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Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The dosage dependent effects of upper limb rehabilitation in chronic neurological patients

Lore Petré
Bram Poelmans

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

PROMOTOR :
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The dosage dependent effects of upper limb rehabilitation in chronic neurological patients

Research question:

- What are the dose dependent effects of upper limb rehabilitation in chronic neurological patients?

Findings:

- The dosage dependent effects of upper limb rehabilitation have a lot more been researched in stroke patients (11 articles) than in other chronic neurological disorders (0 articles).
- A large heterogeneity in patient characteristics was found between and in the several intervention and control groups.
- A large heterogeneity in upper limb rehabilitation techniques, which were used as intervention, (Bobath concept, task-specific training, constraint induced movement therapy…) was found.
- Future research should investigate the dose dependent effects of upper limb rehabilitation in more homogeneous groups in more different chronic neurological disorders (Multiple Sclerosis, Parkinson's Disease,…).
- The dose dependent effects of upper limb rehabilitation in acute, subacute and chronic stroke patients are various whereby only small significant effects are obtained in favor of high dose interventions.

Petré Lore
Poelmans Bram
Promotor: dr. Lamers Ilse
Co-promotor: Prof. dr. Feys Peter

CONTEXT OF THE MASTER THESIS

This master thesis is situated in a chronic neurological context. Neurologic disorders like cerebrovascular accident, multiple sclerosis, Parkinson's disease, … are common diseases that affect the patient in his or her everyday life. The incidence of these diseases has increased over the last few decades. Neurologic disorders show a broad range of symptoms. These symptoms consist of problems of the upper and lower limb, cognitive disturbances, balance, vision, speech, activities of daily living, … For neurological patients, it is often difficult to walk, to eat with cutlery, to come from sit to stand, leading generally to a lower quality of life.

The neurological problems due to chronic neurological disorders may have a large impact on the activities of daily living and quality of life. Therefore, rehabilitation can be an important aspect to minimalize these neurological problems.

Different rehabilitation strategies are used in clinical practice to improve the quality of life and decrease the impact of the symptoms. Examples of these different rehabilitation strategies are task-specific training, balance training, strength training, mobilization, ... The most important goals of rehabilitation are improving the patient independency and increasing their quality of life.

A lot of research has been done on therapy content, which has recently showed the importance of task-oriented rehabilitation in chronic neurological patients. However, little is known about the optimal therapy dose that has to be used for these patients. Due to this unknowingness, we want to examine in this review the dose dependent effects of upper limb rehabilitation in chronic neurological

In general, the idea of 'higher therapy dose gives better motor outcomes', is used. There are other studies hat demonstrate that patients who experienced a stroke did not benefit from high dose interventions early after the stroke. In different articles and rehabilitation centers a large variety in therapy doses is given.

The literature review in this thesis will focus on the effect of different doses of rehabilitation in chronic neurological disorders.

In the second year of the master degree, we will study the effect of CIMT with a dose-matched standard rehabilitation program. We want to investigate whether the task-specific approach of CIMT improves the upper limb capacity more than a standard rehabilitation program. This study will be performed under supervision of our promotor Dr. Lamers and co-promotor Prof. Dr. Feys. The study will be conducted in the rehabilitation center of Herk-de-Stad. Our supervisor in Herk-de-Stad is Marc Michielsen, head of paramedical services of the rehabilitation center in Herk-de-Stad.

The literature review and the master thesis part 2 protocol was written in accordance with the central format.

The general theme was proposed by our promotor and co-promotor. Based on the available literature the research question was formulated by two students (BP and LP). The literature study, articles

selection and quality assessment was done by two independent students. When there was doubt, our promotor was asked for feedback. The writing of the data-extraction, results, and discussion was divided between the two independent students.

TABLE OF CONTENTS

PART 1 SYSTEMATIC REVIEW

PART 2 RESEARCH PROTOCOL

PART 1 SYSTEMATIC REVIEW

1. Abstract

Background: Different upper limb rehabilitation strategies have been investigated over time. But recently it became clear that not only the therapy content may influence outcome results, but also the therapy dose. The aim of this systematic review is to investigate the dose-dependent effects of upper limb rehabilitation in chronic neurological patients.
Methods: Web Of Science and PubMed were used to search for RCTs. Articles were included which consist of patients with chronic neurological diseases, comparing different doses of upper limb rehabilitation, and written in English or Dutch. Articles were excluded when using deep brain stimulation, medication therapy or botulinum toxin as an intervention. Equally excluded were those in which no dose comparison of upper limb rehabilitation was performed and when there was no RCT study design.
Results: Eleven articles were found which investigated the dose-dependent effects of upper limb rehabilitation in stroke patients. No articles of other chronic neurological disorders were found. Five articles found significant differences in favor of the high dose intervention group(s). Five articles concluded there were no significant between-group differences. One article found significant differences in disadvantage of the high dose intervention group.
Discussion and conclusion: The results of this review did not allow an unambiguous conclusion as to whether a higher dose of a rehabilitation strategy has more beneficial effects. Several explanations were found: The first one is the differences in baseline characteristics such as age, time post stroke, type of stroke, and gender. They may all have an influence. Thereby the different types and amounts of dose that are used may affect the results as well. Finally, the most influential factor may be the differences in the intervention strategies that are used (for rehabilitation).
Aim of the research protocol: To compare modified constraint induced movement therapy (mCimt) with a dose matched standard care program in subacute stroke patients.
Operationalization: A sample is randomized in two groups: one group receiving mCIMT and the other group dose matched standard care. Upper limb capacity measures will be taken before, after two weeks of training and one month post-intervention.
Key words: Stroke, upper limb, rehabilitation, dose-responsive, CIMT

2. Introduction

'Chronic neurological disorders' is a term that includes many disorders which may affect the central and peripheral nervous system, such as cerebrovascular accident or stroke, multiple sclerosis, cerebral palsy…
The World Health Organization states that stroke is the second most common cause of death worldwide [312]. Heuschmann et al. (2009) [301] estimated that the stroke incidence in Europe ranges

between 94.6 per 100,000 women and 141.3 per 100,000 males. Cerebral palsy on the other hand occurred in a mean of 2.11 per 1000 live births and multiple sclerosis has a prevalence of ≤ 20/100,000 till ≥ 200/100,000 men in Europe [328,329].
Stroke leads to death in 20% of the patients [304, 328] within the first three months, 80% of the patients survive. Of those who survive circa 40% till 80% suffer from hemiparesis six months after the stroke which has a large impact on their activities of daily living [326]. The percentage of cerebral palsy patients who suffer from hemiparesis was less than that of stroke patients and varied between 21% and 23% [329]. With people with MS a hemiparesis image is less common, however, a mean of 50 % of the MS patients suffer from impairments in the upper limb, which increase throughout the years [331,332].

The neurological disorders mentioned above may present with upper limb disability, caused by muscle weakness, loss of sensation, spasticity or coordination problems [300].
To minimize the impact of upper limb impairment and disability on the independency and quality of life in patients with a chronic neurological disorder, rehabilitation is needed. It is known that larger beneficial effects are obtained when the patient receives rehabilitation compared to patients who don't receive a rehabilitation program [306]. Throughout the years several upper limb rehabilitation strategies have been developed and investigated. The efficacy of rehabilitation strategies like the Bobath concept [307], task-oriented training [308], mirror therapy [309], robot-assisted therapy [310], constrained induced movement therapy [311], … have already been investigated.
Not only the intervention content is important, also the dose of the intervention may have an influence on neural plasticity after brain damage, as mentioned in Kleim et al. (2008) [316].

In recent years, the influence of different doses of rehabilitation in motor outcomes has been studied more and more. [41,121,126,318,320,321]. Three concepts need to be clarified: dose, frequency and duration. They are described in the following ways. Dose is 'The total amount of activity performed during the training period' [187]. Frequency is 'the number of sessions per day or per week' [126]. The duration is described as 'the time period, in days or weeks, over which the intervention is delivered' [126]. A lot of research studies use different doses of rehabilitation in chronic neurological disorders. However, most recent dose-response research has been focused on stroke patients. The optimal dose, however, remains till present unclear according to a study conducted by Lang et al. (2016) [126].

In general researchers described that the mean therapeutic session time for stroke patients ranged from 24 to 64 minutes. However, of that therapy time a mean of 0.7-7.9 minutes were spent on upper limb training per session in acute stroke patients [314,315]. It is possible that the mean therapy time is too short to achieve functional improvements. [314]. Not only therapy time, but also the intensity of the training is important. Dejong et al. (2011) suggest that the speed of a movement can be an important factor for the intensity of the rehabilitation. A higher speed can lead to more repetitions, which can influence motor outcomes [47].

In general, it is stated that longer therapy time results in better motor outcomes [126,317,318,319]. This general statement is confirmed by large systematic reviews that found significant improvements on Barthel index (BI), Motricity Index (MI), knee extension and flexion torque and hand strength in acute, subacute and chronic patients. [41,121,321]. Peiris et al. (2011) [320] even found a significant reduction in time of hospitalization in favor of the high dose therapy in acute stroke patients.

These results are contrary with research that only focused on the influence of a high dose of upper limb rehabilitation. A higher dose of upper limb therapy had no significant improvement in the Action Research Arm Test (ARAT), Rivermead Mobility Assessment (RMA) Score and Brunnstrom Fugl-Meyer Fugl-Meyer assessment (BFMA) [40,121,320]. However, studies that focused on balance and lower limb rehabilitation found small till moderate significant improvements in favor of the high dose of therapy on functional outcomes measurements like the BI index, Motricity Index (MI) and walking speed. [40,121,321].

On the other hand, for the upper limb it is still unclear whether a higher dose of therapy leads to a better motor improvement compared with a low dose of therapy [121,320,321].

Therefore, this systematic review will give a survey of the current evidence for the use of a high dose of upper limb therapy. This systematic review aims to investigate the dose dependent effects of upper limb rehabilitation in acute, subacute and chronic neurological patients.

3. Methods

3.1 Research question

The aim of this systematic review is to answer the following research questions:

- What are the dose dependent effects of upper limb rehabilitation in chronic neurological patients?

3.2 Literature search

To answer the research questions, the databases PubMed and Web of science (WOS) were searched using the following four categories: (1) keywords which include chronic neurological diseases, (2) keywords which refer to the upper extremity, (3) keywords which describe rehabilitation dose, and (4) keywords which refer to physical rehabilitation.

These categories were combined using the boolean operator ‘AND’. The keywords within the different categories were combined using the boolean operator ‘OR’. The boolean operator ‘NOT’ was used to avoid medication therapy, electrical therapy and deep brain stimulation as a result. No restriction on publication date was used.

The following search strategy was conducted in **Pubmed**:
Stroke [Title/abstract] OR Cerebrovascular accident [MeSH Terms] OR Multiple sclerosis [MeSH Terms] OR cerebral palsy [MeSH Terms] AND *Upper extremity [Title/abstract] OR upper limb [Title/abstract] OR arm [Title/abstract]* AND *Rehabilitation [Title/abstract] OR Physical therapy modalities [Title/abstract] OR Exercise therapy [Title/abstract]* AND *Dose [Title/abstract] OR Amount [Title/abstract] OR Treatment intensity [Title/abstract]* NOT *Deep brain stimulation [Title/abstract] OR Electro-stimulation [Title/abstract] OR Medication [Title/abstract] OR Drug [Title/abstract]*
Articles were filtered on level of evidence in which randomized controlled trials were selected.

The following research strategy was used in **Web of Science**:
TS=(Stroke OR cerebrovascular accident OR multiple sclerosis OR cerebral palsy) AND *TS=(Rehabilitation OR physical therapy OR exercise therapy*) AND *TS=(Upper limb OR upper extremity OR arm*) AND *TS=(Dose OR intensity OR amount OR dose-response)* AND *TS=(RCT)* NOT *TS=(deep brain stimulation OR medication OR drug OR botulinum toxin OR protocol OR pilot)*

In WOS the articles were filtered on level of evidence by using the term 'RCT' as a search topic. Besides that, the terms 'protocol' and 'pilot' were used as an exclusion topic.

3.3 Selection criteria

The articles were first screened on title and abstract by using the following inclusion criteria and exclusion criteria. If there was doubt, the full text was read.
Articles were included based on following criteria:

1) the inclusion of patients with chronic neurological diseases like multiple sclerosis, Parkinson's disease, cerebrovascular accident…
2) the comparison of different doses of upper limb rehabilitation;
3) the use of English or Dutch language.

Articles were excluded based on following criteria:

1) the use of any form of medication therapy, deep brain stimulation, electrical therapy or botulinum toxin as an intervention;
2) the lack of upper limb intervention;
3) no randomized controlled study design;
4) no description of the dose of upper limb rehabilitation.

3.4 Quality assessment

Two independent researchers conducted the quality assessment using the Cochrane checklist for RCT for the assessment [333]. The Cochrane checklist for RCT consists of ten items, which were assessed with '*yes - no - unclear*. Any form of disagreement was solved by discussion between the two students. A third researcher was consulted when there was a disagreement.

3.5 Data extraction

To answer our research questions, the following data were extracted from the included articles: (1) disease characteristics, (2) days after diagnosis, (3) patient characteristics, (4) type of intervention, (5) frequency and duration of the intervention and (6) rehabilitation dose ('The total amount of activity performed during the training period', as defined by Page et al. (2012) [187], and (7) upper limb outcome measures used to evaluate pre- and post-rehabilitation effects.

4 Results

4.1 Results study selection

In total 339 articles were found after executing the search strategy in PubMed and WOS. After removing 40 duplicates, a total of 299 articles remained in PubMed (135 articles) and WOS (164 articles). After screening the 299 articles a total of 11 articles met the inclusion criteria. Figure 1 shows an overview of the selection process.

4.2 Results quality assessment

In this systematic review, 11 articles were included. Table 6 gives a detailed overview of the scores on quality of the included articles. In general, the quality of the included articles was moderate. Two articles [25,192] met less than five criteria. These articles were considered as of low quality. Four out of eleven [86,102,128,215] articles had a score between seven and eight. These articles were considered as of high quality. The concealment of allocation was blinded in seven articles [86, 102, 103, 128, 156, 212, 215] and unclear in four articles [25, 53, 192, 246]. There was no blinding of the therapist or patients in any of the articles. On the other hand, all the articles had blinded assessors. Eight out of eleven articles had groups with comparable baseline characteristics [53, 86, 102, 128, 146, 212, 215, 246], the baseline characteristics of the other three articles were unclear [25, 103, 192]. Nine out of eleven researches executed a complete follow-up or sufficient proportion of all included patients, two articles hadn't a complete follow up available [25, 192]. Thereby it was unclear in those two articles if selective loss-to-follow-up could be ruled out. All the patients in the control group and the intervention group were treated the same, except for the dose of rehabilitation. One article mentioned that there was no selective publication of results [215], this was not the case for the other ten articles.

4.3 Results data-extraction

All the articles that were included in this systematic review involved stroke patients. Table 9 gives an overview of the study characteristics and outcome measures of the included articles.

Out of eleven articles, four included only acute stroke patients [25, 53, 212, 246], three included acute-subacute stroke patients [103, 146, 192], one included only subacute stroke patients [86], two included only chronic stroke patients [101, 128] and one included acute, subacute and chronic stroke patients [215].
Most the included studies dealt with patients with severe to mild upper limb disability. [25, 103, 146, 192, 212, 215, 246] Furthermore, most the articles used the ARAT to evaluate the interventional effects on upper limb capacity [53, 86, 103, 128, 146, 192, 212, 215].
For the interventions that were mentioned: two articles used robot-assisted therapy [25,102], one article used constraint induced movement therapy (CIMT) [53], two articles used task-specific interventions for the upper limb [128,215], one article used Mobilization and Tactile Stimulation (MTS) [103] and five articles used additional standard therapy directed at the upper limb [86,146,192,212,246]. The standard therapy consists of motor relearning strategies, principles of Bobath therapy, training of functional activities, correct positioning of the affected arm, passive, active-assisted and active mobilization and strength training. [86,146,192,212,246]. Table 7 gives a detailed description of the interventions used in the included articles.

Dose dependent effects of upper limb rehabilitation in acute stroke patients
Burgar et al. (2003) [25] used robot-assisted upper limb therapy in the intervention group, the intervention group used a mirror image movement enabler (MIME) device. The MIME consisted of four modes. Three modes stimulated unilateral reaching tasks and one mode stimulated bimanual tasks training. Tasks evolved from a passive to a more active-assisted approach. Rodgers et al. (2003) and Sunderland et al. (1992) used additional standard therapy based on the principles of Bobath therapy [212,246] and Dromerick et al. (2009) [53] used CIMT.
The dose of upper limb therapy that was given in the intervention group varied between a mean of 51 minutes and a mean of 480 minutes each week. Patients received 5 days/week therapy over a period of 14 days up to six weeks. In the interventions of Dromerick et al. (2009) and Burgar et al. (2003) a physical therapist individualized the intensity of the exercises and made it progressively more difficult according to the level of recovery of the patient. Sunderland (1992) and Rodgers (2003) [212,246] did not mention how exercises were graded.
Tables 11 and 12 describe the different training parameters in the intervention and the control group for all the articles.

Not all the patients in Rodgers et al. (2003) [212] and Burgar et al. (2011) [25] tolerated the extra therapy. A total of 150 hours of therapy in Rodgers et al. (2003) [212] were not given due to illness or patients declining during the intervention period.
The additional therapy in Sunderland et al. (1992) [246] resulted in an increase of pain in the intervention group compared with the initial assessment. In contrast Dromerick et al. (2009) [53] and Rodgers et al. (2003) [212] found no group difference in pain scores.

Burgar et al. (2011) and Sunderland et al. (1992) [25,246] found a significant difference in favor of the high dose intervention group and the control group in motor recovery assessment, measured by the Functional Independence Measurement (FIM) and the Extended Motricity Index (EMI) posttreatment. Sunderland et al. (1992) [246] found a significant difference in the mild impaired group at six months assessment between the intervention group and the control group in the Motor Club Assessment (MCA), Nine-Hole Peg Test (NHPT) and the EMI in favor of the intervention group. The severe impaired group showed a trend towards a significant difference between groups. However, Dromerick et al. (2009 [53] found that the high intensity CIMT group had significant lower gain in total ARAT-score from baseline to day 90, compared with the control and low intensity CIMT. The high CIMT group had significant lower scores in the stroke impact scale (SIS) hand subscale compared with the low dose CIMT at 90 days.

Dose dependent effects of upper limb rehabilitation in acute - subacute stroke patients

Lincoln et al. (1999) and Parry et al. (1999) followed the principles of Bobath therapy [146,192], Han et al. (2011) used standard arm therapy [86] and Hunter et al. (2011) [103] used MTS therapy. MTS-therapy consists of tactile and proprioceptive stimulation executed by guided sensory exploration, massage, passive joint/soft-tissue mobilization techniques, active-assisted movement and active movements where possible.

The treatment time varied from 420 minutes per patient up to 1680 minutes per patient. The intervention period ranged from two weeks up to five weeks. The degree of exertion of the training in the intervention group was not analyzed in any of the articles. By using a subjective scale like a BORG-scale, the researchers could better have a subjective image of the intensity of the training. The training could now be very intense for one patient and too light for the other.

Half the patients in Parry et al. (1999) [192] and 20% and 14% of the patients in the QPT and APT group in Lincoln et al. (1999) [146] could not tolerate the additional therapy.

Lincoln et al. (1999) and Hunter et al. (2011) [103,146] didn't find any significant difference in motor outcomes between the intervention groups. The groups with the highest doses of therapy in Hunter et al. (2011) [103] had the greatest increased median for the MI. These differences were, however, not statistically significant. Han et al. (2013) [86] found that the groups who received the highest dose of therapy had a significant higher improvement in BFM and ARAT for two up to six weeks after intervention. Parry et al. (1999) [192] also found significant motor improvement in favor of the high dose of therapy on the RMA and ARAT post intervention, three and six weeks later by the less severe patients. No significant between group different was found in any of the severe groups of patients.

Dose dependent effects of upper limb rehabilitation in chronic stroke patients

Hsieh et al. (2012) [101] used the BI-Manu-Track which allows training of two movements patterns (forearm pronation-supination and wrist flexion-extension) using the following three modes: a passive

(mode 1), an active-passive (mode 2) and an active-active mode (mode 3). The therapy time in the high dose intervention group ranged from 90-105 min per week, spread over a period of four up to eight weeks. The intensity in the high dose intervention group in Hsieh et al. (2012) [101] was 600-800 repetitions for mode 1 and mode 2 and 150-200 repetitions for mode 3. The low dose intervention group only had half the repetitions of the high dose intervention group. Hsieh et al. (2012) reported that all the groups showed mild ratings for pain and fatigue. No between-group differences were reported. Hsieh et al. (2012) found significant improvements in favor of the high dose therapy interventions.

In Hsieh et al. (2012) the high intensive robot-assisted therapy (RT) group had significantly more gains in BFM total score than the low intensive RT group and the control group at midterm and posttreatment. A similar effect was found in the BFM distal score.

The high intensity RT group showed significant within-group improvements in the SIS-strength and SIS-activities of daily living. The low intensity group had only significant improvements in the SIS strength. The between-group differences were not significant for the SIS score in Hsieh et al. (2012) [101].

On the other hand, Lang et al. (2016) [128] found no significant differences between the high dose (300 repetitions/ session) and the low dose intervention (100 repetitions/session) groups.

One group had an individualized maximum repetitions program, they continued until they met certain criteria. Lang et al. (2016) [128] found no significant difference in favor of the high intensity intervention group in the ARAT and SIS score.

Dose dependent effects of upper limb rehabilitation in acute - subacute - chronic stroke patients

The experimental group in Ross et al. (2009) [215] received an additional one-hour session of task-specific motor training for the hand and included repetitive practice of tasks which were individualized to the functional goals of each patient five times a week over a six-week period. The control group received standard care and 10 minutes of hand therapy three times a week.

Ross et al. (2009) [215] found no significant improvement comparing the low and high dose group of therapies for the Summed Manual Muscle Test (SMMT) and the ARAT after a six-week intervention. Ross et al. (2009) [215] also found no significant effects in favor of the high dose of therapy in secondary outcome measures (Wolf motor function test (WMFT), Disability of Shoulder Arm and Hand Assessment (DSAHA) and the Canadian Occupational Performance Measure (COPM)). The intensity level of the training of the patients in the intervention group was not recorded.

5 Discussion

5.1 Reflection on the quality of the included studies

In general, the included articles were of moderate quality because of different reasons. First, blinding of the patients or therapist was not accomplished in any of the included articles as it is very difficult to blind patients and therapist in a rehabilitation context. Possibly the patients in the intervention group were more motivated to exercise, because they knew they were in the experimental group, and therefore trained harder than the patients in the control group. Secondly, in four articles [25,53,192,215] the person who randomized the patients was not blinded. The person who randomized could potentially have divided the patients not equal for certain baseline characteristics. This can cause a selection bias. Thirdly, in three articles [25,103,192] it was unclear whether the baseline characteristics of the patients were the same. If the baseline characteristics aren't the same, it is difficult to compare outcome results between the groups. Fourthly, seven out of eleven [25,86,103,146,192,215,246] mentioned they had small sample sizes. Small sample sizes reduce the statistical power of an article. The results of this systematic review have to be interpreted carefully because of these different reasons.

5.2 Reflection on the findings in function of the research questions

Dose dependent effects of upper limb rehabilitation in acute stroke patients

The dose dependent effects of upper limb rehabilitation in acute stroke patients are various. Burgar et al. (2011) and Sunderland et al. (1992) [25, 246] found significant differences on EMI and FIM-score in favor of the high dose intervention. Rodgers et al. (2003) [212] found no differences, and Dromerick et al. (2008) [53] found significant less improvement in disadvantage of the high dose CIMT-group. The results found in Burgar et al. (2011) and Sunderland et al. (1992) [25,246] are similar to results found in other systematic reviews like Kwakkel et al. (2004) and Galvin et al. (2008) [120,321]. The systematic review of Kwakkel et al. (2004) and Galvin et al. (2008) [120, 321] also found a significant increase in measurements for functional independence (BI and EADL) in acute, subacute and chronic patients. However, Kwakkel et al. (2004) and Galvin et al. (2008) [120, 321] included upper and lower limb exercises. Measurements of ADL function like the Barthel index, can increase without an improvement in the affected arm because patients learn to compensate with the unaffected arm. A possible explanation of the general limited improvements of the motor outcome measures in the high dose intervention groups, is the large variance in therapy time. The therapy time of upper limb therapy that was given in the intervention group varied between a mean of 51 minutes and 480 minutes each week.

A potential reason of the significant increase in FIM score in Burgar et al. (2011) [25] is the significant difference in age. The age of the high dose intervention group was significantly lower than the low dose-group and control group. Age has an important influence on neuroplasticity [321] due to the fact that older persons may make improvements less quickly.

On the other hand, the use of robotic technology in Burgar et al. (2011) [25] can be an external motivation. The patients in the intervention group have potentially trained harder because of the external motivation.
Dromerick et al. (2009) [53] had significant lower improvement in ARAT score in the high intensity group compared with the low intensity group. These results are contrary with systematic reviews like Langhorne et al. (1996) and Lohse et al. (2014) [317,318,] which suggest that more therapy leads to more motor improvement in the upper limb. It is possible that the dose in Dromerick et al. (2009) [53] in the high intensity group was too high early after stroke.
Lang et al (2015). [126], for example, found that a high dose of therapy early after stroke, can potentially delay the recovery process which may lead to less motor improvements [126].

Dose dependent effects of upper limb rehabilitation in acute - subacute stroke patients
The dose dependent effects of upper limb rehabilitation in acute - subacute stroke patients are relatively small. The article of Han et al. (2013) and Parry et al. (1999) [86, 192] found significant differences in ARAT and BFM scores in favor of the high dose intervention groups. In contrast, Hunter et al. (2011) and Lincoln et al. (1999) [103, 146] found no significant difference between patients receiving a high or a low dose of therapy.
Although Parry et al. (1999) and Lincoln et al. (1999) [146,192] used the same therapy duration and therapy content, they still have different results. A possible reason could be that Lincoln et al. (1999) [146] did not execute a subgroup analysis like Parry et al. (1999) [192] to correct for level of impairment.
Differences between the study results of Parry et al. (1999) and Lincoln et al. (1999) [146,192] mentioned above may also be due to different baseline characteristics of the study population.
For example, it was unclear if the baseline characteristics in the article of Parry et al. [192] were the same between groups. It is possible that the article of Parry et al. [192] had a lower mean age than the article of Lincoln et al. [146] As seen previously, age can potentially have an important role in motor outcomes [322].
Han et al. (2012) and Parry et al. (1999) [86,192] found significant differences in ARAT and BFM-scores in favor of the high dose intervention groups. The outcomes are contradictory with the results of other systematic reviews that found no significant differences in ARAT-scores [41,121,321]. The effects of the ARAT in individualized studies are possibly too low to find a general significant effect in a systematic review.

Dose dependent effects of upper limb rehabilitation in chronic stroke patients
Lang et al. (2016) [128] did not find significant between-group differences in favor of the high dose intervention group but Hsieh et al. (2012) [101] did find such a difference.
The fact that the article of Hsieh et al. (2012) [101] found significant greater improvements after high dose rehabilitation on the BFM can possibly be explained by three underlying reasons. One possible reason can be the motivational influence of robot-assisted therapy causing an increase of collaboration and effort in stroke patients.

But not only the motivational effect of robot technology can be a determining factor, also the high reproducibility of repetitions can be. Both Hsieh et al. (2012) [101] and Lang et al. (2016) [128] use a high number of repetitions. The difference between the two articles is that one [101] had twice as many repetitions in comparison with the other [128].
A third possible reason is the mean age of the study participants which is nearly 10 years younger compared with the mean age in the study of Lang et al [128]. Research suggests that neuroplasticity decreases with age and thus may influence recovery after stroke [128].
The study of Lohse et al. (2014) which investigated the dose dependent effects of upper limb rehabilitation in chronic stroke patients, found small significant upper limb motor effects in favor of a high dose intervention [317].
The reason why Lang et al. (2016) [128] found no significant between-group differences can be explained by several possible reasons. As mentioned previously, the mean age in these two articles is approximately 10 years higher. Besides that, there is a large heterogeneity within the groups, such as time post stroke. As discussed previously, it is possible that the time after stroke may have an influence on the motor results [126].

Dose dependent effects of upper limb rehabilitation in acute - subacute - chronic stroke
The dose dependent effects of upper limb rehabilitation in favor of high dose in acute – chronic stroke patients are uncertain.

Ross et al. (2009) [215] found no significant between-group differences neither in primary outcome measures (ARAT, SMMT) nor in secondary outcome measures (WMFT, DSAHA , COPM). A first possible explanation is the small sample size that is used. Thereby there is heterogeneity in time post stroke which may influence the outcome.

Furthermore, the small difference in dose between the control group and the intervention group can be a possible reason why the intervention group didn't have better outcomes than the control group. Besides the influence of the dose of therapy, the intervention itself can be a possible cause of the poor results. In this article, the intervention group received an additional session which only focused on the hand. A proper shoulder function is needed for a proper hand function. It is possible that specific focus on hand without shoulder training limited the rehabilitation.

Lastly, also the use of the ARAT and WMFT can be questioned because of the possible floor effects [215]. Twelve of the included patients attained 0 on the ARAT at the baseline measures and in the end of the trial. Although these patients could have made some progress in hand function during the intervention the ARAT isn't perhaps sensitive enough to measure this small evolution.

5.3 Reflection on the strengths and weaknesses of the literature study

A limitation of this systematic review is that the included articles are only based on two databases. Possibly, some articles were missed. However, this chance will be rather small because of the large number of articles in PubMed and web of science. Although chronic neurological diseases were entered as a key word in the search none of the included articles investigated the effects in other chronic neurological pathologies than stroke. The articles analyzed in this systematic review had a large heterogeneity in baseline characteristics of the patients and rehabilitation techniques. These variances impede a comparison between the different articles and making a general conclusion about specific techniques in a specific population. A major strength of the study was the inclusion of the results in severe and less severe patients which increases the generalisability of the results.

5.4 Recommendations for further research

Future research should focus more on specific subgroups of stroke patients. It is possible that time after stroke and severity of the impairment can influence motor recovery. Dividing the patients in different treatment groups according to these factors will lead to a higher clarification of the optimal effect of the therapeutic interventions.

Larger RCTs with high quality are needed. However, it is hard to blind patients or therapists in a rehabilitation context. Most articles compare a high dose intervention group with a dose matched control group. It is recommended to compare different doses of the same therapy with each other to find the optimal dose of therapy.

Only six articles [25, 101, 146, 192, 212, 246] measured pain or fatigue in the high dose intervention group. If more articles are going to compare different doses of rehabilitation it's recommended to measure fatigue or pain. Furthermore, it is important to obtain results of the long-time effects of the intervention. Only six out of eleven articles in this systematic review [25, 53, 101, 128, 146, 212] used a follow-up. It is important in the future that more articles use a follow-up period after the intervention. It is possible that the intervention time was too short to achieve significant improvements but the Intervention time can't be increased repeatedly because not all the patients can tolerate a large additional therapy time.

6 Conclusion

The dose dependent effects of upper limb rehabilitation in acute, subacute and chronic stroke patients are various whereby only small significant effects are obtained in favor of high dose interventions.

7 List of references

Included articles are marked with (*).
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8 Appendices part 1

Figure 1: Flowchart of literature search and article selection.

Table 1: List of abbreviations
Table 2: Definitions of training parameters
Table 3: Keywords, combinations and hits in PubMed
Table 4: Keywords, combinations and hits in WOS
Table 5: Overview of excluded articles and reasons of exclusion
Table 6: Cochrane checklist for quality assessment.
Table 7: Description of the interventions in the included articles
Table 8: Strengths and limitations of the included articles.
Table 9: Overview of the study characteristics and outcome measures of the included articles
Table 10.1 Overview of the effects after intervention: 1 intervention group vs. 1 control group
Table 10.2: Overview of the effects after intervention: 2 intervention groups vs. 1 control group
Table 10.3: Overview of the effects after intervention: 3 intervention groups vs. 1 control group
Table 10.4: Overview of the effects after intervention: 3 intervention groups vs. no control group
Table 11: Training parameters intervention group
Table 12: Training parameters control group

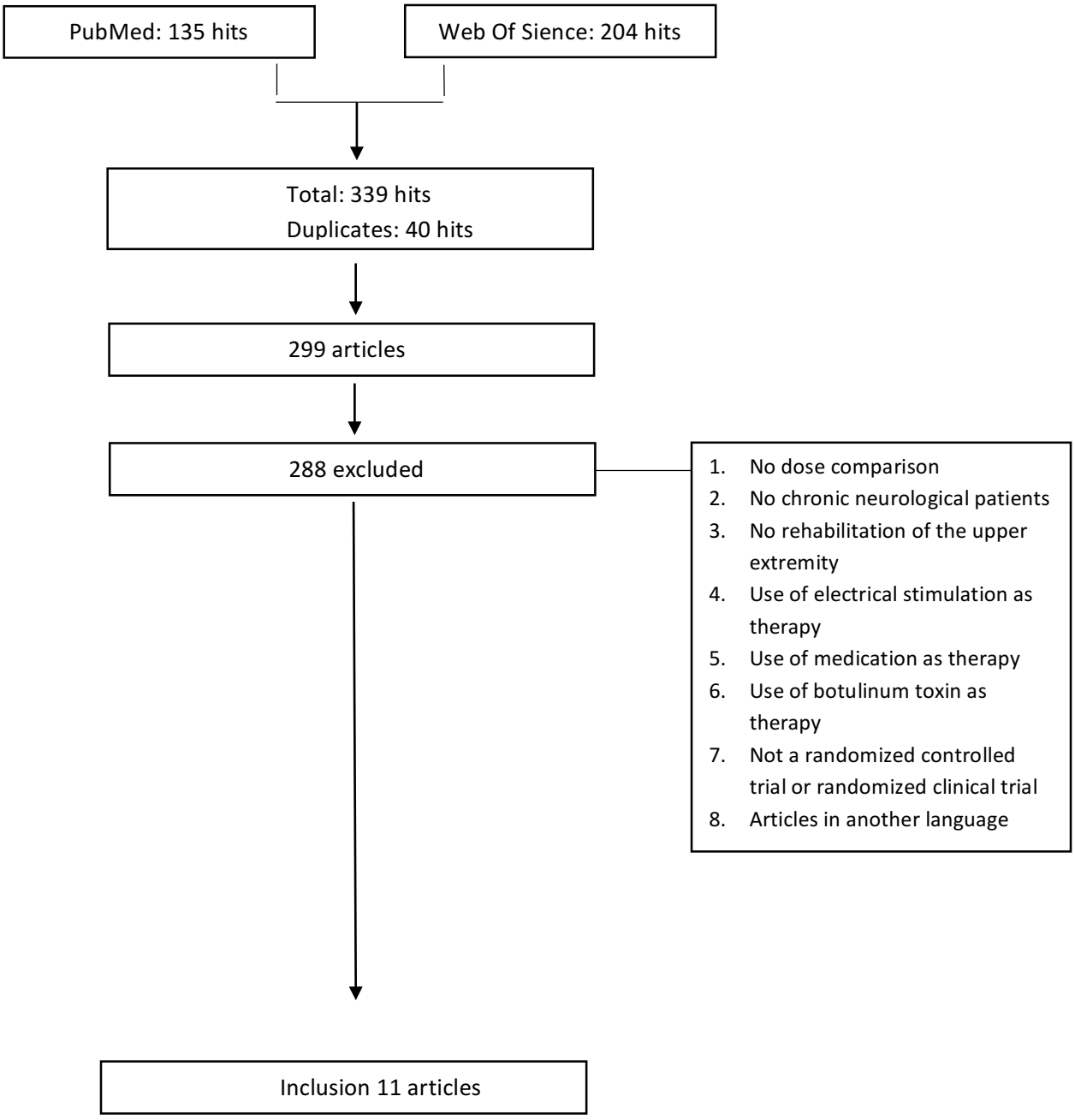


Figure 1: Flowchart of literature search and article selection

Table 1: List of abbreviations

A	Activity (ICF)
ADL	Activities of daily living
APT	Assistant physiotherapy
ARAT	Action research arm test
AQoL	Australian Quality of Life
BI	Barthel Index
CIMT	Constrained induced movement therapy
COPM	Canadian occupational performance
DSAHA	Disability of shoulder, arm and hand assessment
EMI	Extended motricity index
F	Function (ICF)
FAC	Functional ambulation classification
FIM	Functional independence measure
FMA	Fugl-Meyer assessment
IM	Individualized maximum
OHS	Oxford handicap scale
LACI	Lacunar infarct
LBST	Learning-based sensorimotor training
LOS	Length of Stay
MAL	Motor activity log
MAL-AOU	Motor activity log – amount of use
MAL-QOM	Motor activity log – quality of movements
MAS	Modified Ashworth scale
MCA	Motor club assessment
MCIMT	Modified constraint induced movement therapy
MI	Motricity index
MIME	Mirror image movement enabler
MMSE	Mini-mental state examination
MRC	Medical research council
MTS	Mobilisation and tactile stimulation
NHPT	Nine hole peg test
NIHSS	National Institutes of Health Stroke Scale
PACI	Partial anterior circulation infarct
POCI	Posterior circulation infarct
RMA	Rivermead motor assessment
RT	Robot therapy
SMMT	Summed manual muscle test
TACI	Total anterior circulation infract
THPT	Ten-hole peg test
QPT	Qualified physiotherapist
WMFT	Wolf motor function test

Table 2: Definitions of training parameters

Dose	'The total amount of activity performed during the training period (Page et al., 2012, p. 4) [187].
Frequency	'Number of sessions per day or per week' (Lang et al. 2015, p3)
Duration	'The time period, in days or weeks, over which the intervention is delivered.' (Lang et al. 2015, p3)
Amount	'The number of repetitions' (Lang et al 2015, p3)
Number of active therapy	'The amount of time a person is active during each therapy session' (Host et al. 2014, p3)
Total number of sessions	The total amount of therapy sessions followed by the patient.
Total therapy hours	The total amount of hours of therapy followed by the patient.
Dose-response	The pattern of physiological response to varied dosage https://www.merriam-webster.com/medical/dose-response

Table 3: Keywords, combinations and hits in PubMed

#	Keywords in the search bar	January 2017	May 2017
#1	Stroke [Title/abstract]	183.307	189.826
#2	Cerebrovascular accident [MeSH Terms]	103.226	105.224
#3	Multiple sclerosis [MeSH Terms]	49.580	50.000
#4	cerebral palsy [MeSH Terms]	17.699	17.870
#5	Y = stroke OR cerebrovascular accident OR multiple sclerosis OR cerebral palsy	282.102	289.446
#6	upper extremity [Title/abstract]	16.071	16.550
#7	upper limb [Title/abstract]	14.390	14.861
#8	arm [Title/abstract]	114.907	118.432
#9	X = upper extremity OR upper limb OR arm	138.934	143.201
#10	Rehabilitation [Title/abstract]	129.342	133.119

#11	Physical therapy modalities [Title/abstract]	225	245
#12	Exercise therapy [Title/abstract]	3.520	3.627
#13	X = rehabilitation OR physical therapy modalities OR exercise therapy	1.310.350	136.221
#14	Dose [Title/abstract]	946.602	966.549
#15	Amount [Title/abstract]	390.189	398.459
#16	Treatment intensity [Title/abstract]	945	987
#17	X = dose OR amount OR treatment intensity	1.313.600	1.338.137
#18	Deep brain stimulation [Title/abstract]	7.742	8.106
#19	Electro-stimulation [Title/abstract]	202	208
#20	Medication [Title/abstract]	165.741	170.867
#21	Drug [Title/abstract]	944.983	971.401

#22	NOT = deep brain stimulation OR electro-stimulation OR medication OR drug	1.083.537	1.114.319
#23	Stroke [Title/abstract] OR Cerebrovascular accident [MeSH Terms] OR Multiple sclerosis [MeSH Terms] OR cerebral palsy [MeSH Terms] AND upper extremity [Title/abstract] OR upper limb [Title/abstract] OR arm [Title/abstract] AND Rehabilitation [Title/abstract] OR Physical therapy modalities [Title/abstract] OR Exercise therapy [Title/abstract] AND Dose [Title/abstract] OR Amount [Title/abstract] OR Treatment intensity [Title/abstract] NOT Deep brain stimulation [Title/abstract] OR Electro-stimulation [Title/abstract] OR Medication [Title/abstract] OR Drug [Title/abstract] Filter: randomized controlled trial	135	

Table 4: Keywords, combinations and hits in WOS

#	Keywords in the search bar	January 2017	May 2017
#1	TS=(stroke)	259.595	266.094
#2	TS=(cerebrovascular accident)	5.678	5.781
#3	TS=(multiple sclerosis)	102.529	104.754
#4	TS=(cerebral palsy)	24.988	25.569
#5	TS=(stroke OR cerebrovascular accident OR multiple sclerosis OR cerebral palsy)	381.226	394.450
#6	TS=(upper extremity)	23.937	24.521
#7	TS=(upper limb)	28.318	29.017
#8	TS=(arm)	226.704	231.718
#9	TS=(upper extremity OR upper limb OR arm)	261.192	270.097
#10	TS=(rehabiliation)	155.065	159.386
#11	TS=(physical therapy)	56.616	58.416
#12	TS=(exercise therapy)	32.381	33.206

#13	TS=(rehabilitation OR physical therapy OR exercise therapy)	220.368	260.814
#14	TS=(dose)	1.085.709	1.106.055
#15	TS=(amount)	1.080.414	1.105.346
#16	TS=(treatment intensity)	79.758	82.009
#17	TS=(dose response)	59.412	268.803
#18	TS=(dose OR amount OR treatment intensity OR dose response)	2.815.372	2.229.945
#19	TS=(RCT)	344.453	14.597
#20	TS=(deep brain stimulation)	15.326	15.748
#21	TS=(electrical stimulation)	65.365	66.287
#22	TS=(medication)	216.750	223.526
#23	TS=(drug)	1.381.223	1.414.220
#24	TS=(botulinum toxin)	18.980	19.293
#25	TS=(protocol)	502.084	516.638

#26	TS=(pilot)	197.180	202.843
#27	TS=(deep brain stimulation OR electrical stimulation OR medication OR drug OR botulinum toxin OR protocol OR pilot)	2.262.921	1.000.656
	#5 AND #9 AND #13 AND 18 AND #19 NOT #27	204	

Table 5: Overview of excluded articles and reason of exclusion

#	Reason for exclusion	Number of studies	Author and year
1	No dose comparison	127	Abdollahi et al. (2014) Almhdawi et al. (2016) Arya et al. (2012) Ballinger et al. (1999) Bleyenheuft et al. (2015) Birkenmeier et al. (2010) Boake et al. (2007) Brandao et al. (2014) Brunner et al. (2016) Chang et al. (2015) Chatterjee et al. (2016) Chen et al. (2012) Chen et al. (2014) Chen et al. (2015) Connell et al. (2014a) Connell et al. (2014b) Connell et al. (2014c) Connell et al. (2016) Dahl et al. (2008) de Bode et al. (2007) DeJong et al. (2012) Donaldson et al. (2009) Dromerick et al. (2006) Dromerick et al. (2009) English et al. (2007) Fan et al (2016) Feys et al. (2004) Fleming et al. (2014)

			Fluet et al. (2015) Fraile et al. (2016) Franceschini et al. (2012) Gauthier et al. (2008) Giuffrida et al. (2008) Globas et al. (2011) Green et al. (2012) harris et al. (2009) Harris et al. (2010) Haworth et al. (2009) Hayne et al. (2010) Horne et al. (2015) Housman et al. (2009) Hunter et al. (2008) Huseyinsinoglu et al. (2012) Hwang et al. (2012) Imms et al. (2015) In et al. (2012) Ishida et al. (2011) James et al. (2015) Kitago et al. (2015) Krawczyk et al. (2012) Kwakkel et al. (1999) Kwakkel et al. (2002) Kwon et al. (2012) Lang et al. (2007) Lang et al. (2009) Lang et al. (2013) Lee et al. (2012) Lee et al. (2013) Lemmens et al. (2014)

			Li et al. (2012) Liao et al. (2012) Lima et al. (2014) Lin et al. (2008) Lin et al. (2009) Lin et al. (2011) Luft et al. (2004) Lum et al. (2005) Lum et al. (2006) Masiero et al. (2007) Masiero et al. (2014) Massie et al. (2009) McCombe Waller et al. (2008) McNulty et al. (2015) Morris et al. (2008) Myint et al. (2008a) Nef et al. (2007) Page et al. (2005) Page et al. (2011) Page et al. (2012) Page et al. (2012) Pang et al. (2006) Platz et al. (2009) Ploughman et al. (2008) Prange et al. (2015a) Renner et al. (2016) Ross et al. (2016) Rostami et al. (2012) Schaefer et al. (2013) Schweighofer et al. (2009) Severinsen et al. (2014) Sevick et al. (2016)

			Shim et al. (2015) Shin et al. (2015b) Shin et al. (2016) Slijper et al (2014) Smania et al. (2009) Smania et al. (2012) Subramanian et al. (2013) Taub et al. (2004) Thielbar et al. (2014) Timmermans et al. (2014) Trammell et al. (2017) Tyson et al. (2015) Underwood et al. (2006) van Delden et al. (2013) van Delden et al. (2015) van der Lee et al. (1999) van der Lee et al. (2004) Verbunt et al. (2008) Vural et al. (2016) Wang et al. (2013) Whitall et al. (2011) Winstein et al. (2016) Wolf et al. (2006) Wolf et al. (2009) Wolf et al. (2014) Wolf et al. (2015) Wolfe et al. (2000) Wu et al. (2007a) Wu et al. (2007b) Wu et al. (2011) Wu et al. (2012)

			Wu et al. (2013) Yates et al. (2016) Zondervan et al. (2015) Zondervan et al. (2016)
2	No chronic neurological patients	54	Azizi et al. (2014) Azoulay et al. (2004) Barakat et al. (2006) Brodin et al. (1990) The Choroidal Neovascularization Prevention Trial Research Group. (1998) Coviello et al. (2001) Crosby et al. (1993) Dackis et al. (2012) Edwards et al. (1994) Einsiedel et al. (2005) Engert et al. (2010) Faulhaber-Walter et al. (2009) Ferguson et al. (2015) Fey et al. (2013) Foley et al. (2012) Freyer et al. (2011) Fu et al. (2015) Gadner et al. (2008) Harley et al. (1979) Hatschek et al. (1993) Hendriks et al. (2011) Herpertz-Dahlmann et al. (2014) Katz et al. (2011) Kurtz et al. (2009)

			Le et al. (2015) Lennard et al. (2015) Leon et al. (2005) Long et al. (2000) Lysaker et al. (2009) Mancia et al. (2014) Masmiquel et al. (2016) Monnikes et al. (2013) Mouncey et al. (2015) Mouncey et al. (2015) Muench et al. (2007) Noll et al. (1997) O'Connor et al. (2014) Parsons et al. (2012) Pellegrini et al. (2014) Penno et al. (2013) Pui et al. (2009) Rittenhouse et al. (1990) Rosenblum et al. (1999) Ryan et al. (2006) Sherwood et al. (2016) Stergiopoulos et al. (2015) Thoolen et al. (2006) Timko et al. (2004) van der Werf et al. (2015) Van Eys et al. (1989) Vora et al. (2013) Woynaroski et al. (2014) Wyllie et al. (2006) Zandsteeg et al. (2009)

3	Electrical stimulation	6	Ackerley et al. (2016) Hsu et al. (2010) Kwakkel et al. (2015) Rofes et al. (2013) Shen et al. (2015) Shindo et al. (2011)
4	Studies which use medication	3	Meythaler et al. (1999) Nadeau et al. (2004) Schuster et al. (2011)
5	No rehabilitation of the upper extremity	13	Alterman et al. (2001) Baumgaertner et al. (2013) Braun et al. (2007) Britton et al. (2008) English et al. (2015) Godecke et al. (2016) Harvey et al. (2011) Lindgren et al. (2012) Lohse et al. (2016) Morone et al. (2014) Page et al. (2007) Tang et al. (2014) van Vliet et al. (2005)
6	Use of botulinum toxin as a therapy	4	Gracies et al. (2014) Kaji et al. (2010) Meythaler et al. (2009) Wolf et al. (2012)
7	Not an RCT	80	Albert et al. (2012) Anttila et al. (2008) Brauer et al. (2013) Breceda et al. (2013)

			Brosseau et al. (2006) Brunner et al. (2014) Byl et al. (2008) Casadio et al. (2013) Chang et al. (2013) Chiu et al. (2016) Ciccone et al. (2013) Cooke et al. (2010) Dennis et al. (2012) Dobkin et al. (2007) Dobkin et al. (2009) Farmer et al. (2014) Foley et al. (2012) Forrester et al. (2008) French et al. (2007) French et al. (2008) Galvin et al. (2008) Hammer et al. (2009) Hayward et al. (2014) Hillier et al. (2011) Hsieh et al. (2011) Iruthayarajah et al. (2017) Knols et al. (2016) Kwakkel et al. (2004) Kwakkel et al. (2006) Kwakkel et al. (2015) Lang et al. (2015) Langhorne et al. (2009) Laver et al. (2011) Laver et al. (2015) Lima et al. (2014) Linder et al. (2013)

			Marchal-Crespo et al. (2009) McIntyre et al. (2012) Mehrholz et al. (2008) Mehrholz et al. (2012a) Mehrholz et al. (2012b) Motl et al. (2013) Nijland et al. (2011) Norouzi-Gheidari et al. (2012) Rand et al. (2015) Page et al. (2004) Page et al. (2005) Pidcock et al. (2009) Pinter et al. (2012) Platz et al. (2003) Pollock et al. (2014) Pomeroy et al. (2005) Pomeroy et al. (2006) Puh et al. (2013) Rabadi et al. (2011) Reid et al. (2015) Schneider et al. (2016) Scrivener et al. (2015) Sheehan et al. (2006) Sheehy et al. (2016) Shi et al. (2011) Siegert et al. (2004) Sirtori et al. (2009) Sivan et al. (2014) Stevenson et al. (2012) Teasell et al. (2004) Teasell et al. (2006) Thrane et al. (2014)

			Timmermans et al. (2010) Toh et al. (2012) van Delden et al. (2012) van der Lee et al. (2001) Vinas-Diz et al. (2016) Vloothuis et al. (2016) Winstein et al. (2013) Winstein et al. (2016) Wolf et al. (2014) Wu et al. (2012) Yoo et al. (2016) Zimmermann-Schlatter et al. (2008)
8	Articles in another language than English	2	Fazekas et al. (2016) Shimodozono et al. (2013)

Table 6: Cochrane checklist for quality assessment

Author and year	Score	Study design	Cochrane checklist items									
			Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10
Burgar et al. (2011)	4/10	RCT	Y	U	N	Y	U	U	U	Y	U	Y
Dromerick etl. (2009)	5/10	RCT	Y	U	N	Y	Y	Y	U	Y	U	U
Han et al. (2013)	8/10	RCT	Y	Y	N	Y	Y	Y	Y	Y	U	Y
Hsieh et al. (2012)	7/10	RCT	Y	Y	N	Y	Y	Y	Y	Y	U	U
Hunter et al. (2011)	6/10	RCT	Y	Y	N	Y	U	Y	U	Y	U	Y
Lang et al. (2016)	7/10	RCT	Y	Y	N	Y	Y	Y	Y	U	U	Y
Lincoln et al. (1999)	5/10	RCT	Y	Y	N	Y	Y	Y	U	U/N	U	U
Parry et al. (1999)	4/10	RCT	Y	U	N	Y	U	N/U	U	Y	U	U
Rodgers et al. (2003)	5/10	RCT	Y	Y	N	Y	Y	Y	U	U	U	U
Ross et al. (2009)	8/10	RCT	Y	Y	N	Y	Y	Y	Y	U	Y	Y
Sunderland et al.(1992)	5/10	RCT	Y	U	N	Y	Y	Y	U	Y	U	U

Item 1: Was the application of the patients to the intervention randomized?
Item 2: Was the person who randomised the patients blinded?
Item 3: Were the patients and the therapist blinded for the intervention?
Item 4: Were the outcome assessors blinded for treatment?
Item 5: Were the groups at baseline comparable?
if the answer was no: Was this corrected in the analyzes?
Item 6: Was there a complete follow-up available from a sufficient proportion of included patients?

if the answer was no: could selective loss to follow-up be / have been excluded?
Item 7: Were all the included patients analysed in the group in which they were randomised?
Item 8: Were the groups treated the same way, except for the intervention.?
Item 9: Was selective publication of results sufficiently excluded?
Item 10: Was undesirable influence of sponsoring sufficiently excluded?

Table 7: description of the interventions in the included articles

Author and year	Treatment of the intervention group(s)	Treatment of the control group
Burgar et al. (2011)	- High robot assisted group: received 30 one-hour sessions over a 3-week period of the mirror image movement enabler (MIME) device - Low robot assisted group: received 15 one-hour therapy sessions over a 3-week period of the mirror image movement enabler (MIME) device The MIME consisted of four modes. Three modes stimulated unilateral reaching tasks and one mode stimulated bimanual tasks training. Tasks were progressively made more difficult. The tasks went from a passive to a more active-assisted approach.	The control group received 15 hours of additional conventional therapy in addition to usual care. The 5-minute preparatory and terminal segments of each session were identical in all three groups.
Dromerick et al. (2009)	- Standard constraint induced movement therapy (CIMT): consisted of two hours of sham therapy and the patients wore a padded constraint mitten for six hours a day. - High intensity CIMT: received two hours sham therapy, but they wore the padded constraint mitten for 90% of waking hours. The intervention duration was five days/week for two weeks.	The control group received five days/week for two weeks traditional occupational therapy: - 1 hour of ADL training - ROM training - Strength training - 1 hour of upper extremity bilateral training
Han et al. (2013)	All patients received regular rehabilitation therapy and medical treatment. The content of the arm treatment was determined by a motor relearning program. - Group A received one hour of arm treatment a day - Group B received two hours of arm treatment a day - Group C received three hours of arm treatment a day. They were treated for five days a week for a period of six weeks. The arm training included correct positioning and caring of the arm, passive, assisted and active movements, strength training and practice of functional activities.	No control group was used.
Hsieh et al. (2012)	- High-intensity robot assisted therapy group practiced 600 to 800 repetitions of mode 1 and 2 for 15 to 20 minutes and 150 to 200 repetitions of mode 3 for 3 to 5 minutes.	The control group received an intensive therapist administered control therapy matched in duration. Occupational therapy techniques included: neuro-development treatment, strength training, fine-motor training and functional task training.

	- Low intensity robot assisted therapy group practiced 300 to 400 repetitions of mode 1 and 2 for 15 to 20 minutes and 75 to 100 repetitions of mode 3 for 3 to 5 minutes. Patients in the intervention groups practiced with the BI-Manu-Track. The BI-Manu-Track allows two movements patterns, forearm pronation-supination and wrist flexion-extension. There are three modes in the device. A passive (mode 1), active-passive (mode 2) and an active-active mode (mode 3). Before the patients started to exercise in the intervention group, a warm-up was done for 5 minutes. After the training, patients received 15 to 20 minutes of functional activities training. The therapy was given five days a week for 4 weeks.	
Hunter et al. (2011)	All of the experimental groups received mobilization and tactile stimulation (MTS) therapy in a different dose. MTS-therapy consisted of the provision of tactile and proprioceptive stimulation through actions such as guided sensory exploration, massage, passive joint/soft-tissue mobilization techniques, active-assisted movement and active movements where possible. -Group 2 received 30 minutes per day spread over 14 days in addition with conventional therapy -Group 3 received 60 minutes per day spread over 14 days in addition with conventional therapy -Group 4 received 120 minutes per day spread over 14 days in addition with conventional therapy	The control group received conventional physical therapy with no additional treatments spread over 14 days.
Lang et al. (2016)	The patients were divided into four groups of task-specific upper limb training. The patients practiced functional exercises. The exercises consisted of four components: reaching, grasping, moving/manipulating and releasing an object. - Group 1 received a maximum of 100 repetitions during 1-hour sessions - Group 2 received a maximum of 200 repetitions during 1-hour sessions - Group 3 received a maximum of 300 repetitions during 1-hour sessions - Group 4 received individualized maximum (IM) repetitions during 1-hour sessions	No control group was used.

Lincoln et al. (1999)	The patients in the intervention group received two hours of additional therapy per week. - The qualified-physiotherapist (QPT) group received standard physiotherapy and 2-hours/week additional therapy by a senior research physiotherapist. - The assistant-physiotherapist (APT) group received standard physiotherapy and 2-hours/week additional therapy by a physiotherapist assistant. - The routine-physiotherapist group received standard physiotherapy which included Bobath therapy for 30-45 minutes a day.	No control group was used.
Parry et al. (1999)	-The qualified physiotherapist group received 10 additional treatment hours from a qualified physiotherapist spread over 5 weeks. -The assistant physiotherapist group received 10 additional treatment hours from a trained assistant spread over 5 weeks. - The routine physiotherapist group received no additional physiotherapy. The intervention was based on the Bobath approach	No control group was used.
Rodgers et al. (2003)	Patients in the intervention group received stroke unit care plus 30 minutes of enhanced upper limb rehabilitation five days/week for six weeks.	The control group received stroke unit care.
Ross et al. (2009)	The experimental group received an additional one-hour session of task-specific motor training for the hand and included repetitive practice of tasks which were individualized to the functional goals of each patient five times a week over a six-week period. Usual arm care consisted of half an hour of motor training for the shoulder and elbow five times a week.	The control group received standard care and 10 minutes of hand therapy three times a week.
Sunderland et al. (1992)	The therapy used in the intervention group consisted of Bobath therapy, EMG biofeedback, micro-computer games, goal-setting and behavioural methods to encourage the patient to use the affected arm. The intervention group received a median of 51 minutes of arm therapy per week.	The control group followed a median of 21 minutes of arm therapy per week.

Table 8: Strengths and limitations of the included articles

Author and year	Strengths	Limitations
Burgar et al. (2011)	- Random group allocation - Outcome raters were blinded - Therapists were blinded - Project staff was trained before the study took place - Comparable baseline measurements with exception of age - Use of different doses - Follow-up (six months)	- Due to significant differences in age, outcomes can be affected - It is possible that subjects did not remain blinded - Relatively small sample - Variation in severity level - Overlap in dose between high intensity group and low intensity group - No clear difference between high- and low-dose groups - High drop-out rate after six months follow-up
Dromerick et al. (2009)	- Random group allocation - Rater blinding - Sample size (n = 52) - Trained raters - Comparable baseline measurements - Use of protocols - Use of different doses - Follow-up (14 days and three months after intervention)	- Possibility of overtraining - Blocked practice schedule - Extra time spent by the high-intensity CIMT group may have interfered with motor learning
Han et al. (2013)	- Random group allocation - Assessor blinding - Measurement of motor function and activities of daily living - Follow-up (two weeks, four weeks, and six weeks after intervention) - Comparable baseline measurements - Use of different doses	- Small sample size - No measurements immediately after treatment - No long-term study - Same intensity of ADL-training in all groups
Hsieh et al. (2012)	- Random group allocation - Rater blinding - Sample size (n = 54) - Follow-up - Use of a protocol - Comparable baseline measurements - Use of different doses	- Unclear when follow-up took place - No evaluation of sensory function - No blinding of participants and intervention providers - Only one intermediate assessment was conducted

Hunter et al. (2011)	- Random group allocation - Assessor blinding - Comparable baseline measurements - The study used multiple groups with different doses. - Group allocation done by an independent researcher - Measurements batteries for ICF-function and activity level.	- There is no comparison in outcome between the intervention groups -The sample was relative small (possibility underpowered) - Delivered less rehabilitation time in the intervention groups than expected. - Only two outcome measurements (ARAT and MI) - ARAT possibly unsuitable to evaluate effectiveness of different approaches to stroke rehabilitation - No follow-up
Lang et al. (2016)	- Random group allocation - Assessor blinding - Comparable baseline measurements - Group allocation done by a computer program - Follow-up (two months) - The study used multiple groups with different doses.	- No measurements on ICF function level - ARAT possibly unsuitable to evaluate effectiveness of different approaches to stroke rehabilitation
Lincoln et al. (1999)	- Assessor blinding - Group allocation done by a computer program - Comparable baseline measurements - Random group allocation - Measurements batteries for ICF-function and activity level. - Follow-up (three and six months)	- About half of the QPT and APT patients did not complete 10 hours of additional treatment - The intensity of the extra therapy was possibly too low. - The sample size may have been insufficient to detect small but statistically significant changes. - ARAT possibly unsuitable to evaluate effectiveness of different approaches to stroke rehabilitation
Rodgers et al. (2003)	- Random group allocation - Assessor blinding - Comparable baseline measurements - Follow-up (3 and 6 months after stroke) - Measurements batteries for ICF- function and activity level. - Randomization was done by an independent telephone computerized service - Measurements batteries for ICF function and activity level. - Divided patients in different groups according to arm function	- The control group received more unidisciplinary rehabilitation and more therapy assistant time. This can lead to a competitive therapy bias. - ARAT possibly unsuitable to evaluate effectiveness of different approaches to stroke rehabilitation -The intensity of the extra therapy was possibly too low - A total of 150 hours (2.5 per patient) were not given due to illness or patients declining during the intervention period - The provision of the intervention by a single physiotherapist and a single occupational therapist reduces the generalizability of the results.
Ross et al. (2009)	- Random group allocation - Assessor blinding	- The intervention focused specifically on hand training

	- Comparable baseline measurements - Measurements batteries for ICF function and activity level. - Group allocation done by a computer program	- ARAT possibly unsuitable to evaluate effectiveness of different approaches to stroke rehabilitation - The standard care provided already half an hour motor training for the shoulder and elbow five times a week. - No follow-up - A much larger sample size than estimated was required to provide a definitive answer to the research question.
Parry et al. (1999)	- Random group allocation - Assessor blinding - Divided patients in two groups (severe and less severe) according to their score on the RMA arm scale - Measurements batteries for ICF function and activity level.	- Unclear if baseline outcome measurements where the same in the groups - No table of biographical characteristics and pre-intervention motor outcomes. - The method used for randomization is unknown - The study used older techniques of upper limb rehabilitation (Bobath) - Unclear if the sample (n=186) was large enough to detect small significant changes (not mentioned in article) - Only half of the patients tolerated all the additional rehabilitation - No follow up - ARAT possibly unsuitable to evaluate effectiveness of different approaches to stroke rehabilitation
Sunderland et al. (1992)	- Random group allocation - Assessor blinding - Comparable baseline measurements - Divided patients in different groups according to arm function - Measurements batteries for ICF-function and activity level	- The study used older techniques of upper limb rehabilitation (Bobath and Johnstone) - It is unknown if the person who randomly allocated the patients was aware of the randomization order. - The control group received addional physiotherapy every week. - The study needed 160 patients to have a 90% chance of detecting a 20% improvement in outcome. The study only included 132 patients. - Unknown how much therapy was given each day. - No follow up

Table 9: Overview of the study characteristics and outcome measures of the included articles

Author and year	Study design	Study population			Aim of the study	Outcome measure		
		Details	Baseline ARAT	n		F	A	Other
Burgar et al. (2011)	RCT	Acute stroke Days post stroke: Robot-Lo 17.3 ± 2.7 Robot-Hi 16.6 ± 2.4 Control 10.6 ± 1.2	/	54	To evaluate whether MIME could facilitate similar or greater motor recovery as the same amount of early hands-on therapy. A secondary aim was to assess the dose-response effect of RA upper-limb therapy which had not previously been reported.	FMA Motor Power Ashworth	FIM WMFT FIM	/
Dromerick et al. (2009)	RCT	Acute stroke Time post stroke: 9,7 ± 4,6 Stroke type: 77% ischemic	Mean: Control: 19,7 ± 13,9 Low CIMT: 22,7 ± 14,3 High CIMT: 25,4 ± 18,0	52	To examine whether CIMT was superior to an equivalent amount of traditional occupational therapy To examine whether CIMT treatment effects would be dose dependent	NIHSS Wong-Baker Faces scale SIS	ARAT FIM	Geriatric depression -15 scale
Han et al. (2013)	RCT	Subacute stroke Stroke type: infarction or hemorrhage	Mean: Group A: 0.80 ± 1.14 Group B: 1.50 ± 1.58 Group C: 1.10 ± 1.52	32	To investigate the effects of different intensities of arm rehabilitation training on the functional recovery of hemiplegic upper extremity.	FMA	ARAT Barthel Index	/
Hsieh et al. (2012)	RCT	Chronic stroke (>6 months)	/	54	To examine the treatment effects of two different RT	FMA distal score FMA proximal score	Motor activity log SIS-ADL	/

		Months post stroke: High RT group 28.67m ± 13.67m Low RT group 23.28m ± 15.37m Control group 22.44m ± 15.34m Stroke type: Ischemic, hemorrhagic or subarachnoid			intensities and the effect on outcomes of the severity of initial motor deficits.	MRC SIS-strenth SIS-mobility SIS-hand function MAL-QOM MAL-AOU		
Hunter et al. (2011)	RCT	Acute/subacute Days since stroke: NO MTS (Mean): 29.4 (15.2) MTS 30 min (Mean): 35.6 (23.6) MTS 60 min (Mean): 25.7 (16.4) MTS 120 min (Mean): 28.3 (19.5) stroke subtype: ICH, LACI, PACI, TACI, missing data. -stroke type: Infarct or hemorrhage	ARAT median: No MTS: 0 (0-3) MTS 30 min: 0(0-0) MTS 60 min: 0(0-19) MTS 120 min: 0(0-6.5)		The authors aimed to find the most effective and feasible dose of mobilisation and tactile stimulation.	/	-MI upper limb -ARAT	-Adverse events
Lang et al. (2016)	RCT	chronic stroke (>6 months) Months past stroke: 100 repetitions: 12 200 repetitions: 13 300 repetitions: 13 IM: 11.5 stroke locations:	Mean: 100 repetitions group: 33.7 ±7.9 200 repetitions: 31.0 ±13.4 300 repetitions: 32.1 ±12.3 IM group:	81	The objectives of this work were to (1) determine whether higher doses of motor therapy in chronic post-stroke hemiparesis result in better outcomes compared to lower doses, and (2) evaluate potential	-SIS	-ARAT	-COPM -7-point likert scale

		Corical, subcortical, cortical and subcortical, post. Circ. and unknown stroke type: Ischemic, hemorrhage.	31.6 ±10.3		modifiers of the dose-response relationship.			
Lincoln et al. (1999)	RCT	acute/subacute Days after stroke (median): 12 (9-17) stroke subtype: TACI, PACI, LACI, POCI, Uncertain.	Median: RPT group: 0 QPT group: 0 APT group: 0	282	To determine wheter increasing the amount of physiotherapy early after stroke improved the recovery of arm function and to compare the effects of this therapy when administered by a qualified therapist or a trained, supervised assistant.	-Grip strength	-THPT -Barthel index -ARAT -Extended ADL scale -RMA gross function scale -RMA	
Parry et al. (1999)	RCT	acute/subacute patients: 1-5 week after stroke	/	186	To investigate effect of iniatial severity of arm impairment on response to additional physiotherapy for the arm after stroke.	-MAS	-ARAT -Barthel index -RMA -extended ADL scale	-Ritchie articular index -self-rating scale for pain
Rodgers et al. (2003)	RCT (pragmatic single center radomized controlled trial)	Acute stroke Days post stroke: Control (median): 5 (3-5) Intervention (median) 5 (3-8) Stroke subtype: TACS, PACS, LACS, POCS. Stroke type: Infract, haemorrhage and not known.	Median: Control group: 0 (0-45) Intervention group: 6(0-41)	96	To determine whether an early increased-intensity upper limb therapy programme following acute stroke improves outcome.	-MI upper limb function	-Barthel index -ARAT -Frenchay arm test -OHS - Nottingham E-ADL	-cost to health and social services

		severe stroke (Arat=0) and mild/moderate stroke (ARAT >0)						
Ross et al. (2009)	RCT	patients were acute/subacute (n<3 months) and chronic (n>3 months) Months post stroke: Control (Median): 0.7 Experimental (Median): 2.3 months stroke type: Infarct Hemorrhage Stroke subtype: TAC, POC, PAC, LAC	Mean: Control group: 10 (14) Intervention group: 10(15)	37	To determine the benefits of additional therapy specifically directed at the hand in people with acquired brain impairment	-SMMT -The test of passive extensibility of the long finger flexor muscles	-ARAT -WMFT	-DSAHA -COPM
Sunderland et al. (1992)	RCT	acute stroke: Time past stroke unknown	/		To compare orhodox therapy with an enhanced therapeutic regime which increases the amount of therapy for the arm and uses behavioral methods to encourage active learning during treatment sessions.	-EMI -Sub-test for the MCA -Resistance to passive movement -sensory loss in terms of response to light touch	-Frenchay arm test -NHPT -Barhel index	-paint on passive movement

Table 10.1 Overview of the effects after intervention: 1 intervention group vs. 1 control group

		Control group (1)			Intervention group (2)			1 vs 2
	Outcome measures	**Pre**	**Post**	**Change**	**Pre**	**Post**	**Change**	**P-value**
Rodgers (2003)	ARAT (Median IQR)	0 (0-45)	54 (1-57)	/	6 (0-41)	53 (20-57)	/	0.548
	Upper limb MI (Median IQR)	55 (14-77)	78 (51-100)	/	61 (15-81)	85 (65-92)	/	0.693
	FAT (Median IQR)	0 (0-3)	4 (0-5)	/	0 (0-2)	4 (2-5)	/	0.236
	BI	9 (6-14	17 (10-19)	/	8 (6-13)	17 (8-19)	/	0.580
Ross (2009)	ARAT Mean (SD)	10 (14)	24 (26)	17 (23)	10 (15)	21 (23)	11 (16)	0.371
	SMMT Mean (SD)	44 (36)	50 (37)	10 (21)	35 (33)	49 (35)	14 (17)	0.651
	WMFT Mean (SD)	1.7 (1.3)	2.3 (1.5)	0.8 (1.5)	1.3 (1.2)	2.3 (1.5)	1.1 (1.1)	/
	Finger flexion (degrees) Mean (SD)	68 (18)	61 (18)	0 (22)	67 (11)	62 (17)	-5 (13)	/
	DSAHA Mean (SD)	48 (16)	33 (15)	14 (23)	55 (21)	42 (19)	13 (19)	/
	COPM Mean (SD)	3.0 (1.7)	5.4 (2.9)	2.6 (2.2)	2.7 (1.7)	5.4 (1.9)	2.5 (1.9)	/
Sunderland (1992)	BI (Median, range) [1]	7 (2-19)	16 (7-20)	/	7 (2-20)	17 (2-20)	/	/
	Extended MI (Median, range)	9 (0-58)	/	/	0 (0-37)	/	/	/
	NHPT (Median, range)	0 (0)	/	/	0 (0)	/	/	/
	FAT (Median, range)	0 (0)	/	/	0 (0)	/	/	/
	BI (Median, range) [2]	12 (6-20)	19 (13-20)	/	13 (2-20)	20 (7-20)	/	/
	Extended MI (Median, range)	66 (34-91)	/	/	67 (30-96)	/	/	/
	NHPT (Median, range)	0.05 (0-0.39)	/	/	0.08 (0-0.38)	/	/	/
	FAT (Median, range)	2 (1-5)	/	/	4 (1-5)	/	/	/

[1] Severe sub-group
[2] Mild sub-group

Table 10.2 Overview of the effects after intervention: 2 intervention groups vs. 1 control group

		Control group		Intervention group 1[3]		Intervention group 2[4]		
	Outcome measures	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**BG-difference[5]**
Burgar (2011)	FM Mean (SD)	24.2 ± 4.8	14.0 ± 3.6	26.7 ± 5.0	6.8 ± 1.9	19.1 ± 3.7	14.4 ± 3.6	0.47
	FIM Mean (SD)	26.9 ± 2.0	15.9 ± 1.5	28.4 ± 2.6	17.7 ± 1.9	27.9 ± 1.7	21.5 ± 2.1	0.04[6]
	Motor Power Mean (SD)	24.9 ± 4.2	15.4 ± 3.7	27.9 ± 4.8	13.7 ± 2.3	21.5 ± 4.2	16.0 ± 3.0	0.86
	Ashworth Mean (SD)	0.33 ± 0.08	0.11 ± 0.10	0.44 ± 0.10	0.0 ± 0.06	0.31 ± 0.08	0.19 ± 0.09	0.15
	WMFT FAS (Mean ± SD)	1.1 ± 0.4	1.2 ± 0.3	1.6 ± 0.4	0.7 ± 0.2	1.0 ± 0.3	0.9 ± 0.3	0.75
	WMFT MT (Mean ± SD)	88 ± 18	-34.4 ± 18.0	81 ± 19	-16.8 ± 19.0	85 ± 17	-29.8 ± 17.0	0.65
Dromerick (2009)	ARAT total (Mean ± SD)	19.65 ± 3.73	36.20 ± 4.05	22.68 ± 3.52	42.10 ± 3.82	25.43 ± 3.84	33.93 ± 4.16	/
	ARAT grip (Mean ± SD)	4.58 ± 0.88	8.32 ± 0.87	5.00 ± 0.83	9.31 ± 0.81	5.19 ± 0.90	7.43 ± 0.89	/
	ARAT pinch (Mean ± SD)	2.94 ± 1.26	7.62 ± 1.68	4.73 ± 1.19	10.58 ± 1.58	6.37 ± 1.30	8.75 ± 1.72	/
	ARAT grasp (Mean ± SD)	7.11 ± 1.34	13.53 ± 1.40	7.31 ± 1.27	14.21 ± 1.32	8.56 ± 1.38	11.56 ± 1.43	/
	ARAT gross motor (Mean ± SD)	4.88 ± 0.62	7.00 ± 0.54	5.53 ± 0.58	7.79 ± 0.50	5.31 ± 0.64	6.19 ± 0.55	/
	FIM upper extremity (Mean ± SD)	22.88 ± 1.22	30.23 ± 1.17	22.73 ± 1.15	30.21 ± 1.11	23.69 ± 1.26	26.93 ± 1.21	/
	SIS (Mean ± SD)	/	59.71 ± 6.21	/	45.26 ± 5.87	/	44.33 ± 6.61	0.02
Hsieh (2012)	FMA total (Mean ± SD)	44.61 ± 11.06	47.56 ± 10.50	43.11 ± 9.18	46.33 ± 10.27	42.78 ± 8.86	48.00 ± 8.22	/

[3] Low dose intervention group
[4] High dose intervention group
[5] Between group difference, post intervention
[6] Robot-high > Control

	FMA distal score (Mean ± SD)	13.39 ± 7.65	14.72 ± 7.51	11.44 ± 6.81	13.06 ± 7.53	12.56 ± 6.17	15.17 ± 5.93	/
	FMA proximal score (Mean ± SD)	31.22 ± 4.60	32.83 ± 4.25	31.67 ± 3.96	33.28 ± 3.72	30.22 ± 4.01	32.83 ± 3.62	/
Lincoln (1999)	RMA arm (Median)	1	4	1	3	1	3	0.69
	ARAT (Median)	0	5	0	1	0	1	0.55
	BI (Median)	7	13	6	12	6	12	0.65
	EADL (Median)	/	7.5	/	5	/	6	0.65
	RMA gross function (Median)	1	5	1	3	1	2	0.61
	THPT (Median)	0	0	0	0	0	0	0.75
	Maximum grip (Median)	0	11	0	0	0	6	0.88
Parry (1999)	BI (Median) [7]	/	11	/	10	/	11	0.74
	EADL (Median)	/	6	/	5	/	4	0.26
	RMA arm (Median)	/	1	/	1	/	1	> 0.99
	ARAT (Median)	/	0	/	0	/	0	0.86
	BI (Median) [8]	/	16	/	17	/	14	0.31
	EADL (Median)	/	10	/	14	/	9	0.89
	RMA arm (Median)	/	8	/	9	/	9	0.07
	ARAT (Median)	/	38	/	45	/	37	0.07

[7] More severe patients
[8] Less severe patients

Table 10.3 Overview of the effects after intervention: 3 intervention groups vs. 1 control group

		Control group		Intervention group 1[9]		Intervention group 2[10]		Intervention group 3[11]		BG Difference[12]
	Outcome measures	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	
Hunter (2011)	ARAT Median (IQR)	0 (0-3)	0 (19)	0 (0-0)	0 (12)	0 (0-19)	0 (14)	0 (0-6.5)	0 (19.5)	/
	MI Median (IQR)	10 (1-40)	8 (22)	5.5 (1-35)	3 (23)	12.0 (1-40)	16 (29)	12.5 (1-42)	10.5 (27.5)	/
Lang (2016)	ARAT Mean ± SD	31.6±10.3	/	33.7 ± 7.9	/	31.0 ± 12.3	/	32.1 ± 12.3	/	/
	SIS-ADL (Mean ± SD)	65.4 ± 4.5	70.1 ± 5.2	58.0 ± 4.4	66.2 ± 5.0	61.5 ± 4.3	69.0 ± 5.1	67.8 ± 4.4	75.3 ± 5.4	0.42
	SIS-hf (Mean ± SD)	44.0 ± 5.5	55.5 ± 6.3	46.4 ± 5.3	55.6 ± 6.01	41.7 ± 5.2	51.7 ± 6.2	56.1 ± 5.3	62.7 ± 6.5	0.24
	COPM-p (Mean ± SD)	3.0 ± 0.3	5.6 ± 0.5	2.7 ± 0.3	5.4 ± 0.4	3.0 ± 0.3	5.3 ± 0.4	3.4 ± 0.3	6.0 ± 0.5	0.43
	COPM-s (Mean ± SD)	2.1 ± 0.3	5.1 ± 0.5	2.2 ± 0.3	5.5 ± 0.5	2.5 ± 0.3	5.4 ± 0.5	1.8 ± 0.3	5.5 ± 0.5	0.49

[9] Low dose intervention group
[10] Moderate dose intervention group
[11] High dose intervention group
[12] Between group difference, post intervention

Table 10.4 Overview of the effects after intervention: 3 intervention group vs. no control group

		Intervention group 1		Intervention group 2		Intervention group 3		
Han (2012)	**Outcome measures**	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**	**BG difference**[13]
	FMA (Mean ± SD)	6.70 ± 2.26	7.80 ± 2.90	8.20 ± 3.43	12.30 ± 6.55	6.50 ± 3.06	12.40 ± 5.50	0.098
	ARAT (Mean ± SD)	0.80 ± 1.14	1.90 ± 2.33	1.50 ± 1.58	3.50 ± 3.47	1.10 ± 1.52	4.60 ± 3.27	0.160
	BI (Mean ± SD)	51.50 ± 22.49	61.00 ± 20.11	62.50 ± 20.98	71.00 ± 19.97	50.50 ± 23.33	67.50 ± 21.25	0.548

[13] Between group difference, post intervention

Table 11: training parameters intervention group

Author, title and year	Dose				Total number of sessions	Total therapy hours
	Intensity	Frequency (d/w)	Session duration (Min)	Duration of intervention (weeks)		
Burgar et al. (2011)	/	5 5	±30 ±32	3	30 15	15.8±2.2 8.6±0.7
Dromerick et al. (2009)	-2 hours of therapy and 6 hours of constrainment -3 hours of therapy and 90% of waking hours constrainment	5 5	120 180	2	10 10	80 220
Han et al. (2013)	/	5 5 5	60 120 180	6	6 12 18	6 12 18
Hsieh et al. (2012)	-600-800 repetitions of mode 1 and 2 150-200 repetitions of mode 3 -300-400 repetitions of mode 1 and 2 75-100 repetitions of mode 3	5 5	90-105 90-105	4	20 20	30-35 30-35
Hunter et al. (2011)	/	5 5 5	30 60 120	2	10	7 14 28
Lang et al. (2016)	-group 1 did 100 repetitions each session -group 2 did 200 repetitions each session -group 3 did 300 repetitions each session	4 4 4 4	±26.25 ±37.5 ±48.75 ±55	8	32 32 32 36	13.6 20 26.3 32.8

	-group 4 continued repetitions each session till meeting stopping criteria					
Lincoln et al. (1999)	/	5 5	U	5	25	± 9.58 additional therapy ±7.1 additional therapy
Parry et al; (1999)	/	U	U	5	U	U
Rodger et al. (2003)		5	30 minutes additional treatment time each session for the upper limb	6	30	U
Ross et al. (2009)	/	5	60	6	30	30
Sunderland et al. (1992)	/	U	U	24	U	±72

Table 12: training parameters control group

Author, title and year	Dose				Total number of sessions	Total therapy hours
	Intensity	Frequency (d/w)	Session duration (min)	Duration of intervention (weeks)		
Burgar et al. (2011)	/	5	± 36	3	15	9.4±0.7
Dromerick et al. (2009)	/	5	120	2	10	20 hours
Han et al. (2013)	/	/	/	/	/	/
Hsieh et al. (2012)	/	5	90-105	4	20	30-35
Hunter et al. (2011)	/	/	/	/	/	/
Lang et al. (2016)	/	/	/	/	/	/
Lincoln et al. (1999)	/	5	30-45	5	25	12.5-18.75
Parry et al; (1999)	/	U	U	5	U	U
Rodger et al. (2003)	/	5	U	6	30	U
Ross et al. (2009)	/	3	10	5	15	150
Sunderland et al. (1992)	/	U	U	24	U	± 29.6

PART 2 - RESEARCH PROTOCOL

1. Introduction Master Thesis part 2

Stroke is a common disorder that effects a large amount of people in the world. In 2013, there were almost 25.7 million stroke survivors and 6.5 million deaths from stroke worldwide. There is a statistically significant increase in disability adjusted life years (DALY's) in ischemic and hemorrhage stroke survivors [14]. The costs of these stroke patients are high. More than 3% of the Dutch annual healthcare budget is spent on patients suffering from cerebrovascular disorders [8]. The incidence of stroke increases with age.

Of the patients who survive stroke circa 40% have hemiparesis six months later with a large impact on their activities of daily living and upper limb function [33]. Causes of these disabilities are largely determined by the severity of spasticity, muscle weakness, and loss of sensation [34]. To minimize these disabilities, a good rehabilitation is needed.
There is a broad range of rehabilitation strategies used after stroke such as positioning of the affected arm, strength training, virtual reality training, robot-assisted training, task-specific training, Bobath concept, constraint induced movement therapy…

That last one, constraint induced movement therapy (CIMT), has been studied more recently [7,24]. The main characteristic of CIMT is that the patient is forced to use their affected arm for several hours during the day [21].
There are three different types of CIMT: (1) the traditional CIMT, (2) forced use therapy, and (3) Modified CIMT (mCIMT). (1) The traditional CIMT consists of three important items. Firstly, it contains task-oriented practice of the affected arm for up to six hours each day for a minimum of two consecutive weeks. Secondly, activities are not only trained in a rehabilitation context as a transfer is made to the ADL of the patient. And thirdly, the unaffected arm of the patient is constrained for 90% of the waking hours, so the patient is forced to use the affected arm during the day [21]. (3) mCIMT consists of less hours of therapy and constrainment of the affected arm [3,21,22,23,30] mCIMT can range from 30 min - 6 hours of task-oriented training of the affected arm for 3-5 times a week. The constrainment of the unaffected arm ranges from 2 up to 6 hours of therapy spread over 2-10 weeks [24,30]. (2) In forced used therapy, the patient's unaffected arm is immobilized by a sling or resting splint. The patient wears the sling at least 90% of the waking hours. No additional task-specific therapy is given by the therapist [3].

A recent systematic review found a general small significant improvement on upper extremity function scales like the Fugl meyer assessment (FMA) and the Wolf motor function test (WMFT) in stroke

patients in favor of CIMT [7]. Another systematic review found that CIMT for six hours five times a week spread over 2 weeks leads to faster use of the affected arm in daily activities [24]. These two systematic reviews included stroke patients in different stages of rehabilitation (acute, subacute and chronic patients). On the other hand, articles that only focused on a specific stage of rehabilitation like, for example, the chronic stage also found significant improvement of the upper limb in favor of CIMT therapy. They found a significant improvement of the ARAT, Motor activity log (MAL) and the use of the affected upper limb [18]. However, the large heterogeneity of patients makes it difficult to find significant improvements. There is also a large variance of quality in the included articles, which makes it difficult to interpret the results [3].

However, CIMT interventions are time consuming, mCIMT seems as good as or even better than traditional CIMT therapy. Shi et al. (2011) found significant improvements for the FMA and ARAT-scores in favor of the intervention group which received mCIMT, compared with the traditional CIMT [27]. Peurala et al. (2011) [24] found that 2-6 hours of mCIMT practices, spread over 2 weeks, increased the hand mobility compared with control treatment. Even mCIMT for 30 minutes till one hour three times a week for 10 weeks, increased the hand mobility compared with no treatment or control treatment. mCIMT can improve the ability to use the paretic hand [24]. However, most of the intervention groups that found significant improvements in upper limb function in favor of mCIMT are compared with no dose-matched therapy. It is possible that the improvements are due to higher therapy duration compared with traditional therapy instead of the mCIMT protocol itself [15].

Due to the large heterogeneity within the intervention and control groups, and a lack of a dose-matched control therapy it is difficult to interpret the results of these earlier studies. Therefore, the aim of this RCT is to investigate whether a two week Modified CIMT-program improves the upper limb capacity more, compared to a dose-matched standard care program in stroke population.

2. Aim of the study

2.1 Research objective

The research protocol aims to answer the following research question: ‘Does a two week Modified CIMT program improve the upper limb function in subacute or chronic stroke patients, compared with dose-matched standard care therapy?’

2.2 Hypotheses

The researches hypotheses:

- A mCIMT-program which is focused on the relearning of ADL activities, improves fine and gross motor movement of the impaired upper limb more compared to a standard care program in stroke patients.

- mCIMT has more long term effects on ADL and upper limb function measured by the Fugl-Meyer assessment (FMA) and ARAT, compared to a standard care program in stroke.

3. Method

3.1 Research design

The study is a randomized control trial. The study consists of two groups: an intervention group and a dose matched control group. Patients will be randomly assigned to the intervention group or the control group.

The intervention group receives mCIMT while the control group receives standard care. The patients in both groups will receive therapy five days/week for two consecutive weeks. An independent assessor will evaluate the patients at baseline, post-treatment one and six months after intervention.

3.2 Participants

3.2.1 Patient recruitment

Patients will be recruited in the Jessa rehabilitation center in Herk-de-Stad. Patients will be blindly randomized in two groups of 20 patients. Only inpatients will be included. Patients willing to participate in the study will receive a written consent.

3.2.2 Inclusion criteria

The patients are included when they meet the following criteria: (1) stroke onset more than one month ago, (2) > 18 years, (3) The patient should meet the Taub criteria which means they should be able to: actively extend the wrist on the affected side for a minimum of 10 degrees, and actively extend two digits on the affected side for a minimum of 10 degrees, and actively abduct the thumb on the affected side for a minimum of 10 degrees, (4) The patient should be able to walk independently or with the help of a device.

3.2.3 Exclusion criteria

The patients are excluded when they meet one of the following criteria: (1) the patient's general condition is too weak to tolerate the Modified CIMT therapy, (2) the patient's medical condition is unstable, (3) the patient has a peripheral neurologic disorder, rheumatoid arthritis, fractures of the upper limb, or arthrosis that causes upper limb impairment, (4) the patient is unable to understand verbal instructions, (5) the patient has experienced a new stroke in the intervention period.

3.3 Medical ethics

Ethical approval will be asked to the Medicial Ethic Committee of Hasselt University and the local Ethical Committee of JESSA

3.4 Intervention

3.4.1 Therapy content

The intervention group will receive 5 hours of CIMT therapy each day, five days/week for two weeks. The five hours of therapy are divided in five different blocks of one hour of therapy with 30 minutes of rest between the blocks. The therapy is given by a physiotherapist alone or in combination with an occupational therapist. The therapists will focus on a correct posture and movement of the affected arm of the patient. The principles of motor learning will be applied. (These principles will be discussed later). The patient will be encouraged to use the affected hand between the therapeutic sessions as much as possible. The staff in the rehabilitation centre will be informed to stimulate the patients to use the affected arm during the day.

In the first and the third block of therapy patients will work on having a breakfast and dinner. All the goals of the patients are individually determined by a physiotherapist and an occupational therapist. Patients will learn how to use cutlery correctly with the affected side and to lay the table and to clean it up afterwards. The second block consists of specific arm-hand rehabilitation. Individual goals such as how to take money out of their wallets or how to fill a cup with water... will be practised during this hour of therapy.

The fourth block consists of ADL sport exercises. The patients will participate together in different sports for the upper limb such as basketball, badminton... The sports are played in groups of 10 patients. One physical therapist and two occupational therapists will attend the sessions. The different stages of motor learning (cognitive, associative, and autonomous stage) will be used to see if the difficulty level of the sport activity could be increased. When a patient is in the autonomous stage, different rules and materials will be used to make the exercise more difficult.

The last block consists of easy exercises to end the day. These exercises can be chosen by the patients. These various exercises can range from playing a card game with the affected arm to yoga for the upper limb.

The control group will receive a dose matched standard care program. Patients will receive 5 hours of therapy each day, five days/week for 2 weeks. The therapy consists of upper rehabilitation exercises. There is a minimum of 30 minutes rest between each session. The control therapy consists of 4 hours

of standard care and one hour of group therapy. The standard care therapy consists of one hour of active and passive mobilization, two hours of strength training and task-specific training (following the principles of motor learning) and one hour of cardiovascular training. The patients receive one hour of group therapy each day. The group therapy consists of one hour of yoga exercises.
Table 1 gives a detailed description of the therapy given in the control and the intervention group.

Table 1. Therapy content of the intervention and the control group

	Intervention group	**Control group**
Block 1	Exercise to learn the patient to use cutlery correctly and to lay the table and to clean it up afterwards	Active and passive mobilisation
	30 minutes rest	30 minutes rest
Block 2	Specific arm-hand rehabilitation based on the principles of motor learning strategies	Strength training and task-specific training according to the principles of motor learning strategies
	30 minutes rest	30 minutes rest
Block 3	Exercise to teach the patient to use cutlery correctly and to lay the table and to clean it up afterwards	Cardiovascular training: cycling, walking, running, arm cycling
	30 minutes rest	30 minutes rest
Block 4	ADL sport exercises. The different stages of motor learning will be used. The different sports: hockey tennis ping Pong badminton viking cup volleyball basketball handball petanque baseball	Strength training and task-specific training according to the principles of motor learning strategies
	30 minutes rest	30 minutes rest

Block 5	Tranquil exercises to end the day card games board games memory creative activities: drawing, paining puzzle making	Group yoga therapy

3.4.3 Training principles

Every training block will take one hour. In all the blocks the principles of motor learning will be used. There are three stages of motor learning. The therapist will adjust his feedback, according to the stage of rehabilitation.

The first stage is the cognitive stage. In this stage, the patient must understand the goal of the task and recognise the movements needed to complete the task. In this stage, the patient will try a variety of strategies to find the best to complete the task. In the cognitive stage the patient will give a large amount of auditory and visual feedback [2]. The therapist will mainly give feedback about the performance. In the early stages of motor learning it is more important to perform the movement correctly instead of the result of the movement [28].

The second stage is the associative stage. In this stage, the patient will use the best strategy found in the previous stage and he will try to refine this strategy. He will learn from his mistakes to make the performance less variable [2]. The amount of feedback given will be reduced in this stage and will be more focused on internal feedback. In this stage, the patient will have to correct himself. They will receive more knowledge of result than performance [28].

The last stage is the autonomous stage. The acquired skill will become more automatic. The patient can perform the task during different regulatory and non-regulatory features [2]. In the autonomous stage it is assumed that the quality of the performance is good, the focus is on the result of the movement [28].

The rehabilitation content consists of part practise and whole practice. Part practice means that the exercise is divided into different parts. For example: the task is to drink from a cup filled with water with the affected arm. (1) Reach to the cup with the affected side, (2) open your hand, (3) take the cup, (4) bring the cup to your mouth, (5) drink, (6) bring the cup back to the table, (7) release the cup.

The task will be divided by the physical therapist. More complex tasks will consist of a larger amount of parts. When the patient is able to perform the different parts separately, the performance will be trained in its entirety, which is called whole practise [28].

Progression to a more difficult task is made when a patient has a Borg score of eight or less during the task. The Borg score will be taken frequently by a physical or an occupational therapist.

When the patient has excessive pain or a Borg score of minimal 18, the task is too difficult. The physio or the occupational therapist will have to make the task more difficult or easier when necessary.

3.5 Outcome measurements

Different baseline characteristics of the patient will be measured before the intervention. Age (years; ratio), gender (man, female; nominal), time after stroke (months; ratio), hemi side (left, right; nominal), dominant hand effected (yes, no; nominal), stroke classification (intracerebral haemorrhage (ICH), lacunar infarct (LACI), Partial anterior circulation infarct (PACI), total anterior circulation infarct (TACI), missing data; nominal), medication use (nominal) and stroke lesion (ischemic or haemorrhage; nominal)) will be measured. The Barthel index (BI) will be used to measure the ADL level of the patients and consists of 10 test items. The total score of the BI is between 0 (complete dependence) and 20 (fully independent) [5]. The Post-Stroke depression rating scale will be used because patients who suffer from a depression could have less motivation. The scale is composed of 10 items. Each test item receives a score between 0 (normal stage) and 5 (severe disorder). The last item in the scale gives a score between -2 (unmotivated, clear prevalence of depression) and + 2 (motivated) during stressing situations [9]. The Modified Ashworth Scale (MAS) will be used to assess the level of the spasticity of shoulder abductors, elbow flexors and wrist flexors [1]. The MAS has a score between 0 (no increased muscle tonus) and 4 (affected limb is fixed in flexion or extension).

3.5.1 Primary outcome

The primary outcomes are measured on the activity level according to the international classification of function, disability, and health (ICF).

Measurement on the ICF-activity level.
The Action research arm test (ARAT) evaluates the hand dexterity. The test consists of 19 items evaluating the grasp, grip, pinch function of the hand and gross movements of the whole upper limb. Every item receives an ordinal score, ranging from 0 (not able to perform the task) till 3 (able to perform the task in time), with a maximal total score of 57. The ARAT is a reliable and valid test in stroke [17, 20].
The Wolf motor function test (WMFT) consists of 17 tasks for the shoulder, the elbow and the hand. The WMFT test has 15 functional tasks and 2 strength tasks. The WMFT can be divided in the WMFT-FAS and the WMFT-TIME. In the WMFT-FAS each test item receives an ordinal score between 0 (unable to perform the task) and 6 (able to perform the task). The WMFT-TIME measures the time the patient needs to perform the task. Each item has a maximal time limit of 120 seconds.
The WMFT is a reliable and valid test in stroke patients [16, 27].

The functional independence measure (FIM) is a test that evaluates the patient degree of independence in ADL-function. The test consists of 17 items. 13 Items include motor tasks and 5 items include cognitive tasks. The maximal total score of the FIM is 126. Each item receives an ordinal score between 0 (complete dependence for a task) and 7 (complete independence for a task). The FIM is a valid and reliable test in stroke patients [12].

3.5.2 Secondary outcome

Measurement on the ICF-body function level and measurement for the feasibility of the intervention.

Brunnstrom Fugl-Meyer assessment (BFMA) is a test that evaluates the degree of synergy formation in the upper and lower limb, and balance. The test consists of 55 items. Each test item receives an ordinal score between 0 (unable to perform the movement) and 2 (able to perform the movement). The total score of the BFM test is 114. The BFM is a reliable and valid test in stroke patients. [6, 11, 26]
Measurements for the feasibility of the intervention

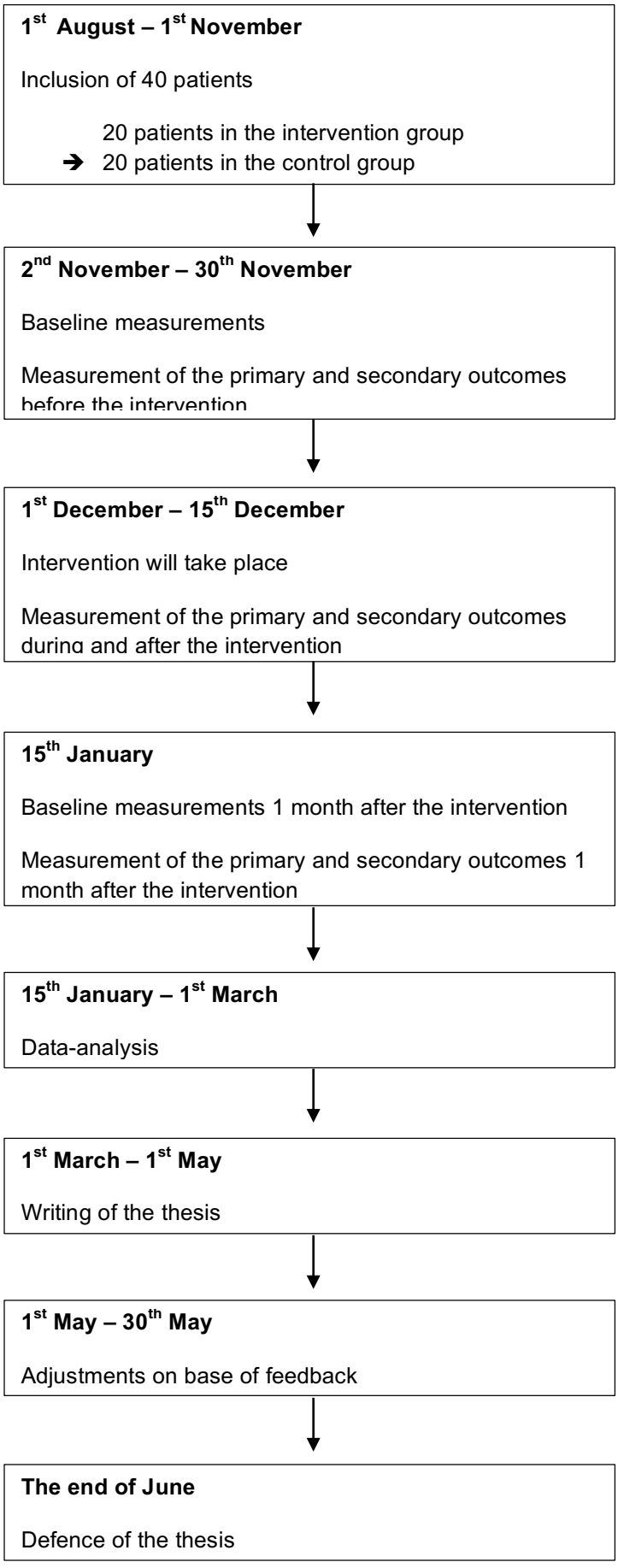
The VAS-scale is used to determine if the patients in the intervention group experience more pain during or after the intervention compared with the control group. The VAS-scale consists of a 10-point ordinal score (0= no pain and 10 = extreme pain). The VAS scale is measured before and after each block, and after the intervention period.
The Borg Rating of Perceived Exertion (RPE) scale is a subjective questionnaire of the level of exertion. The Borg-scale consists of a 20-point ordinal score (6= no exertion, 20= maximal exertion). The Borg-score is measured before and after each block, and after the intervention period.

3.6 Data analyses

Statistical analyses will be performed with SAS JMP Pro 12.2.0.
The Kruskal–Wallis test will be used for baseline difference.
A mixed model will be used to analyse the effects of the intervention in both groups at the different time points (the subjects are entered as random effect and the time, group and time*?groups fixed effect).

For feasibility, the VAS and the BORG score are measured at the beginning and ending of each block, day and after the intervention period. A between group comparison is made using independent t-tests for each block, day, after the intervention and one month post-intervention.

4. Time planning



5. Reference

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APPENDIX RESEARCH PROTOCOL

Appendix 1: Voortgangsformulier Wetenschappelijke Stage Deel 1

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VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 1

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
24/10	Bespreking onderwerp, deadlines, format Bouke	Promotor: Copromotor: Student(e): Student(e): BP
28/10	Bespreken van onderzoeksvraag	Promotor: Copromotor: Student(e): Student(e): BP
3/01	Bespreking zoekstrategie	Promotor: Copromotor: Student(e): Student(e):
28/02	Bespreking 'quality assessment'	Promotor: Copromotor: Student(e): Student(e):
28/04	Bespreking feedback	Promotor: Copromotor: Student(e): Student(e):
18/05	Bespreking protocol in Hert-De-Stad	Promotor: Copromotor: Student(e): Student(e):
03/07	Bespreking feedback	Promotor: Copromotor: Student(e): Student(e):
27/07	Bespreking feedback	Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):
		Promotor: Copromotor: Student(e): Student(e):

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Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
The dosage dependent effects of upper limb rehabilitation in chronic neurological patients

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij neurologische aandoeningen**
Jaar: **2017**

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