1,00 for $D_{add-uni}$; p=0,88 for D_b) *No significant between-group differences for $I_{tot-aff}$ between baseline and after 8 weeks of training (p=0.88), or between the end of training and 6-month follow-up (p=0.20)

		* no significant p-value Lifestyle * no significant p-value Moderate *BT p is significant *UT p<0,05 *Non-affected side* *Amount of arm activity* Axis y * no significant p-value Axis x * no significant p-value Axis z * no significant p-value Axis total * no significant p-value *Intensity of arm activity* Sedentary *BT p<0,05 *UT p<0,05 Light * no significant p-value Lifestyle * BT p<0,05 *UT no p-value Moderate * no significant p-value			*No significant between-group differences were found for either unimanual or bimanual use of arm between baseline and after 8 weeks of training (p=0,80 for $I_{aff-uni}$; p=1,00 for I_{aff-bi}), or between the end of training and 6-month follow-up (p=0,65 for $I_{aff-uni}$; p=0,23 for I_{aff-bi}) *No significant between-group differences were found regarding the ratio of arm use (p≥0,674)
Effect on other outcomes	No p-values of the within-group improvements *Body function and impairment*: Between-group changes *FMA p=0,812 *BBT p=0,383 *Grip p=0,548 *Quality of life*: Between-group changes *SIS/strength p=0,012 *SIS/hand p=0,534 *SIS/ADL p=0,0554 *SIS/mobility p=0,556 *Fatigue p=0,244 *Participation:* Between-group changes *mRS p=0,065 *FIM p=0,647	*Body function and impairment*: No outcome measures *Capacity and disabilities*: MFT(affected) *BT p<0,01 *UT p<0,05 MFT (non-affected) * no significant p-value *Participation:* FIM/Motor *BT p<0,05 *UT p<0,05 FIM/Cog * no significant p-value FIM/Total *BT p<0,01 *UT p<0,05	*Body function and impairment*: WMFT/arm strength *Post p=0,172 *6m p=0,268 WMFT/grip strength *Post p=0,119 *6m p=0,931 Fugl-Meyer UE *Post p=0,116 *6m p=0,296 *Capacity and disabilities*: WMFT/FAS *Post p=0,148 *6m p=0,506 WMFT/time * no p-value logWMFT time *Post p=0,018 *6m p=0,209 NHPT *Post p=0,035 *6m p=0,635 *Quality of life:*	*Body function and impairment*: FMA *FMA total p<0,01 *FMA distal p=0,01 *FMA prox p=0,15 *Capacity and disabilities*: WMFT *WMFT-FAS p=0,01 *WMFT-time p=,028 *Perceived performance:* MAL *MAL-AOU p=0,20 *MAL-QOU p=0,54	In this study, no clinical scales or tests were used as outcome measures These outcome measures are described in the previous study of TEST-TRACS in Timmermans, Lemmens et al (2014) No between-group differences on any of the outcome measures, considering both experimental and control group showed significant improvements Experimental group *Body function and impairment*: *FMA no significant p-value *Capacity and disabilities*: *ARAT p= 0,008 *Perceived performance:* *MAL p=0,013 *Quality of life:* *EuroQol-5D no significant p-value *SF-36 no significant p-value Control group

			SIS/hand *6m p=0,405 SIS/ADL *6m p=0,623 SIS/participation *6m p=0,919 SIS/overall recovery *6m p=0,571		*Body function and impairment*: *FMA no significant p-value *Capacity and disabilities*: *ARAT no significant p-value *Perceived performance:* *MAL p=0,008 *Quality of life:* *EuroQol-5D p=0,015 *SF-36 p=0,01

Randomised Controlled Trials (RCT)					
STUDY	Timmermans, Verbunt et al. (2013)	Liao, Wu et al. (2012)	Lang, Edwards et al. (2008)	Uswatte, Taub et al. (2006)	Uswatte, Guiliani et al. (2006)
Aim of the study	To evaluate the effectiveness of a task-oriented mental practice (MP) approach as an addition to regular arm-hand therapy on arm-hand function and performance of daily activities, compared to additional NDT therapy, in patients with subacute stroke	To compare the outcome of robot-assisted therapy with dose-matched active control therapy by using accelerometers to study functional recovery in chronic stroke patients	To estimate minimal clinically important difference values of several upper extremity measures early after stroke	To study the Motor Activity Log's reliability and validity for assessing real-world quality of movement (QOM scale) and amount of use (AOU scale) of the hemiparetic arm in stroke survivors	To examine the psychometric properties of an objective method for assessing real-world am activity in a large sample with subacute stroke
Study design	Multicentre, prospective, single-blind, Randomized clinical trial (RCT)	Multicentre, prospective, Randomized controlled trial (RCT)	Validation and clinimetric study Part of larger VECTOR study VECTOR trial is an acute, single-blind Randomized Controlled trial	Validation and clinimetric study Part of larger EXCITE trial EXCITE trial is a single-blind, multisite randomised clinical trial	Validation and clinimetric study Part of larger EXCITE trial EXCITE trial is a single-blind, multisite randomised clinical trial
Participants	42 subacute stroke patients *Eligibility criteria* – 2 to 6 weeks after stroke	20 chronic stroke patients *Eligibility criteria* – More than 6 months after stroke – Initial FMA score of 28-56	52 acute stroke patients *Eligibility criteria* – Stroke within 28 days of admission to inpatient rehabilitation – Persistent hemiparesis (score of 1-3 on motor arm item of NIHSS motor arm item) *Criteria for CIMT:* – Ability to move proximal and/or distal joints against gravity	222 subacute stroke patients *Eligibility criteria* – 3 to 12 months post stroke – Deficits in more-impaired arm use (average MAL score <2,5) *Criteria for CIMT:* – Actively extend the wrist, the metacarpophalangeal and interphalangeal joints of the thumb and of any two other digits of 10 degrees – 45 degrees of active shoulder flexion and abduction – 20 degrees of active elbow extension	169 subacute stroke patient *Eligibility criteria* – 3 to 12 months post stroke – Ability to transfer to and from the toilet independently and safely *Criteria for CIMT:* – 10° or more active wrist extension – 10° or more active metacarpophalangeal and interphalangeal extension of 2 fingers of the impaired hand – 10° or more active MP and IP abduction and extension of the thumb on the impaired hand
Intervention	*Type of intervention:* Task-oriented mental practice with video instructions of the tasks *Control therapy:* Neurodevelopmental therapy-based exercise therapy *Dose of intervention:* 3 times a day, no precisely weekly dose of therapy 6 weeks	*Type of intervention:* Robot-assisted therapy with Bi-Manu-Track and additional active task-oriented therapy *Control therapy:* Dose-matched active control therapy *Dose of intervention:* 90-105 min, 5 days (450-525 min/week) 4 weeks	*Type of intervention:* 2 types of dose-matched Constraint-Induced movement therapy *Traditional CIMT received 2 hours of shaping therapy and wore a padded constraint mitt for 6 hours *High-intensity CIMT underwent 3 hours of shaping therapy and wore a padded constraint mitt for 90% of waking hours *Control therapy:* Traditional occupational therapy for 2 hours per day *Dose of intervention:* *Traditional CIMT: 600min/week with additional 6 hours mitt	*Type of intervention:* Constraint-Induced movement therapy (immediate treatment group) consist of 6 hours of shaping, and wore a padded constraint mitt for 90% of waking hours per day *Control therapy:* Physical rehabilitation consists of 6 hours of general fitness program (delayed treatment group) *Dose of intervention:* *Immediate treatment: 1800min/week with additional 13-14 hours a mitt *Delayed treatment: 1800min/week 10 consecutive workdays	*Type of intervention:* Constraint-Induced movement therapy (immediate treatment group) consist of 6 hours of shaping, and wore a padded constraint mitt for 90% of waking hours per day *Control therapy:* Physical rehabilitation consists of 6 hours of general fitness program (delayed treatment group) *Dose of intervention:* *Immediate treatment: 1800min/week with additional 13-14 hours a mitt *Delayed treatment: 1800min/week 10 consecutive workdays

			*High-intensity CIMT: 900min/week with additional 13-14 hours a mitt *Control therapy: 600min/week 10 consecutive workdays		
Setting	4 medical inpatient centers	Three medical centres with an outpatient programme	Inpatient rehabilitation hospital	Outpatient community setting	Outpatient community
Accelerometer type	ActiWatch-AW7 device is a uniaxial piezoelectric accelerometer	MircoMini-Motionlogger	Uniaxial accelerometer (model 7164-2.4 Activity Monitors)	Biaxial accelerometers were placed in snug pouches sewn into cloth and elastic bands	Biaxiale accelerometer were placed in snug pouches sewn into cloth and elastic bands
Accelerometer placement	Both wrists	Both wrists	Both wrists	Both wrists	Both wrists
Accelerometer wearing time	3 consecutive days	3 consecutive days	24 hours, except when the devices would be exposed to water	Three days during all waking hours, except when washing themselves	Three days during all waking hours, except when washing themselves
Parameters of accelerometer	*Sample frequency is 32 Hz *Epoch length is unknown	*Sample frequency is 10 Hz *Epoch length is 1 min	*Sample frequency is unknown *Epoch length is 2 seconds	*Sample frequency is 10 Hz *Epoch length is 2 seconds	*Sample frequency is 10 Hz *Epoch length is 2 seconds
Data collection and statistical analysis of accelerometer recordings	*Definition of unit of arm activity:* *The amplitudes of maximal signal intensity $I_{max/sec}$ (= the highest peak within each consecutive second) is summed for every 2 consecutive seconds, and expressed as an 'activity count' *Method for data collection:* *Duration of use = hours of arm-hand use relative to the uptime *Intensity of use = sum of counts, (signal intensity per data point) within a given time epoch *Ratio of affected-to-unaffected arm intensities	*Definition of unit of arm activity:* Not reported *Method for data collection:* The ratio of the intensity between affected and unaffected arm activity was calculated with Proportional integrating measure (PIM) mode	*Definition of unit of arm activity:* Not reported *Method for data collection:* *Duration of use = sum of epochs in which the upper limb moved	*Definition of unit of arm activity:* Raw counts represent a rough index of the amount of arm movements *Method for data collection:* Ratio of affected-to-unaffected arm movements	*Definition of unit of arm activity:* Raw counts represent a rough index of the amount of arm movements *Method for data collection:* Transforming of accelerometer recordings by dichotomizing the raw value recorded for each epoch around a low threshold Summary variables from each arm represent duration of movement *Impaired arm summary variable *Unimpaired arm summary variable Ratio variables * Ratio of affected-to-unaffected arm movements
Effect on actual performance	*Actual performance:* No significant improvements over time, apart from the increase of the ratio affected/non-affected arm in the control group between baseline and after treatment (p=0,045)	*Actual performance:* Arm use ratio *p=0,026 *r=0,26	Sample improved on all measures from study day 0 to study day 14 *Actual performance:* *mean change of 1,2±1.4 hours on duration of use, but no p value was calculated *Duration of upper limb use had no clear relationship with perceived ratings of change *Regardless of which side was affected, the largest changes in use were found in those people who considered their affected upper limb as having not meaningfully changed or not changed at all	No before-after changes of arm use ratio were reported Correlation for accelerometry ratio and MAL was moderate *QOM r=0,52 *AOU r=0,47 Correlations with caregiver MAL was a bit higher *QOM r=0,61 *AOU r=0,57	Changes in the summary variable values were not significant from period 1 to 2 *p range >0,48 No significant differences in summary variable values between treatment and control participants at period 1 (P range >0,58) Low-pass filtered accelerometer recordings were reliable (r range>0,80) and stable (p range>0,48) Validity was also supported
Effect on other outcomes	Baseline (T0) – 6-week training (T1) 6w training (T1) – 12 months (T4)	*Body function and impairment*: Fugl-Meyer Assessment Scale (FMA)	Sample improved on all measures from study day 0 to study day 14	No before-after changes of other outcome measures were reported	No other outcome measures were reported

	Control group *Body function and impairment*: FMA *T0-T1 p<0,05 *T1-T4 p<0,01 WMFT/lift *geen significante p WMFT/GS *T0-T1 geen p *T1-T4 p<0,001 *Capacity and disabilities*: Frenchary arm test *geen significante p WMFT/FAS *T0-T1 p<0,01 *T1-T4 p<0,05 WMFT/time *T0-T1 geen p *T1-T4 p<0,01 Experimental group *Body function and impairment*: FMA *T0-T1 p<0,05 *T1-T4 p<0,01 WMFT/lift *T0-T1 geen p *T1-T4 p<0,05 WMFT/GS *T0-T1 geen p *T1-T4 p<0,01 *Capacity and disabilities*: Frenchary arm test *T0-T1 p<0,01 *T1-T4 p<0,05 WMFT/FAS *T0-T1 p<0,001 *T1-T4 p<0,01 WMFT/time *T0-T1 geen p *T1-T4 p<0,01 No between-group difference in training effects were demonstrated	*p=0,002 *r=0,46 *Perceived performance:* Motor Activity Log MAL/AOU *p=0,007 *r=0,36 MAL/QOU *p=0,002 *r=0,44 ABILHAND questionnaire *p=0,043 *r=0,22 *Participantion:* Functional independence measure (FIM) *p=0,88 *r=0,002	Mean change scores, but no p value *Body function and impairment*: *Grip strength Mean change of 6.9 ± 7.3 *Composite strength Mean change of 0.22 ± 0.20 *Capacity and disabilities*: *ARAT Mean change of 15.1 ± 11.4 *WMFT/time Mean change of -22.6 ± 28.8 *WMFT/function Mean change of 1.2 ± 0.8 *Perceived performance:* *MAL Mean change of 1.2 ± 0.9 Minimal clinically important difference values for grip strength were 5.0 and 6.2 kg for the affected dominant and non-dominant sides MCID values for ARAT were 12 and 17 points, for the WMFT function score 1.0 and 1.2 points and for MAL score 1.0 and 1.1 points Minimal clinically important difference values were indeterminate for the dominant (composite strength) and the non-dominant side (WMFT time score)	MAL QOM scores were reliable (r=0,82) and construct validity was supported Correlation between the patient QOM and AOU test scores and other measures of more impaired arm function were strong *SIS Hand Function scale r=0,72 *Accelerometry ratio r=0,52 Correlations between the patient MAL scales and measures of overall physical activity were weak *Community mobility scale r=0,14 *Less impaired arm accelerometer recordings r=0,14 Participant QOM and AOU scores were highly correlated (r=0,92 and p<0,001) Delayed treatment participants show a trend towards an increase from test 1 to 2 *QOM p=0,02 *AOU p=0,04 Correlation between participant and caregiver forms of the MAL was 0,59 (p<0,001) for each of the scales Correlations with caregiver MAL were a bit lesser	

	Controlled intervention studies			Case series
STUDY	Wang, Lin et al. (2011)	Uswatte, Foo et al. (2005)	Uswatte, Taub et al. (2005)	Taub, Uswatte et al. (2013)
Aim of the study	To investigate the criterion-related validity, responsiveness and clinically important differences of the ABILHAND questionnaire in patients with stroke.	To evaluate the reliability and validity of accelerometry for measuring upper extremity rehabilitation outcome	To examine the psychometrics of the 14-item version of this instrument in a chronic stroke sample with mild-to-moderate upper extremity hemiparesis	To determine whether the combination of Constraint Induced therapy and conventional rehabilitation techniques can produce meaningful motor improvement in chronic stroke patients with initially fisted hands
Study design	Validation and clinimetric study	Validation and clinimetric study	Validation and clinimetric study Part of a controlled clinical trial (AutoCITE)	Pilot case series
Participants	51 patients with chronic stroke *Eligibility criteria* – Capacity to reach Brunnstorm stage II or above for the proximal and distal UE *Baseline characteristics* – Average of 17 months after stroke – Brunnstorm stage of 4 on the proximal UE and 3 on the distal UE – ABILHAND score of 0,08 logits	20 chronic stroke patients *Eligibility criteria* – More than one year post stroke – No specific inclusion criteria *Extra criteria for CIMT* – No extra criteria for CIMT	27 chronic stroke patients *Eligibility criteria* – More than 1 year after stroke – Substantial deficits in real-world more-impaired arm use (MAL score<2,5) *Extra criteria for CIMT* – Ability to actively extend the wrist >20° – Actively extend metacarpophalangeal and interphalangeal joint of all digits at least 10°	6 community resident with chronic stroke *Eligibility criteria* – More than 1 year post stroke – Severe plegic hands with initially fisted hands – All subjects meet the active Range of Motion criteria for inclusion in the Grade 5 category *Extra criteria for CIMT* – No extra criteria for CIMT
Intervention	*Type of intervention:* Bilateral UE robot-assisted rehabilitation *Control therapy:* Unilateral UE robot-assisted rehabilitation Conventional rehabilitation *Dose of intervention:* 1,5 hours, 5 sessions (450min/week) 4 weeks	*Type of intervention:* Consecutive Constraint-Induced Movement therapy (CIMT) *Control therapy:* An equivalent no-treatment group *Dose of intervention:* Precise dose was not reported	*Type of intervention:* Automated form of CIMT (AutoCITE) Additional wearing of a padded safety mitt on the less-affected arm for 90% of the waking hours *Control therapy:* 25 to 25% supervision during the automated form of CIMT (AutoCIMT) *Dose of intervention:* 3 hours, 5 days (900 min/week) 2 weeks	*Type of intervention:* *Phase A: adaptive equipment in the home, orthotics and splints *Phase B: Constraint Induced therapy, along with selected neurodevelopmental treatment techniques (NDT) – Intensive more affected arm training on functional tasks for several hours daily – Package of behavioural techniques – Restraint of the less affected arm to discourage its use *Control therapy:* NDT techniques like tapping, weightbearing, placing and holding, as well as the use of ice baths and vibration *Dose of intervention:* No specific duration of the CIMT sessions *Phase A = 15 days or 3 weeks *Phase B = 15 consecutive weekdays (3weeks)
Setting	Three inpatient medical centers	Outpatient community at an urban medical center	Not reported	University hospital outpatient laboratory
Accelerometer type	Stroke upper limb activity monitor	Model 71256 activity monitor is anbiaxial accelerometer	Not reported	Not reported
Accelerometer placement	Both wrists	Both wrists additive accelerometers were placed on the chest and more-affected leg	Both wrists	Both wrists
Accelerometer wearing time	Not reported	Three days during all waking hours, except when washing	Three days	3 consecutive days

Parameters of accelerometer	Not reported	*Sample frequency is 10 Hz *Epoch length is 2 seconds	Not reported	Not reported
Data collection and statistical analysis of accelerometer recordings	*Definition of unit of arm activity:* Not reported *Method for data collection:* Ratio of affected-to-unaffected arm movements	*Definition of unit of arm activity:* Raw counts represent a rough index of the amount of arm movements *Method for data collection:* Summary variables *Duration of impaired and non-impaired movements is expressed as a percentage of the recording period Ratio summary variables * Ratio of affected-to-unaffected arm movements	Not reported	*Definition of unit of arm activity:* Not reported *Method for data collection:* Ratio of affected-to-unaffected arm movements
Effect on actual performance	No before-after changes of arm use ratio were reported Correlation coefficients were moderate between the ABILHAND and accelerometer data (r=0,45-0,54)	*Actual performance:* Significant and large increase in the ratio of transformed more- to less-impaired arm recordings in CIMT therapy patients (d'=0,9; p<0,05), while there was no change for controls Test-retest reliability of transformed accelerometer recordings were greater than 0,86 (range 0,82-0,94) Validity of the ratio of more-impaired to less-impaired arm threshold-filtered recordings (ratio summary variable) Correlations between this ratio and mal was strong (r=0,74; p<0,001) Correlation coefficient was not a function of extreme scores Ceiling effect accounted for the lack of change in the ratio summary variable???	No before-after changes of arm use ratio were reported	*Actual performance:* Increases in the accelerometry ratio *p=0,016 *d'=1,2 Significant gains for both the Grade 4/5 MAL and accelerometry ratio were observed in each phase
Effect on other outcomes	No before-after changes of arm use ratio were reported Correlation coefficients were moderate to large between the ABILHAND and SIS physical domains (r=0,54-0,66) and fair to moderate between the ABILHAND and FIM-motor and NEADL (r=0,28-0,48) Responsiveness of ABILHAND was large(SRM=1,27) Minimally clinically important difference for ABILHAND was 0,26 to 0,35 51% of patients showed a positive change that exceeded the lower bound of a clinically important difference after intervention	No other outcome measures were used	No before-after changes of arm use ratio were reported Correlations between pre-to-posttreatment change scores on the participant QOM scale and caregiver MAL QOM scale, caregivers AOU scale and accelerometer recordings were 0,70, 0,73 and 0,91 (p<0,001) Internal consistency was adequate (chronbach α=0,81) and responsiveness was high Median change on the QOM scale was only 0,05 points, which is 10 times smaller than what is considered a minimal clinically important difference	*Body function and impairment*: Large improvement on FMA *p=0,005 *Increase in active Range of Motion *Perceived performance:* Grade 4/5 MAL *p<0,001 *d'=3,07 Significant gains for both the Grade 4/5 MAL and accelerometry ratio were observed in each phase Large shift from pre- to post-treatment in the proportion of upper extremity tasks on the Grade 4/5 MAL score 0 to 3

Observational cohort studies					
STUDY	Doman, Waddell et al. (2016)	Urbin, Waddell et al. (2015)	Waddell, Birkenmeier et al. (2014)	Rand and Eng (2012)	Reiterer, Sauter et al. (2008)
Aim of the study	To explore how upper extremity functional capacity and daily performance change during the course of outpatient rehabilitation in people with stroke	To determine of acceleration metrics derived from monitoring outside of treatment are responsive to change in upper-extremity function	To investigate the feasibility of delivering an individualized, progressive, high-repetition upper extremity task-specific training protocol for people with stroke in the inpatient rehabilitation setting	To determine the change in daily use of the upper and lower extremities of stroke patients during rehabilitation and to compare these values with that of community-dwelling older adults	The evaluation of actigraphy as a tool to objectify the recovery process after motor paresis due to stroke
Study design	Pilot prospective observational cohort	Before-After observational cohort study	Single cohort, repeated measures	Observational cohort study	Observational longitudinal cohort study
Participants	15 stroke participants with upper extremity paresis *Eligibility criteria:* – Spared motor capacity, indicated by 29 – 91 on Motricity Index on paretic side	8 acute individuals with stroke and UE hemiparesis after stroke *Eligibility criteria:* – Less than 30 days after stroke – MI score between 42 and 93 –	15 acute stroke patients with unilateral paresis *Eligibility criteria:* – MI score between 42 and 93	60 subacute stroke patients *Eligibility criteria:* – Within 60 days of sustaining a stroke	38 stroke patients *Eligibility criteria:* – Stroke was supposed to have occurred not more than 24-36h prior to the first actigraphical monitoring – At least a minimal motor deficit
Intervention	*Type of intervention:* Occupation therapy services included both therapeutic activities and therapeutic exercise to address UE-related goal areas and improve upper extremity function for each participant *Control therapy:* no control group *Dose of intervention:* not reported	*Type of intervention:* Individualized, high-repetition, task-specific training *Control therapy:* no control group *Dose of intervention:* 13 sessions	*Type of intervention:* Task-specific training was scheduled during occupation therapy During each session, participants were challenged to complete ≥ 300 repetitions of various tasks *Control therapy:* no control group *Dose of intervention:* 60 min, 4 days per week	*Type of intervention:* General subacute rehabilitation *Control therapy:* older, community-dwelling adults *Dose of intervention:* not reported	*Type of intervention:* The course of rehabilitation *Control therapy:* no control group *Dose of intervention:* not reported
Setting	Outpatient or day rehabilitation setting	Inpatient hospital	Inpatient hospital stay	2 inpatient rehabilitation centers	Not reported
Accelerometer type	ActiGraph is a triaxiale accelerometer	Triaxial, solid-state digital accelerometer	Actigraph GT3X	Actical (lower extremity) is a triaxial accelerometer, but is more sensitive in the vertical direction	Actiwatch, locomotion and reaching movements constituted the main components of wrist motor activity
Accelerometer placement	Both wrists	Both wrists	Both wrists	Both wrists Extra accelerometer on the hip (lower extremity)	Both wrists
Accelerometer wearing time	24 hours	22 hours	24 hours	3 consecutive weekdays (Tuesday, Wednesday and Thursday)	24 hours
Parameters of accelerometer	*Sample rate is 30 Hz *Epoch length is 1 second	*Sample rate is 30 Hz *Epoch length is 1 second	Not reported	*Sample rate is 32 Hz *Epoch length is 15 second	*Sample rate is 40 Hz *Epoch length is unknown
Data collection and statistical analysis of accelerometer recordings	*Definition of unit of arm activity:* Not reported *Method for data collection:* Recorded as activity counts Primary variables of interest *Bilateral magnitude (= intensity of movement across both upper limbs)	*Definition of unit of arm activity:* Accelerations registered as activity counts *Method for data collection:* *Ratio of movement characteristics between paretic and non-paretic upper extremities	*Definition of unit of arm activity:* Not reported *Method for data collection:* *Use ratio was calculated to express the amount of use of the affected side, compared to the non-affected side	*Definition of unit of arm activity:* Not reported *Method for data collection:* Mean daily use (activity counts for the upper limbs divided by 3 days) *Entire day	*Definition of unit of arm activity:* Total activity score (TAS) was defined as the summation of all the activity scores in all the epochs within the period of start and end of recording *Method for data collection:*

	*Magnitude ratio (=contribution of each upper limb to activity) *Use ratio (=length of time that the paretic upper extremity was active relative to the non-paretic upper extremity)	*Paretic UE movements *Movement characteristics of both UE combined		*Daily use not including the occupational and physical therapy sessions *Upper extremity activity counts outside of therapy is variable of interest	*TAS for the impaired side (TASi) *TAS for the non-impaired side (TASni)
Effect on actual performance	*Actual performance:* Results were categorised into three possible patterns – Change in ARAT score and a change in the accelerometry profile (n=2) – Increase in ARAT score, but no change in the accelerometry profile (n=4) – No change in ARAT score and no change in the accelerometry profile (n=7) Several patients had large, impressive changes in UE functional capacity, but no change in performance	*Actual performance:* Five acceleration metrics also improved significantly: use ratio (p<0,01), magnitude ratio (p=0,01), variation ratio (p=0,03), median paretic UE acceleration magnitude (p=0,03) and paretic upper extremity acceleration variability (p=0,03)	*Actual performance:* Improvements of the activity level outcome measures from baseline to discharge was found *Use ratio, measured by accelerometer (p=0,005 at discharge, no 1 month follow-up)	*Actual performance:* Daily use of the paretic upper extremity on assessment 2 was very similar to the daily use measured on assessment 1 (d=5861, p-values were not significant for paretic arm) (d=15110, p-values were not significant for non-paretic arm) On assessment 2, daily use of the paretic upper extremity was significantly lower than the daily use of both the right (p<0,001) and left hands (p<0,001) of healthy controls, but the daily use of the non-paretic upper extremity was not significantly different from the daily use of either hand of the healthy controls	*Actual performance:* TASni only increased between the first (24-36h) and last measurement (6 months) Only TASi improved significantly from 5th-7th day till 3 and 6 months later, but TASni remained unchanged TASi and TASni differed significantly at the first (24-36h) and second (5-7 days) recording, but this was no longer evident 3 and 6 months later after stroke Increase of arm activity of the impaired side between the first two time points and the subsequent ones, but this is not significant
Effect on other outcomes		*Capacity and disabilities*: *ARAT p<0,01	Improvements of the impairment and activity level outcome measures from baseline to discharge was found *Body function and impairment*: *Grip, measured by JAMAR hydraulic handheld dynamometer (p=0,007 at discharge and p=0,052 at 1 month) *Pinch, measured by three-jaw-chuck pinch (p=0,001 at discharge and p=0,02 at 1 month) *Capacity and disabilities*: *ARAT (p=0,000 at discharge and p=0,018 at 1 month) *Participation:* *UE-FIM items (p=0,000 at discharge and p=0,009 at 1 month)	Despite significant improvements in paretic hand function, no increase in daily use of the paretic and non-paretic hand was found over the entire day or in the physical therapy Motor and functional abilities of arm improved significantly over the 3-week period from assessment 1 to 2 *Body function and impairment*: *FMA (p=0,005) *Capacity and disabilities*: *ARAT (p<0,001) *Participation:* *FIM (p<0,001)	Significant positive correlation was found between the actigraphically recorded motor activity and the SSS, BI, RS and MI during the first week, which corresponds to the time when neurological deficits were most pronounced *Body function and impairment*: *MI (r=0,44 p=0,01 on TI; r=0,5 p=0,01 on T2) *Participation:* *SSS (r=0,43 p=0,046 on T1; r=0,53 p=0,01 on T2) *Rankin Scale (ρ=-0,57 p<0,07 on T1; ρ=-0,60 p<0,01 on T2) *Barthel Index (ρ=0,48 p=0,03 on T1; ρ=0,64 p<0,01 on T2) No significant correlation was found after 3 and 6 months after stroke on any of these clinical scales

TABEL 4: Baseline characteristics

Randomised Controlled Trials (RCT)					
STUDY	Hsieh, Wu et al. (2016)	Shim and Jung (2015)	Thrane, Askim et al. (2015)	Hsieh, Lin et al. (2014)	Lemmens, Timmermans et al. (2014)
	Baseline characteristics – Average 2,4 months post stroke – FMA-UE score of 26.81 in experimental group and 29.07 in control group – BBT score of 5.31 in experimental group and 8.60 in control group – Grip score of 5.54 in experimental group and 4.38 in control group – Modified RS of 3.69 in experimental group and 3.27 in control group – FIM score of 95.87 in experimental group and 90.87 in control group – Actigraphy score of 3060.22 activity count in experimental group and 3312.13 in control group – SIS score SIS/Strength: 30.47 in experimental group and 27.50 in control group SIS/Hand function: 13.46 in experimental group and 20.36 in control group SIS/ALD/iADL 65.47 in experimental group and 57.75 in control group Mobility: 70.31 in experimental and 60.23 in control group – Fatigue score of 3.34 in experimental and 1.87 in control group	*Baseline characteristics* – Average 7.9 (BT) and 7.7 months (UT) after stroke onset – FMA-UE score of 33.2 in BT group and 28.7 in UT group – FIM/motor score of 51.7 in the BT group and 53.8 in UT group – FIM/cog score of 30.1 in BT group and 27.1 in UT group – FIM/total score of 81.8 in BT group and 80.9 in UT group – MFT (affected hand) of 15.8 in BT group and 11.1 in UT group – MFT (non-affected hand) of 29.3 in BT group and 29.4 in the UT group – Accelerometer of affected arm Amount/y of 328.2 counts in BT group and 195.4 counts in UT group Amount/x of 373.8 counts in BT group and 260.4 counts in UT group Amount/z of 443.2 counts in BT group and 275.6 in UT group Amount/total of 1145.2 counts in BT group and 731.4 in UT group Intensity/sedentary 67.2% in BT group and 76.9% in UT group Intensity/light 23.6% in BT group and 17.3% in UT group Intensity/lifestyle 6.3% in BT group and 4.9% in UT group Intensity/moderate 2.5% in BT group and 0.9% in UT group – Accelerometer of affected arm Amount/y of 1078.9 counts in BT group and 748.3 counts in UT group	*Baseline characteristics:* – Average of 17.3 days post stroke – Mean score of 1.7 on NIHSS – Mean score of 2.6 on Modified Rankin scale – WMFT/time score of 13.8 sec in CIMT group and 13.7 sec in control group – WMFT/log time score of 0.69 in CIMT group and 0.62 in control group – WMFT/FAS score of 3.3 in CIMT group and 3.4 in control group – WMFT/strength score of 5.0 kg in CIMT group and 5.0 kg in control group – WMFT/grip score of 19.0 kg in CIMT group and 15.1 kg in control group – FMA score of 49.4 in CIMT group and 50.1 in control group – NHPT score of 0.16 peg/sec in CIMT group and 0.16 peg/sec in control group – Arm use ratio score of 0.73 in CIMT group and 0.63 in control group – SIS/hand score of 85.0 in CIMT group and 79.2 in control group – SIS/ADL score of 91.9 in CIMT group and 89.9 in control group – SIS/participation score of 81.9 in CIMT group and 81.3 in control group – SIS/overall score of 70.4 in CIMT group and 73.7 in experimental group	*Baseline characteristics:* – Time after stroke Average 20.56 months in RT+dCIT, 23.56 in RT and 27.81 in CR group – FMA score of 32.19 in RT+dCIT, 35.69 in RT and 35.94 in CR – FMA/distal score of 7.88 in RT+dCIT, 9.06 in RT and 8.25 in CR group – FMA/proximal score of 24.31 in RT+dCIT, 26.63 in RT and 27.69 in CR group – WMFT/FAS score of 2.24 in RT+dCIT, 2.84 in RT and 2.76 in CR group – WMFT/time score of 6.36 in RT+dCIT, 6.79 in RT group and 6.15 in CR group – MAL/AOU score of 0.62 in RT+dCIT, 0.61 in RT group and 0.47 in CR group – MAL/QOM score of 0.62 in RT+dCIT, 0.61 in RT group and 0.53 in CR group – Accelerometer score of 0.65 in RT+dCIT, 0.69 in RT group and 0.65 in CR group	*Baseline characteristics:* – Average 12.5 months in the experimental and 25.5 months in control group post stroke – FMA score of 49.5 in the experimental and 52.5 in the control group – ARAT score of 31.5 in the experimental and 40.0 in the control group – MAL score of 3.57 in the experimental and 4.55 in the control group – $D_{add\text{-}uni}$ (=the duration of unimanual use of the affected arm hand) score of 0.91 in the experimental and 1.01 in the control group – D_{bi} (=the duration of bimanual use) score of 49.38 in the experimental and 68.27 in the control group – $I_{tot\text{-}unaff}$ (= the intensity of use of the affected arm-hand) score of 17826 counts in the experimental and 17728 counts in the control group – $I_{tot\text{-}aff}$ (= the intensity of use of the affected arm-hand) score of 7634 counts in the experimental and 10186 counts in the control group

		Amount/x of 1035.0 counts in BT group and 811.6 counts in UT group Amount/z of 1193.6 counts in BT group and 826.4 in UT group Amount/total of 3307.5 counts in BT group and 2386.3 in UT group Intensity/sedentary 30.8% in BT group and 39.5 % in UT group Intensity/light 26.4% in BT group and 30.5% in UT group Intensity/lifestyle 33.1% in BT group and 25.0% in UT group – Intensity/moderate 9.7% in BT group and 5.0% in UT group			

Randomised Controlled Trials (RCT)					
STUDY	Timmermans, Verbunt et al. (2013)	Liao, Wu et al. (2012)	Lang, Edwards et al. (2008)	Uswatte, Taub et al. (2006)	Uswatte, Guiliani et al. (2006)
	Baseline characteristics – 32 days in control group and 36 days in experimental group after stroke onset – Barthel index score of 74.4 in control group and 70.3 in experimental group – Frenchary activity index of 56.0 in control group and 56.8 in experimental group – FMA score of 45.4 in control group and 41.6 in experimental group – Frenchary arm test score of 3.7 in control group and 3.1 in experimental group – WMFT/FAS score of 3.1 in control group and 3.01 in experimental group – WMFT/time score of 5.1 in control group and 5.8 in experimental group – WMFT/strength score of 3.8 in control group and 3.3 in experimental group – WMFT/grip score of 14.5 in control group and 14.5 in the experimental group – Total arm activity counts of 87 for the affected arm and 217 for non-affected arm in the control group Total activity counts of 92 for the affected arm and 188 for the non-affected arm in the experimental group – Arm activity per hour 1924 counts for the affected arm and 4588 counts for the non-affected arm in the control group 1973 counts for the affected arm and 4995 for the non-affected arm in the experimental group	*Baseline characteristics* – Average of 24 months after stroke in the experimental group and 22 months after stroke in the control group – FMA score of 44.9 in the experimental and 39.6 in the control group – FIM score of 116.4 in the experimental group and 115.4 in the control group – MAL score of 0.79 on AOU and 0.88 on QOM in the experimental group, and 0.57 on AOU and 0.60 on QOM in the control group – ABILHAND score of 0.99 in the experimental group and 0.92 in the control group – Arm use ratio of 0.71 in the experimental and 0.69 in the control group	*Baseline characteristics* – Average of 9.5 days since stroke – NIHSS score of 5.3 – Barthel index of 99.6 – Modified rankin index of 0.3 – Grip strength of 9.6 kg – Composite strength of 0.34 kg – ARAT score of 22.5 – WMFT/time score of 42.5 sec – WMFT/function score of 2.4 – MAL score of 0.5 – Duration of use of 3.3 hours	*Baseline characteristics* – 80% of high level of function (n=177) – 20% of low level of function (n=45) – SIS mobility scale score of 72.0 – Duration of unimpaired arm movement of 22.1% – Patient QOM scale score of 1.5 – Patient AOU scale score of 1.4 – Caregiver QOM scale score of 1.1 – Caregiver AOU scale score of 1.1	*Baseline characteristics* – High level of function (n=132) – Low level of function (n=37) – SIS/mobility scale score of 72.1 – Mean duration of impaired arm movement score of 22.1 – Mean ratio of impaired-to-unimpaired arm movement score of 0.56 – Mean MAL of 1.4 points – Mean AAUT of 0.9 point

	– Arm use ratio of 0.4 in the control group and 0.3 in the experimental group				

	Controlled intervention studies			**Case series**
STUDY	Wang, Lin et al. (2011)	Uswatte, Foo et al. (2005)	Uswatte, Taub et al. (2005)	Taub, Uswatte et al. (2013)
	Baseline characteristics – Average of 17 months after stroke – Brunnstorm stage of 4 on the proximal UE and 3 on the distal UE – ABILHAND score of 0,08 logits	*Baseline characteristics* – Mild to moderate impairments (n=19) – Moderate to severe impairments (n=1) – Mean arm use score of 1.1 points in the experimental group and 2.8 points in the control group	*Baseline characteristics* – Average of 5.5 years since stroke – WMFT/time score of 4.8 – WMFT/FAS score of 2.7 points – Patient QOM score of 1.2 – Patient AOU score of 1.1 – Arm use ratio of 0.60	*Baseline characteristics* – Average of 5.1 years since stroke – Real-world more affected arm use LF-MAL AOU score of 0.7 ± 0.5 Accelerometry ratio of 0.46 ± 0.07 – More affected arm motor capacity FMA score of 24 ± 7 points – Active ROM Shoulder flexion of 58 ± 39 Shoulder abduction of 75 ± 40 Elbow extension of 77 ± 45 Forearm pronation of 43 ± 23 Forearm supination of 4 ± 6 Wrist extension of 56 ± 49

Observational cohort studies					
STUDY	Doman, Waddell et al. (2016)	Urbin, Waddell et al. (2015)	Waddell, Birkenmeier et al. (2014)	Rand and Eng (2012)	Reiterer, Sauter et al. (2008)
	Baseline characteristics: No average values of the baseline characteristics	*Baseline characteristics:* – Chronicity of 14 ± 6.4 days post stroke – ARAT score of 23.4 ± 13.2 – Motricity index of 64 ± 8.2 – Ratio of 0.54 ± 0.18 – Paretic arm movements of 0.05 ± 0.09 – Bilateral arm movements of 1.0 ± 0.2	*Baseline characteristics:* – Average of 20 days poststroke – Average of 29 days in length of stay in inpatient rehabilitation – ARAT score of 25 ± 13 – Grip strength of 7.5 ± 5.9 kg – Pinch strength of 0.87 ± 1.3 kg – UE-FIM score of 20 ± 4.5 – Use ratio of 0.47 ± 0.14	*Baseline characteristics:* – Average of 33.4 days since stroke – FIM score of 91.4 – FMA score of 40. – ARAT score of 32.5	Baseline characteristics: – Barthel index of 99.8 ± 1.2 – Rankin scale of 0.4 ± 0.6

Part 2 – Research protocol

1 Introduction

Multiple Sclerosis is a neurodegenerative disorder characterized by a demyelination process in the Central Nervous System (CNS). Gradually several diffuse plaques arise on different locations in brain areas, with highly variable symptoms as a result (Kister, Bacon et al. 2013)[109]. Additional to common sensorimotor deficits, patients with MS typically suffer from extreme fatigue (Kluger, Krupp et al. 2013)[110]. In this context, fatigue is defined as a sense of exhaustion, lack of energy or tiredness. Furthermore, cognitive dysfunctions often occur in Multiple Sclerosis, which clearly interacts with the performance of dual tasks. Compared to other neurological disorders, upper limb impairments in PwMS do not solely affect one side of the body. According to Bertoni, Lamers et al. (2015)[2], both uni- and bilateral upper limb abnormalities are quite common at all level of ICF. Overall disability level is depending on the severity of upper limb impairments (Yozbatiran, Baskurt et al. 2006)[7] and hand dominance (Lamers, Kerkhofs et al. 2013)[28]. The decrease of real-life performance is associated with less self-efficacy and quality of life.

In the International Classification of functioning, disability and health (ICF), actual performance is defined as the objectively detectable level of functioning of a person in a given domain at a given moment in his/her current environment (Lemmens, Timmermans et al. 2012)[108]. Because actual performance is a different construct from capacity and perceived performance, an adequate assessment tool has to be established. Recently, accelerometer is highly recommended as an optimal tool to objectively evaluate real-life upper limb performance. This device is considered as compact and user-friendly, which is essential for the ability to register objective upper limb use during daily activities in the home environment. Up to now, accelerometers indicate a lot of promising opportunities for an easily assessment of actual performance at home. Although validity and reliability of the accelerometer has been established in small-scale studies, evidence of large-scale studies are lacking (Uswatte, Giuliani et al. 2006)[16] (Reiterer, Sauter et al. 2008)[17] (van der Pas, Verbunt et al. 2011)[18] (Shim, Kim et al. 2014)[19] (Gebruers, Truijen et al. 2008)[20] (Urbin, Waddell et al. 2015)[21] (Thrane, Emaus et al. 2011)[22]. Moreover, cross-sectional studies incorporated the accelerometer to describe daily functioning of the arm (Lang, Wagner et al. 2007)[23] (Hildebold et al. 2011)[24] (Birkenmeier et al. 2015)[25] (Michielsen, Selles et al. 2012)[26]. However, few clinical trials investigating effectiveness of rehabilitation approaches are lacking accelerometer assessment. A reasonable explanation is probably the difficult implementation of the accelerometer. There is an urgent need for clear statements and recommendations on the exact parameters to accurate measure daily use of the affected upper limb in home environment.

Considering mostly daily life activities are affected in MS, rehabilitation interventions should aim to restore these functional disabilities. According to Bonzano et al [111], voluntary movement in therapy is essential for a preservation of white matter integrity. Moreover, a variability of exercises addressing specific tasks and selective targets of function, activity and participation, are clearly preferred. Additional benefits can be accomplished through the application of high intensity training with repetitive patient-oriented training of tasks in a natural environment, in concordance with principles of motor learning

(Timmermans, Seelen et al. 2009)[112]. However, most rehabilitation interventions do not satisfy on these recommendations in the clinical practice. Training mainly targets motor function and isolated activities with a lack of variable high intensive therapies.

In clinical evidence, task-oriented training is considered as an excellent rehabilitation approach to increase the daily use of arm and hand in stroke patients. Task-oriented practice selectively chooses a specific task and context that is meaningful to the patient to practice variable task-related exercises. The ultimate goal is to improve functional independence. The high-intensity, real-world practice of motor skills in a familiar environment with real objects enlarged the re-acquisition of actual performance, instead of using compensatory strategies in daily activities (Bosch, O'Donnell et al. 2014)[99] (Rensink, Schuurmans et al. 2009)[100]. Additional to clinical improvements, neural reorganization of brain areas can be triggered. Regarding basic principles of motor learning, varied mass and repetitive practice of functional ADL tasks is mostly emphasized. Thereby, complexity of tasks can be easily increased with other settings, tasks and objects, along with precise and timed feedback in different forms. Task-oriented training is mostly applied in supplement with other traditional interventions.

Although evidence for task-oriented practice has been established in stroke patients, the effectiveness of this rehabilitation approach is still unknown for Multiple Sclerosis (Bosch, O'Donnell et al. 2014)[99] (Rensink, Schuurmans et al. 2009)[100] (Timmermans, Spooren et al. 2010)[113]. Regarding the strengths of this rehabilitation approach, it could be suspected that task-related practice is also effective in PwMS. Though clinical evidence is necessary to reveal the clinical results on different outcome measures. Moreover, severe upper limb impairments in PwMS often results in a different recovery process, and consequently different results in intervention studies. Up to now, it is not clear whether a high-intensity task-related practice is even feasible in severely affected PwMS. Due to many comorbidities, like decreased physical fitness, presence of motor fatigue and reduced neural recruitment, it would be more difficult for these MS patients to execute a high intensity arm training. If the intervention can be performed, it is indistinct whether improvements after rehabilitation intervention occur in the same extent as to less severely affected PwMS. A second obstacle in applying task-oriented training in PwMS is the unknown dose-response relationship. The same problem arises in stroke patients, where there is no standard protocol regarding the best intensity of training. Lack of evidence results in a highly variable dose of task-specific arm training across clinical studies.

This study protocol discussed the methodology of an explorative RCT evaluating the effectiveness of task-oriented practice on actual and perceived performance in PwMS. Moreover, a high intensity task-related practice is conducted in PwMS with severe UE impairments, in order to evaluate the feasibly and any adverse effects. Further, the degree of change is compared among different levels of UE impairments in Multiple Sclerosis. At last, different intensities of functional task practice are tested to reveal recommendations among who benefits the most on which intensity of arm training. The challenge lies in selecting and structuring functional training to address the movement dysfunction (restorative and compensatory approach) and underlying impairments (restorative approach only).

2 Aim of the study

2.1 Research questions, related to master thesis

The main purpose of this study protocol is to precisely determine the clinical effects of task-oriented training on the actual and perceived performance in PwMS. Further, this research question addresses two underlying components. First, the level of upper limb deficits is discussed. The feasibility and the appearance of potential adverse effects during task-oriented practice among severe impaired MS patients are investigated. Afterwards it is unknown whether low level upper limb deficits will change in the same extent as the high level upper limb impairments. Secondly, the dose-response relation of task-specific practice is discussed. Two different intensities of task-oriented training are compared to each other to reveal any superior effects of either low or high intensity programs. Up to now, it is unclear who will benefit the most from different intensities of task-oriented arm training.

Bringing all the factors of interest together, the main research question will be as followed: *"What are the intensity-dependent clinical effects of task-oriented training on actual and perceived performance in persons with MS (PwMS) with different upper limb disabilities?*

Regarding the purpose of this study protocol, design is an explorative randomized controlled trial.

2.2 Hypotheses

The intention of this study protocol is based on three major hypotheses:

1) Actual and perceived performance will improve significantly after both task-oriented training programs, along with other clinical outcome measures
2) Although some adverse effects might occur, high-intensity arm training is feasible in severe UE impairments
3) General recovery pattern and results on clinical outcome measures will be significantly more favorable in low upper extremity disabilities in PwMS
4) A higher dose of task-related practice will result not only in preserved neural brain structures, but also cause additional beneficial effects

3 Methods

3.1 Research design

During an 8-week intervention program, each participant was assigned to one of three possible rehabilitation approaches: high-intensity task-related practice, low-intensity task-related practice and control therapy. Descriptive measures of baseline characteristics and initial experimental outcomes of interest will be executed before the start of the intervention. To exclude any possible fatigability of the study participants, tests were randomly spread over two days' assessments. Additionally, the participants were asked to fill in a short questionnaire (VAS and Neuropathic pain scale) before and after each training session and after every last day of the week during this 8-week training program to document the training tolerance and possible adverse effects if present. At the end of 8-week rehabilitation program, a second assessment of the experimental outcomes of interest will be conducted to evaluate any possible posttreatment effects. These assessments will be conducted in the same sequence by the same blinded assessor. The study procedure is shown in figure 1.

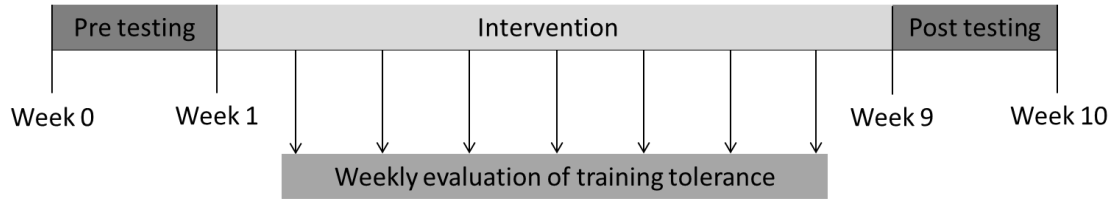


Figure 1. Study procedure

3.2 Participants

Recruitment of a convenience sample took place at the "Rehabilitation and MS centrum Overpelt" and "MS-centrum Melbroek". Based on eligibility criteria, the selection procedure of the participants was conducted by prof. dr. Bart Van Wijmeersch criteria. Both MS patients following an in- and outpatient rehabilitation program, are allowed to participate in the study.

3.2.1 Inclusion criteria

Inclusion criteria were the following:

- Adults older than 18 years
- Diagnosis of Multiple Sclerosis according to the McDonald criteria (Polman, Reingold et al. 2011)[114]
- Progressive type of Multiple Sclerosis, including primary and secondary progressive MS
- Score ≤ 1 on performance scale – item hand function

The latest criteria assure the presence of some hand dexterity and motor ability. Also stage of the disease, represented by an EDSS score or time since diagnosis, were not added to the inclusion criteria. Furthermore, no specific types or severity levels of upper limb deficits were distinguished considering the purpose of this protocol.

3.2.2 Exclusion criteria

Based on the following criteria, PwMS were excluded from participation:

- A relapse or relapse-related treatment within the last 3 months prior to the study
- Complete paralysis of both upper limbs
- Marked or severe intention tremor, indicated by score > 3 on the Fahn's tremor rating scale
- Other medical conditions interfering with the upper limb, like othopaedic or rheumatoid impairments
- Severe cognitive or visual deficits interfering with test assessments and training program (MSSE<22)

3.2.3 Patient recruitment

When a MS patient is willing to participate, the informed consent will be discussed together with dr. Ilse Lamers. After 2 weeks of reflection, the patient can finally decide to participate in the study by signing the informed consent. According to Helsinki declaration (Carlson, Boyd et al. 2004)[115], recruitment of participants will be performed. After the selection procedure, in total 45 participants were recruited. In order to differentiate between low and high level of upper limb disabilities, an additional blocking variable was jointed. Based on the capacity to raise the arms to 90° and the cut-off score of 33 seconds on the NHPT, all participants could be categorized in three subsamples of different levels of upper extremity impairments (Lamers, Cattaneo et al. 2015)[116] (figure 2).

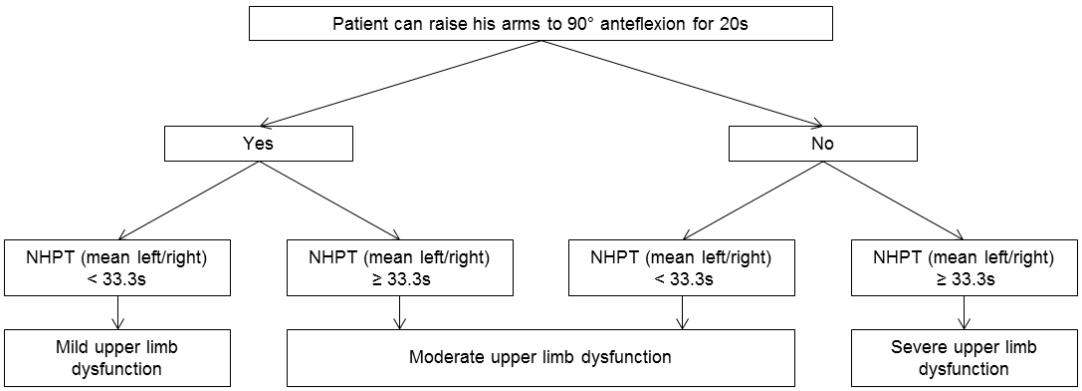


Figure 2: Determination of the upper limb dysfunction level.

Afterwards, participants were blindly randomized in a high intensity group (n=15), a low intensity group (n=15) or a control group (n=15). Details on the recruitment procedure are illustrated in figure 3. Since no previous pilot data is available, precise sample size calculations could not be performed. The results of this study will be used for the power calculations of the RCT.

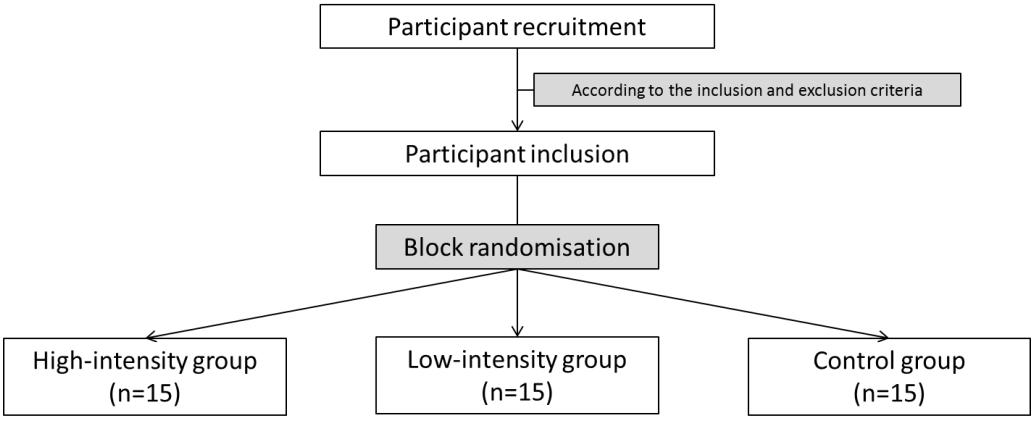


Figure 3. flowchart participant recruitment, inclusion and randomization

3.3 Intervention

The experimental group receive task-oriented upper limb intervention at either low or high intensity during 8 weeks. This exercise program will be added on their regular occupational therapy hours provided in the conventional multidisciplinary rehabilitation program. All participants receive conventional multidisciplinary rehabilitation program for 8 weeks, which consist of physiotherapy, occupational therapy and additional speech or cognitive therapy if needed. Participants were blinded for group allocation and the difference between training programs in the other groups. The experimental intervention is described in more detail.

3.3.1 Equipment

Both high and low intensity experimental groups performed task-oriented upper limb training with support of the Tagtrainer of SymbioTherapy (www.symbiotherapy.com) (Tetteroo, Timmermans et al. 2014)[117]. This technology-based device aids the independent training of functional tasks with real objects of different size and weights. Due to a high flexible set up of the boards, the Tagtrainer allows to adjust each exercise to the specific needs of the participant. Variation in the environment and trained tasks is possible through different objects, location of the objects, location of the tagboards etc. Feedback is provided though a green color associated with a good performance of the related task. Additional to visual feedback, an auditory cue will be heard if the task-related movement is executed right (Rosati, Oscari et al.)[118]. These two form of feedback belong to Knowledge of Results. However, Timmermans et al. advised the additional use of Knowlegde of performance (Timmermans, Seelen et al. 2009)[112]. Therefore, a camera of Mircosoft Kinect was placed in front of the patient to record the performed movements [119]. Because it would be overwhelming for the patients to see themselves moving during the arm training, the video images were watched together with the therapist after the practice of that task. In this way, participants could focus completely on the performance of the difficult tasks.

Some severely affected MS patient require an additional assistance for support against gravity to assure an independent performance of the different upper limb tasks. For this purpose, The Diego of TyroMotion (www.tyromotion.com) is preferred. It provides bilateral support of the upper limb and allows freedom of movement during the performance of ADL tasks with real-life objects.

To accomplish a standardization of the training dosage, both devices can be programmed beforehand. In addition, the system can provide precise data on the therapy dosage, regarding the duration of training, the number of repetitions etc., and on tasks grading, regarding the location of objects, amount of assistance, etc.

In the literature overview, four included studies evaluated robot-aided training with an additional task-oriented practice. In three studies, Bi-Manu-Track was preferred for the robot-assisted therapy, but no functional daily tasks were performed during this robot-aided intervention (Hsieh, Lin et al. 2014)[33] (Hsieh, Wu et al. 2016)[32] (Liao, Wu et al. 2012)[37]. Task-oriented training was implemented as an additional active, non-supported intervention. The Bi-Manu-Track facilitates motor learning of the paretic hand through symmetrical and simultaneous movements of the wrist and forearm. Despite the promising opportunities, the Bi-Manu-Track did not allow freedom of movement. So the practice of functional tasks with real-life objects, in addition to support of the robotic system was not possible. However, Liao, Wu et al. (2012) did succeed to find significant results on motor function and actual performance. These improvements could be partially explained through the high intensity of the combined training. Another RCT by Lemmens, Timmermans et al. (2014)[35] preferred the Haptic master as robotic tool to support stroke patients in the practice of functional tasks. However, no significant results were found. As a major limitation of the study, the lack of an additional non-robotic arm training, in supplement to the task-related robot-supported practice, was reported. Despite disappointing results, a robot system allowing free movements is highly preferable.

Diego of Tyromotion GmbH, Austria

TagTrainer of Symbio therapy, The Netherlands

Figure 4. Training devices

3.3.2 Therapy content

Task-oriented training can show up in clinical evidence under various synonyms, like task-specific training, goal-directed training and functional task practice. In general, these rehabilitation approach emphasized the repetitive practice of functional daily tasks, with the intention to (rel)earn a motor skill. Most functional upper limb tasks can be split into basic essential movement component, like reaching, moving, positioning, transporting, lifting the upper limb and/or an object and grasping, releasing,

stabilizing, manipulating an object. To guarantee the practice of relevant tasks in function of individual needs and goals, the participants were asked to select two bilateral tasks and one unilateral task of all activities of the MAM-36 and ABILHAND, before the start of the intervention.

3.3.3 Therapy dosage

The dose of the interventions is determined by the frequency of therapy sessions in one week, but also by the duration and the number of repetitions within one training session.

3.3.3.1 Duration, frequency of training sessions/week and duration of training session

The therapy sessions are scheduled for 90-120 min per day and 5 days per week during the occupational therapy time slots for the duration of 8 weeks. In total, a summed therapy duration of 450-600 min per week was obtained. Similar to the literature overview, a high intensity rehabilitation programs usually range from 450 to 600 min per week, but these interventions were only implemented for 6 weeks. In Constraint-Induced movement therapy (CIMT), dose of intervention was increased to 1800 min per week, but these programs are only implemented for 2 weeks. The chosen dose of therapy is similar with the applied dose of 8 weeks in Lemmens, Timmermans et al. (2014)[35]. However, the duration of weekly therapy duration is increased from 240 min in Lemmens, Timmermans et al. (2014) to 450-600 min in this study protocol. A major drawback in Lemmens, Timmermans et al. (2014) was the low intensity in every therapy session. In addition to the dose of training, the content of the task-oriented robot-supported arm training was also comparable. Though, Lemmens, Timmermans et al (2014) preferred the Haptic Master as implemented robotic system. Although the Haptic Master has the strength of haptic feedback, the set up of the device is less flexible, compared to the multiple tagboards of the Tagtrainer. As a results, variety in the tasks and environment is slightly decreased.

On the remaining workday in the week, participants receive occupational therapy aiming to improve self-care deficits, cognitive deficits or other deficits. Furthermore, the standard physiotherapy program and occupational therapy sessions was maintained, also for the upper limb training. This was preferred, because a lack of an additional non-robotic arm training was reported as a major drawback in Lemmens, Timmermans et al. (2014)[35].

3.3.3.2 Intensity: number of repetitions

To determine the individual maximal number of repetitions for each selected task, the participants were asked to perform as many repetitions as they can of each task before the start of the intervention. These number of repetitions are counted, and represent the intensity of training regarding the individually capacities and motor skills. Before the start of the training and after every 25 repetitions, the following measures are conducted.

- A score on the BORG scale

  BORG scale is a measurement tool for perceived exertion. The patient is instructed to rate his/her physical effort between 6 and 20. A score between 6 and 11 is considered as a light exertion. Next, a score between 12 and 16 represents a moderate to hard exertion. Finally, a score between 17 and 20 is considered as very hard to maximal effort of physical activity.
- Box & Block test

Box & Block test is a motor capacity test of hand function. In this test, 150 blocks are situated on one side of the partition that is close to the dominant hand of the person. The goal is to carry as many blocks from one side to the other side of the partition in one minute. The test is administered twice to evaluate each hand separately. The score indicates the number of blocks, that are carried from the started compartment to the other side.

The individual maximum number of repetitions is determined when one of the following cut-off points are reached.

- The BORG score is 20
- 25% decrease of the number of blocks transported in 1 min (Box & Block test)
- Clear compensations observed during the performance of the task, evaluated using the Fysio-friends system (www.fysiofriends.com)
- Exceeding a 1 hour training

Depending in which experimental group the participant is randomized, they receive a high or low intensity training program. Participants in the high intensity group are asked to perform their individual maximum number of repetitions for each task in the training. Participants in the low intensity group are asked to perform 50% of their maximal number of repetitions for each task.

In the study by Liao, Wu et al. (2012)[37], high intensity of the robot-assisted training was guaranteed by a fixed number of 2700 to 3600 repetitions per movement. However, a fixed number of repetitions does not account for the individual capacities of the patient. It is preferred to first determine the maximal effort of each task for every participant. Based on these scores, intensity can be more accurate measured.

3.3.4 Therapy progression

The included tasks in the training program are adapted individually and progressively according to the participant's progress over time. Changing the difficulty of the tasks can be obtained by changing the weight or size of the object, by increasing the workspace, by changing the position of the task material or by the amount of gravity support. The task-oriented training program and the principles of training progress are based on the successful protocols described for stroke, but never applied in MS. Three different difficulty level are identified for each task in the training program are. The following rules for up- and downgrading of difficulty levels are developed to standardize the training progression.

- When the participants easily reached their individual maximum number of repetitions in one hour, without abnormal movement compensations and adverse effects for 2 training sessions on a row, the difficulty level of the task will be upgraded with 1 level
- When participants are not able to perform their individual maximum number of repetitions in one hour without abnormal compensations or adverse effects for 2 training sessions on a row, the difficulty level of the task will be downgraded with 1 level
- When a participant is able to perform the task at difficulty level 3 without any compensations or adverse effects, the participant is asked to select a new task out of the pre-defined list of training tasks
- When a participant is not able to make progression for 4 weeks, another task of the list is chosen

3.4 Outcome measures

At baseline, initial characteristics of the population are described through the following measures.

Demographic data

- Sex (nominal)
- Age (ratio)
- Hand dominance, as indicated by the Edinburg Handedness inventory (nominal)

MS-specific data

- Type of MS (nominal)
  - Secondary progressive (SP)
  - Primary progressive (PP)
- Time since diagnosis (ratio)
- Medication use (nominal)
- Neurological severity, as indicated by the Expanded Disability Status Scale (EDSS)
- Spasticity, as indicated by the modified Ashworth scale (MAS)
- Fatigue, as indicated by the modified fatigue impact scale
- Tremor, as indicates by the Fahn tremor rating scale

The effect of high and low intensity task-oriented robot-supported practice is evaluated by the following experimental outcome measures. Considering that no single measure encapsulates a complete image of the upper limb function, capacity or performance, several outcome measures have been selected. Primary and secondary outcome measures were assessed at pre- (T1) and post-treatment (T2). An additional follow-up period of three (T3) and 6 months (T4) is preferred, considering effect on actual performance are suspected to be delayed. The assessor which conduct these experimental measures, is blinded for group allocation. Every time point, the same assessor will conduct the experimental measurements to exclude a possible bias.

3.4.1 Primary outcome measures

The main outcomes of interest are the actual and perceive performance of the affected upper limb.

Accelerometer is a non-invasive, wearable wristwatch-sized device, that registers acceleration of arm movements. The type of accelerometer reveals the capacity to record movements in respectively one, two or three orthogonally axes. Regarding the data collection, several activity counts are integrated over a certain timespan, called ‘epoch length’. Apart from the epoch length, sample rate will determine how often the sensor registered during one minute. Both construct and divergent validity of the accelerometer is established (Uswatte, Giuliani et al. 2006)[16] (Reiterer, Sauter et al. 2008)[17] (van der Pas, Verbunt et al. 2011)[18] (Shim, Kim et al. 2014)[19] (Gebruers, Truijen et al. 2008)[20] (Urbin, Waddell et al. 2015)[21] (Thrane, Emaus et al. 2011)[22].

Despite a lack of clinical guidelines or recommendations, most clinical studies choose a certain parameter based on their own knowledge and experience. Based on preliminary advices by Hayward, Eng et al. (2016)[107], the following parameters of the accelerometer were selected. Participants were asked to wear two triaxial actigraphy (Motionlogger) (Shapiro and Goldstein 1998)[120] for consecutive

5 days. Sample size of accelerometer was set to 50 Hz, along with a small epoch length of 1 second. These parameters were recommended to detect subtle and small movement of the upper limb.

For perceived performance, an additional primary outcome measure was selected. The Manual Ability Measure (MAM-36) is a task-oriented and patient-centered self-report tool to evaluate the capacity of the paretic arm. Items can be scored from 0 to 100 points. All 36 items consist of daily uni- and bilateral functional tasks, that cover a wide range of difficulties. Reliability and validity has been established (Chen and Bode 2010)[121] (Lamers and Feys 2014)[15] (Lamers, Kelchtermans et al. 2014)[122]

3.4.2 Secundary outcome measures

Secondary outcome measures reflect the motor function and skills of the paretic arm. For each level of ICF, various measurements were chosen in function of the research question. Several motor aspects on body function could be correlated with the performance of functional tasks in real-life.

Body function and structure level:

- Isometric hand grip and pinch strength (E-link biometrics) (Allen and Barnett 2011)[123]
  The E-link Biometrics is a measurement tool that evaluates active Range of Motion (ROM), grip and pinch strength in different starting positions of the hand. Because a high variability of measurement tools, this device provides reliable and valid measurement for grip and pinch strength
- Muscle fatigue indices
  It is suspected that general motor fatigue in PwMS is directly associated with the amount of daily use of the paretic arm.
- General isometric muscle strength (Croarkin, Danoff et al. 2004)[124]
  Motricity index evaluates the maximal voluntary muscle force during three upper limb movements; pinch strength, elbow flexion and shoulder abduction. On a 6-point ordinal scale with score ranges from 0, 11, 19, 22, 26 and 33, a maximum score of 100 indicate a normal muscle strength.
- Active Range of motion of shoulder, elbow and wrist movement
  X-sens 3D motion tracking produces miniature electromechanical-based motion tracking devices that accurately measure active ROM of different joints.

Different capacity measurements evaluate the same construct, namely UE motor skills. For capacity, it is important to both measure unimanual and bimanual tasks correctly. Since most daily activities the use of both hands require, it is important to measure bilateral capacity, in function of real-life use of the affected upper extremities. Therefore, it was preferred to include three unimanual and two bimanual capacity test

Capacity on activity level:

- Unilateral measurement tools
  - Nine hole peg test (NHPT) (Rosti-Otajarvi, Hamalainen et al. 2008)[125] (Lamers and Feys 2014)[15] (Lamers, Kelchtermans et al. 2014)[122]
    NHPT is a commonly used capacity test, in which fine manual dexterity is executed with the dominant hand. The person needs to remove 9 pegs from the holes and put it in a

container, afterwards the person needs to put the peg back in the holes. The time of these task is measures.

- Box and block test (BBT) (Platz, Pinkowski et al. 2005)[126]
  Box & Block test is a motor capacity test of hand function. In this test, 150 blocks are situated on one side of the partition that is close to the dominant hand of the person. The goal is to carry as many blocks from one side to the other side of the partition in one minute. The test is administered twice to evaluate each hand separately. The score indicates the number of blocks, that are carried from the started compartment to the other side.
- Action reach arm test (ARAT) (Platz, Pinkowski et al. 2005)[126]
  ARAT evaluates the execution of different grove and fine motor skills in order to manipulate 19 different subjects. Total score can range from 0 to 57 points. Reliability and validity have been established for Multiple Sclerosis.

- Bilateral test
  - TEMPA
    TEMPA is an performance-based evaluation test that evaluate the execution of a range of tasks, that are presentative for daily life. Time of performance of the 9 ADL tasks has been scored, together with a functional range score. Test is reliable and valid in elderly.
  - Jebsen-Taylor
    Jebsen-Taylor test measures the time of performing 9 ADL-related tasks. Reliability and validity has been proved.

3.4.3 Questionnaire of training tolerane

The feasibility of a high intensity task-practice program in severely impaired PwMS was investigated. The feasibility, potentially induced adverse effects and motor fatigue due to training intensity is evaluated using a questionnaire at fixed assessment points before and after a single training session and after a 1 week of training. The questionnaire contains different questions regarding the possible adverse effects, the fatigue and possible adverse effects on daily life performance. Considering pain is a highly associated to adverse effects after high intensity training, two pain scales were included. The Visual Analog Scale (VAS) measures different pain-related constructs, like general fatigue, muscle fatigue of the arm, pain in the arm, sensory deficits, motivation, task challenge and satisfaction with treatment.

3.4.4 Requested time investment of the participant

The testing before the start of the intervention (descriptive and experimental outcome measure) will be finished in twice 1,5 hour/day with one day rest between the testing days. Before the start of the study, the trainings content and maximal individual number of repetitions will be determined during a separated testing session lasting for 1 hour. Each participant is asked to train each workday for 1 hour 8 weeks long. After the intervention, the participants are tested two times 1,5 hour/day with one day rest between the testing days. In total, the participants are asked to invest 36 hours of their time spread over 8 weeks. The training sessions are planed during regular treatment hours of the occupational therapy.

3.5 Data analysis

For the data collection of the accelerometer recordings, Hayward et al [107] recommended to calculate the frequency and duration of arm activities. Thereby, a ratio of more impaired to less impaired arm use is preferred. Up to now, this metric is the simplest and efficient manner to exclude lower limb movements from any upper limb activities.

Maximal signal intensity per second ($I_{MAX/sec}$), derived from the accelerometer signal, is identified as the highest peak within each second. Amplitudes of two peaks in every 2 consecutive seconds were summed, and is expressed as a 'unit of activity counts'. Thus the intensity of use, indicated by the sum of activity counts (signal intensity per data point) within a given epoch length, was the first direct outcome. Furthermore, the time period between the first activity count in the morning and the last activity count in the evening, identified as uptime, was registered. First and last arm activity of each day was detected through a minimal threshold of signal amplitude. These metrics from both arms were summed, using the resultant accelerometer signal. Duration of use was identified as the hours of upper limb use, relative to the uptime. Thus, these two studies mainly focus on the intensity and amount of arm-hand use. As a third outcome of interest, the ratio between the total intensity of paretic and non-paretic upper limb was also determined.

Table 1. Variables used to calculate the actual amount of arm-hand use.

Abbreviation (unit)	Definition
T_{up} (hour)	Time span between first arm activity detected in the morning and last arm activity detected in the evening/night, displayed in hours
$D_{aff\text{-}uni}$ (%)	(Hours with only activity of the affected arm-hand)/(T_{up}) * 100%
D_{bi} (%)	(Hours with bimanual arm-hand use)/(T_{up}) * 100%
$I_{tot\text{-}aff}$ (activity/hour)	(Sum of acceleration counts of the affected arm-hand during unimanual activity of the affected arm-hand and during bimanual activity)/(hours with only activity of the affected arm-hand + hours with only bimanual activity)
$I_{tot\text{-}unaff}$ (activity/hour)	(Sum of acceleration counts of the unaffected arm-hand during unimanual activity of the unaffected arm-hand and during bimanual activity)/(hours with only activity of the unaffected arm-hand + hours with only bimanual activity)
$I_{aff\text{-}uni}$ (activity/hour)	(Sum of acceleration counts of the affected arm-hand during unimanual activity of the affected arm-hand)/(hours with only activity of the affected arm-hand)
$I_{aff\text{-}bi}$ (activity/hour)	(Sum of acceleration counts of the affected arm-hand during bimanual activity)/(hours with only bimanual activity)
$R_{tot\text{-}aff/tot\text{-}unaff}$	Ratio of $I_{tot\ aff}$ divided by $I_{tot\ unaff}$

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Figure 6 (Lemmens, Timmermans et al. 2014)[35]

Data-analysis are performed by the researchers using SAS JMP. To investigate baseline differences between the different groups descriptive analysis and an ANOVA will be performed. The effects of the different groups are investigated using a factorial ANOVA with repeated measures, with TIME as within-subject factor and GROUP as between-subject factor. Overall significance is set at $p<0.05$, but correction for multiple testing will be applied according to the formula: α/number of outcomes.

3.6 Medical ethics

Each participant signed the informed consent, approved by the medical ethical institution. The original study protocol, edit by dr. Lamers Ilse, was conducted under supervision of Prof. dr. Feys Peter and dr. Lamers Ilse. The adjusted protocol in this master thesis will not be used for clinical research, thus no approval of the medical ethical institution was obtained.

4 Time planning

In both rehabilitation centers, training takes place during two consecutive periods of ten weeks (one week baseline testing, eight weeks training, one week post testing (figure 1). At additional follow-up moments 3 to 6 months after the end of the intervention, a third assessment of the experimental outcome measures was taken.

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What is the effect of rehabilitation interventions on the actual performance of upper limbs, in neurological patients, taken the parameters of the accelerometer into account?

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij neurologische aandoeningen**
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