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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The optimal session length of upper limb rehabilitation of people with moderate to severe upper limb sensorimotor impairments after acute and very early subacute stroke: A dose escalation study

Steff Doumen
Luca Sorba

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :
Prof. dr. Peter FEYS

COPROMOTOR :
dr. Lisa TABONE

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2022

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Acknowledgements

A great letter of thanks to our promotors Prof. dr. Peter Feys and Dr. Lisa Tedesco Triccas who guided us through this challenging process to obtain a scientific master's thesis. The reliable and constructive collaboration gave us the opportunity to develop ourselves in scientific research. Also our sincere thanks to the Acute Stroke Unit of Ziekenhuis Oost-Limburg (ZOL) Genk to provide us the facilities and materials to execute the experimental intervention. At last, thank you to Sofie Cardeynaels, physiotherapist at ZOL, who helped us with the screening of participants and the execution of the experimental intervention.

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Our master's thesis in context

Our master's thesis is situated in the rehabilitation of neurological disorders. More specifically, our research focuses on the rehabilitation of stroke. Stroke is a very frequent and disabling disease (Lawrence et al., 2001; Persson et al., 2012; Wafa et al., 2020). Nevertheless, there is still a paucity in evidence around stroke, especially in the early stages after stroke which was confirmed by our own systematic review. However, new insights about the rehabilitation of stroke are still gaining. Our master's thesis aims to decrease the lack of knowledge about rehabilitation of moderate to severe upper limb impairments in the early stages after stroke.

Stroke requires an interdisciplinary approach where all disciplines need to be involved. All medical specialties in neurology can obtain new insights through our master' thesis. The conducted systematic review was a newly developed research project. Our systematic review could identify certain gaps in the scientific literature like the lack of knowledge about upper limb rehabilitation in the acute stage after stroke. An innovative study protocol was developed in collaboration with Prof. Dr. Peter Feys and Dr. Lisa Tedesco Triccas. The performed clinical trial is a dose escalation study which serves as a pilot feasibility study. This study provides a clear understanding on whether integrating an upper limb therapy program for patients provided after acute stroke (one to seven days after stroke, Bernhardt et al., 2017) and very early subacute stroke (day eight to one month after stroke, Biernaskie et al., 2004; Birkenmeier et al., Krakauer et al., 2012) would be feasible. The current dose escalation study is a phase I- trial after which a phase II- study will be conducted exploring the immediate, short-term (one month) and long-term (six months) effect of an upper limb rehabilitation program in the acute and very early subacute stage after stroke.

The pilot study is executed in collaboration with Prof. Dr. Peter Feys and Dr. Lisa Tedesco Triccas. The clinical setting is the acute stroke unit of Ziekenhuis Oost-Limburg (ZOL) campus Genk. The University of Hasselt and the acute stroke unit of ZOL Genk provided us the required rehabilitation resources to execute the dose escalation study.

The study design and methodology was conceptualized under the management of Dr. Lisa Tedesco Triccas. For the recruitment of participants, a booklet for data collection for the physiotherapists of ZOL and the informed consent for the participants was designed with

approval of our promoters. In collaboration with the ZOL physiotherapists and occupational therapists and our promoter Dr. Lisa Tedesco Triccas, the intervention protocol was applied to the included participants. For each participant, a logbook was completed with all the intervention data. The data analysis and the academic writing of the paper was autonomously done and then presented to our promoters. They provided us feedback and suggestions, after which the necessary improvements were made until the desired result was obtained.

The whole project was a very constructive collaboration where we, as master's students, had a lot of responsibility and autonomy. Every step was discussed with each other and conflicting points were discussed with our promoters. The master's thesis developed in a very gradual and controlled manner. It was also a very qualitative experience to apply the intervention protocol in clinical practice ourselves. In this way, a realistic point of view could be utilized in the academic writing of the paper.

At last, many thanks to our promoters Prof. Dr. Peter Feys and Dr. Lisa Tedesco Triccas again for their investments and the constructive collaboration, through which a satisfying master's thesis was attained.

Abstract

Background

Our review demonstrated an unclear dose-response relationship of improvements in severe upper limb impairments after acute and early subacute stroke, due to low therapy dosages and a lack of reporting pain and fatigue. However, high dosage programs have demonstrated clinically meaningful improvements in chronic stroke. A lack of methodological standardization of experimental studies in the acute stage after stroke hindered high quality evidence.

Objectives

The aim of the study was to identify the feasibility of a single-ascending dose clinical trial and determine the optimal session length of rehabilitation in patients with moderate to severe upper limb impairments after acute and very early subacute stroke.

Participants

Participants were recruited from the acute stroke unit of Ziekenhuis Oost-Limburg (ZOL) Genk and received a three-day multimodal upper limb therapy program of a predetermined dose level (one of two dose levels) including an upper limb movement training program and Functional Electrical Stimulation (FES).

Measurements

Primary outcome measure was the Fugl-Meyer Upper Extremity Assessment (FMA-UE) and secondary was the Action Research Arm Test (ARAT) conducted at baseline and post-intervention. Safety assessment was conducted before, during and after each therapy session to assess Dose-Limiting Tolerance (DLT) and establish the Maximum Tolerated Dose (MTD).

Results

Six participants were recruited until now (on average 4.2 ± 1.64 days after stroke), but only five completed the study. Dose level two did not cause higher ($p=0.648$) or more aggravation of fatigue ($p=0.128$) and was not perceived as more intensive ($p=0.383$). The intervention program had no overall significant effect on improving upper limb impairments ($p=0.25$).

However, dose level two had average improvements on all outcome measures that exceeded the respective Minimally Clinically Important Difference (MCID).

Conclusion

The dose escalation study identified a dose of 67 minutes as feasible and well tolerable. The second dose is therefore more optimal than dose level one for improving moderate to severe upper limb impairments in patients after acute and very early subacute stroke, indicating a trend to a positive dose-response relationship. However, the study is currently ongoing through which the optimal session length has not yet been determined.

Keywords: Stroke, Upper limb, Acute, Severe, Feasibility, Dose, Exercise therapy

1. Introduction

The number of people living with stroke is estimated to increase by 27% between 2017 and 2047. This is mainly because of the ageing population and improved survival rates (Wafa et al., 2020). Immediately after stroke, reduced function of the upper limb is reported in 48-77% of stroke survivors (Lawrence et al., 2001; Persson et al., 2012). So far, recovery rates of upper limb function are lower for patients with moderate to severe initial upper limb impairments, with clear impact upon their quality of life (Dabrowska-Bender et al., 2017). Even more, the prognosis of regaining functional hand activity three and six months later, when suffering from initial severe upper limb impairments, is poor (Kwakkel et al., 2003; Nakayama et al., 1994; Stinear et al., 2017). The PREP2 model of Stinear et al. (2017) showed a limited to poor prognosis of hand activity in the absence of a Motor Evoked Potential (MEP) in the wrist extensors in the first week after stroke. In a qualitative study of Lundquist et al. (2021) the PREP2 model was regarded as potentially useful by experienced neurological therapists.

The critical early window of recovery is very important in stroke rehabilitation as it is the period when there is maximal recovery of impairments. During the first week after stroke, which is defined as the acute stage, waves of growth-promoting genes reach a peak, enhancing endogenous neuroplasticity (Bernhardt et al., 2017). The overarching aim of this study is to promote and optimize neuroplastic changes by providing an intensive motor rehabilitation program for upper limb impairments during the critical acute stage after stroke. The acute stage was proven to be sensitive for intensive exercise therapy by a recent study of Dromerick et al. (2021). High intensive interval training has been associated with an increased concentration of brain-derived neurotrophic factor, a neurotrophin that plays an important role in the structural and functional processes of neuroplasticity (Crozier et al., 2018; Skriver et al., 2014). Besides, our review demonstrated a paucity of high-quality studies of upper limb rehabilitation approaches in the acute stage after stroke. A recent review by Hayward et al. (2021) also concluded that interventional studies focused mainly on the subacute stage of stroke recovery with a retained lack of attention to interventions in the acute stage of stroke.

Hayward & Brauer (2015) reported that during acute and subacute inpatient rehabilitation, activity-related arm training was on average four minutes per session of physical therapy

and 17 minutes per session of occupational therapy per day (Hayward & Brauer, 2015; Serrada et al., 2016). Moreover, in four European rehabilitation centres in the UK, Belgium, Germany and Switzerland, patients with stroke spent more than half of their time not interacting with anyone or anything at all (De Wit et al., 2005). This time could be spent focusing on high dosage upper limb rehabilitation. High dosage programs have been found beneficial for the upper limb in the chronic stage after stroke. The Queen Square Upper Limb Neurorehabilitation (QSUL) program in the UK (Ward et al., 2019) offers a duration of 90 hours of timetabled treatment over three weeks focusing on the upper limb in patients with chronic stroke. QSUL reported clinically meaningful improvements of arm and hand function that were maintained at six months follow-up. However, the QSUL program included participants with a wide range of severity of impairments and stratification was not executed. A long-dose upper limb training protocol for people with moderate to severe impairments, in the chronic stage after stroke with a duration of five hours per session for 12 weeks, resulted in clinically meaningful improvements in motor impairments (Daly et al., 2019). Recently in Herk-de-Stad in Belgium, it was demonstrated that one hour BOOST per session for four weeks plus one hour per week upper limb robot therapy extra (Armeo Power), also resulted in clinically meaningful improvements in patients with exclusively moderate motor impairments only in the subacute stage after stroke. Participants in the early and late subacute stage after stroke were included, but no stratification was executed. Also key characteristics of non-responders to the BOOST therapy could not be unravelled (Meyer et al., 2021).

However, in the acute stage different results have been demonstrated when additional upper limb rehabilitation was provided to usual care. Human studies investigating up to an hour of additional intensive training compared to standard care, did not result in superior improvement on severe upper limb impairments in acute stroke compared to usual care. (Kwakkel et al., 2016; Rabadi et al., 2008; Rodgers et al., 2003). Our review demonstrated that the dose-response relationship in patients with severe upper limb impairments after an acute and early subacute stroke is unclear, due to limited research conducted in this stage for moderate to severe impairments and a lack of methodological standardization. The review showed a paucity of studies in the acute stage after stroke, through which it was almost impossible to establish a reliable dose-response relationship. However, these non-

effects could be due to the low dosage, specifically with a session length from 30 to 60 minutes, of upper limb rehabilitation. A recent review of Hayward et al. (2021) also stated that intervention dose and sample size of studies were often too small to detect clinically important effects in the acute and subacute stage after stroke. It is also questionable how patients after acute stroke with moderate to severe upper limb impairments react to different doses and dose escalations in terms of fatigue, pain and/or well-being. As identified in our review, patient-reported fatigue is not commonly used as a primary or secondary outcome measure or adverse event.

Providing high dosage upper limb programs could result in promising improvements in the upper limb after stroke. However, the feasibility and the effect of an optimal session length of upper limb therapy that could be provided in the acute stage (one to seven days after stroke) and very early subacute stage (day eight to one month after stroke) of stroke (Bernhardt et al., 2017; Biernaskie et al., 2004; Birkenmeier et al., 2010; Krakauer et al., 2012), is still unknown. A dose escalation study is one way to explore the optimal session length of upper limb therapy. The aim is to determine the maximum tolerated dose (MTD) in a small number of patients by assessing the safety and toxicity (the level of harmful side effects) of the intervention. When MTD is reached, the optimal session length can be established. Dose escalation studies are frequently used in pharmacological research but rarely used in rehabilitation research. Two studies have been identified using this methodology for determining the dosage of exercise in chronic stroke (Dite et al., 2015; Peiris et al., 2017). Dite et al. (2015) conducted an exercise dose escalation study with six people after chronic stroke with walking impairments and provided them a multimodal exercise program for the lower limb. They identified that participants were able to conduct the targeted exercise for 603 minutes a week over three sessions. Based on study design, we hypothesize that the similar methodology proposed as the aforementioned study will be feasible and optimal session length of upper limb rehabilitation for moderate to severe upper limb impairments after acute and very early subacute stroke will be identified (Dite et al., 2015; Peiris et al., 2017).

2. Methodology

2.1 Objectives

- To identify the feasibility of a single-ascending dose clinical trial (dose escalation study) in patients with moderate to severe upper limb impairments after acute and very early subacute stroke
    - To explore the safety and toxicity (level of harmful side effects) of an upper limb therapy program.
    - To explore the tolerability (Maximum Tolerated Dose, MTD) of an upper limb therapy program.
- To identify the optimal session length (total time in the intervention environment) (Hayward et al., 2021) of upper limb therapy for patients with moderate to severe upper limb impairments after acute and very early subacute stroke.

2.2 Participants

Medical Ethics

Ethical approval was confirmed by the ethical committee and the board of Ziekenhuis Oost-Limburg (ZOL) Genk (Z-2021046). Eligible participants were informed about the content and aims of the study by giving them a participant information sheet. A maximum of 24 participants could be recruited based on the study design discussed in the procedure part of the methodology. Written consent had to be given before they could be included in the study.

Inclusion criteria

Participants should have had: (a) a first-ever unilateral stroke, diagnosed by a neurologist as defined by the World Health Organisation (WHO, 2022), (b) been admitted to the acute stroke unit of ZOL Genk for rehabilitation, (c) upper limb hemiparesis or hemiplegia with at least a trace of muscle contraction (at least grade one at wrist extensors measured by the Medical Research Council (MRC) Scale), (d) moderate to severe upper limb impairments measured with a score of less than 61 on the Motricity Index (MI) (Demeurisse et al., 1980; Hunter et al., 2011), (e) to be older than 18 years of age and (f) the ability to provide written informed consent.

Exclusion criteria

Participants after acute or very early subacute stroke were excluded if they had: (a) other neurological impairments that could interfere with the protocol such as Multiple Sclerosis and Parkinson's Disease and (b) serious communication, cognitive and language deficits which might hamper the assessment, measured with a score of two on the command-item (item 1c) of the National Institutes of Health Stroke Scale (NIHSS).

Recruitment

The population consisted of participants in the acute (one to seven days according to Bernhardt et al., 2017) and very early subacute stage (day eight to one month after stroke) with moderate to severe upper limb motor impairments. Inclusion of participants up to one month after stroke was because the first month post-stroke is a critical time for neural endogenous plasticity, this time perspective represents an important treatment target to maximize the potential of restorative interventions (Bernhardt et al., 2017; Biernaskie et al., 2004; Birkenmeier et al., 2010; Krakauer et al., 2012). Moreover, due to inclusion until one month post-stroke, recruitment rate aimed to be increased. Participants were recruited from the acute stroke unit of Ziekenhuis Oost-Limburg (ZOL) Genk between October 2021 and April 2022. Screening for eligibility was done by an independent physiotherapist of ZOL Genk on day two after stroke at the earliest or day two after inclusion.

2.3 Procedure

Study Design

A single-ascending dose clinical trial was conducted to identify the Maximum Tolerated Dose (MTD) and the optimal session length in successive cohorts of six participants (based on a cumulative three plus three design, Figure 1) (Dite et al., 2015; Machin et al., 2011). There were four different dose levels through which a maximum of 24 participants could be included in the study. The Maximum Tolerated Dose (MTD) was defined as the ability to reach a fixed maximal level of upper limb exercise therapy (including session length) in the first week after stroke or inclusion without experiencing Dose-Limiting Tolerance (DLT). DLT-thresholds were based on failure to complete more than 20% of prescribed three-day rehabilitation dose due to pain, rate of perceived exertion and/or fatigue. Safety assessment, involved testing of pain, fatigue and fatigability and perceived exertion of each participant. The latter was performed

at the beginning, in the middle of and after each exercise therapy session, except for the assessment of the perceived exertion which was rated only in the middle of and after each therapy session. MTD (Figure 1, D) was reached when two or more participants experienced DLT during the prescribed three-day rehabilitation. The researchers (Tedesco Triccas L., Sorba L., Doumen S.) and a physiotherapist of ZOL Genk (Cardeynaels S.) conducted the clinical tests and the rehabilitation program.

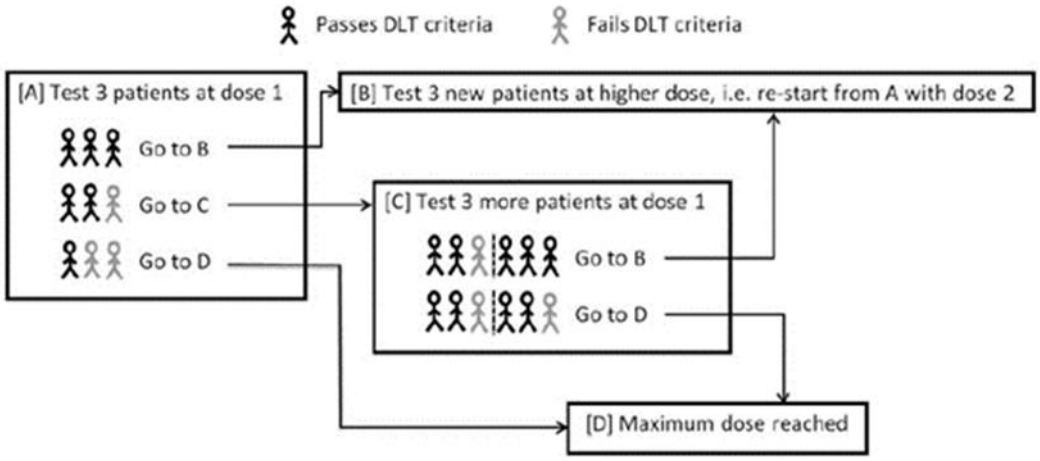


Figure 1: Cumulative three plus three design (Dite et al., 2015; Machin et al., 2011). DLT, Dose-Limiting Tolerance

Dose levels and Escalation

The dose of the prescribed intervention followed a modified Fibonacci scheme (Peiris et al., 2017; Colucci et al., 2017; Penel et al., 2012) whereby four dose levels were established (Table 1). All participants received a preparation session of 20 minutes after inclusion. From day four to six after stroke or inclusion, the three participants received a three-day rehabilitation with their respective dose level (Figure 2). If two or more participants experienced DLT, MTD was reached and the study completed. If one participant experienced DLT, a new cohort of three participants was selected and received the same dose level again (Figure 1). If no adverse events were identified and the three participants managed to tolerate the dose in three days, then the dose was escalated. This plan for this process is to continue until the maximal dose of 133 minutes per session will be reached or two or more participants did experience DLT (then the previous dose will be considered as MTD). The amount of 133 minutes has been identified as a similar value that has been established as beneficial in participants only with subacute stroke (Meyer et al., 2021).

Table 1. Dose levels for upper limb rehabilitation with dose increments following the modified Fibonacci scheme

Dose level	Day after stroke/inclusion	Session length (minutes)	Fibonacci increment
Preparation	3	20	
1	4-5-6	40	X 2.00
2	4-5-6	67	X 1.67
3	4-5-6	100	X 1.50
4	4-5-6	133	X 1.33

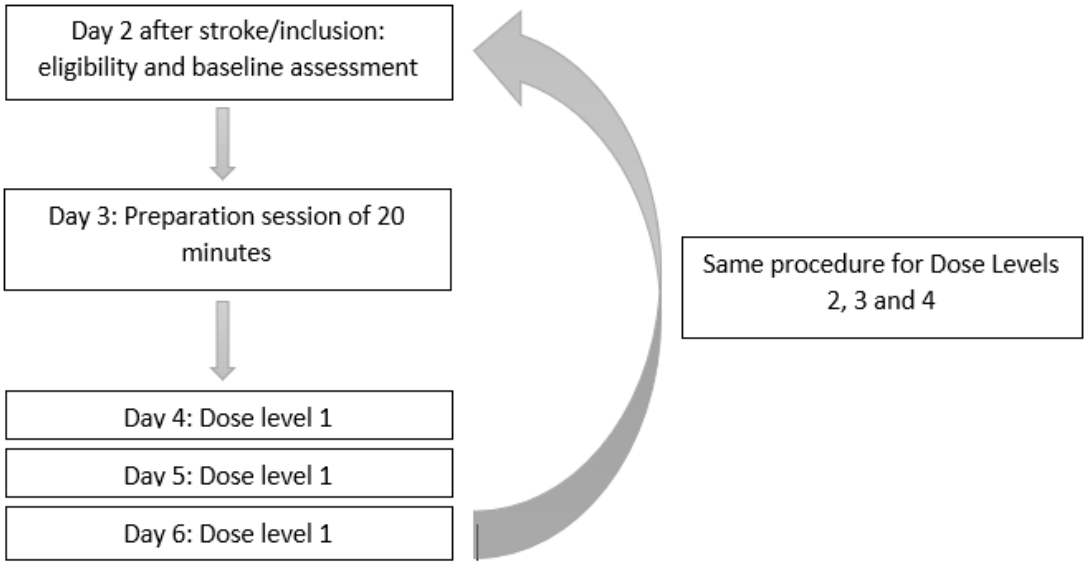


Figure 2. From eligibility assessment to rehabilitation

Safety assessment

As mentioned earlier, Dose-Limiting Tolerance (DLT) thresholds were set as: failure to complete more than 20% of prescribed three-day rehabilitation dose due to pain, fatigue and/or perceived exertion. In Table 2, the DLT-thresholds are presented. A participant reached DLT when the DLT-threshold was exceeded in at least one of the following three items at one of the measurement time points and 20% of the prescribed dose could not be completed. The three items in detail:

i. Fatigue by the Visual Analogue Scale for Fatigue (VAS-f) (Shahid et al., 2011): This questionnaire consists of 18 items relating to the subjective experience of fatigue. Each item asks respondents to place an 'X', representing how they currently feel, along with a visual analogue line. However, to work efficiently, only item one and four were

presented to the participant at the beginning, in the middle of and after each therapy session. In the data analysis, the average score of item one and four was considered. The extremes of item one are “Not at all tired”, corresponding with zero, and “Extremely tired”, corresponding with ten. The extremes of item four are “not at all fatigued”, corresponding with zero, and “extremely fatigued”, corresponding with ten. Tseng et al. (2010) identified a good reliability, responsiveness and validity of the VAS-f to assess fatigue in people after stroke. Whilst tiredness appears to be generally mental or psychological in nature, fatigue is a bodily state.

ii. Rating of perceived exertion by the Borg Scale (Compagnat et al., 2018): The Borg Scale is recommended to measure the intensity of physical exercise during stroke rehabilitation. It included asking: “What was the highest perceived intensity of effort during those tasks on a scale from six to 20, with six being no effort and 20 being maximal intensity or effort?”. Sage et al. (2013) stated that the Borg Scale is a reasonable indicator of exercise intensity after stroke.

iii. Pain by the Numeric Rating Scale (Shahid et al., 2011): The 11-point Numeric Rating Scale (NRS) quantified the intensity of pain, with ten being the most intense level of pain and zero being no pain. Chuang et al. (2014) proved the NRS a reliable measure of pain in people with stroke, with good relative and absolute reliability.

Table 2. Dose-Limiting Tolerance (DLT) thresholds for the three items: fatigue, perceived exertion and pain

Item	DLT-threshold
Fatigue	Visual Analogue Scale for Fatigue - Item one ‘tiredness’ : score > 8 - Item four ‘fatigue’ : score > 8
Perceived Exertion	Borg Scale : score > 16
Pain	Numeric Rating Scale: score > 8

2.4 Outcome Measures

Descriptive measures of each participant entering the study were documented including age, gender, upper limb motor impairment measured by the Motricity Index (MI) (Demeurisse et al., 1980; Hunter et al., 2011) and stroke lesion type, side and location.

Clinical outcome measures were measured at baseline (day two after stroke or inclusion, Figure 2) and at completion of the dose level i.e. at post-intervention (day six after stroke or inclusion). These outcome measures were different to the aforementioned safety assessments.

Primary outcomes

The primary outcome measures were the Motricity Index (MI) (Demeurisse et al., 1980; Hunter et al., 2011) and the Upper Extremity specific part of the Fugl-Meyer Assessment (FMA-UE) (Lee et al., 2015). The MI and FMA-UE assess upper limb motor impairments on the motor function level of the International Classification of Functioning, Disability and Health (ICF). The MI assesses three upper limb movements (shoulder abduction, elbow flexion, pincer grip) and the respective isometric strength with a maximum score of 33 per movement. A total score of 99 is noted as a perfect score of 100. The MI upper limb specific is proven to have a good inter-rater reliability in stroke patients by Collin & Wade (1990). The FMA-UE consists of 33 items graded on an ordinal scale (zero to two), with a total score ranging between zero (loss of motor function) and 66 (intact motor function). Regarding the FMA-UE, the Minimally Clinically Important Difference (MCID) established by Hiragami et al. (2019) was 12.4 points as determined in stroke survivors with moderate to severe upper limb hemiparesis in the subacute stage after stroke. Recently, Lin et al. (2022) concluded that 13 points was the estimated optimal MCID of improvement in the Motricity Index Arm score in the acute assessment and three months post stroke (Lin et al., 2022).

Secondary outcomes

The secondary outcome measure is the Action Research Arm Test (ARAT) (Van Der Lee et al., 2001)(Figure 3). The ARAT assesses the upper limb motor disabilities on the activity level of the International Classification of Functioning, Disability and Health (ICF). The ARAT measures motor capacity and performance in four different subscales, namely grasp, grip, pinch and gross movement, with a maximum score of 57, reflecting good motor performance. The ARAT

has been shown to have strong psychometric properties, with high test-retest and inter-rater reliability (McDonnell M., 2008; Van der Lee et al., 2001) and strong validity (Chen et al., 2012). The ARAT is executed with a standardized positioning following the study of Yozbatiran et al. (2008). The Minimally Clinically Important Difference (MCID) for the ARAT of stroke survivors in the early subacute stage with hemiparesis of moderate severity was established by Lang et al. (2008). They made a distinction between the dominant and non-dominant side. The MCID for the dominant side was 12 points and for the non-dominant side 17 points (Lang et al., 2008).

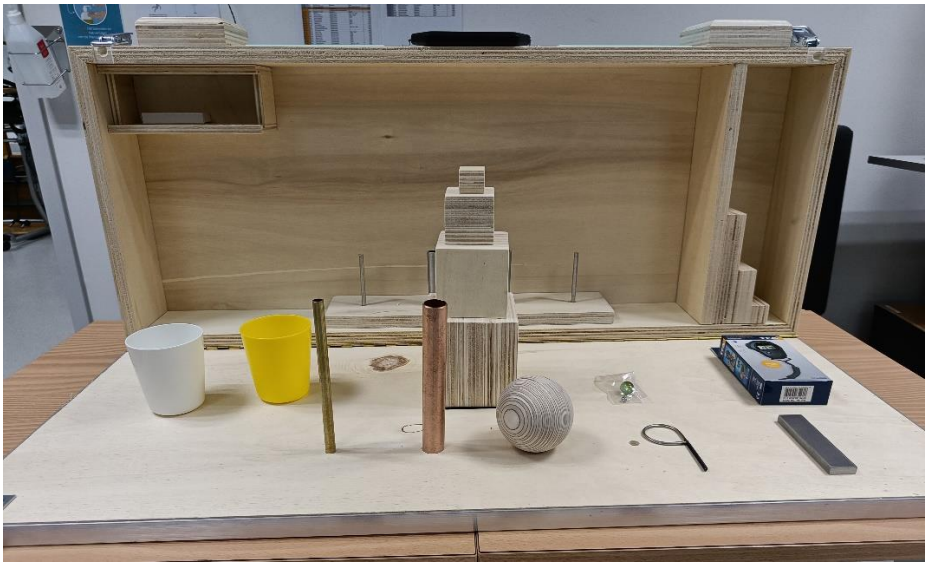


Figure 3. The shelf and items needed for the standardized testing of the Action Research Arm Test (ARAT).

2.5 Intervention

The planned intervention was a multimodal upper limb rehabilitation program consisting of three components: a) Upper limb training protocol; b) Functional Electrical Stimulation (FES); c) Mirror therapy. Component a) and b) were applied at each dose level, but component c) was only included in dose level three and four. The detailed content of each intervention session for each dose level day can be found in the 'Appendix'. Therapy sessions were guided by the researchers and an informed independent physiotherapist of ZOL Genk. The intervention was in addition to the standard care that each participant received daily. Standard care consisted of 60 minutes of physiotherapy mainly focused on the lower limb to promote gait, stability and weight bearing/shifting with little attention for the upper limb and 30 minutes of occupational therapy which included some functional upper limb training.

a) Upper limb training protocol

The upper limb training protocol is based on the 'Treatment Progression Hierarchy for Coordinated Movement Practice' of Daly et al. (2019). The protocol consists of six hierarchical steps (Table 3) from 'Muscle activation in synergy' to 'Full functional task practice'. For each participant, it was individually decided in which of the six steps (A-F, Table 3) the treatment could start and progressions were individually implemented based on the FMA-UE score at baseline ('Appendix'). In dose level one and two, the upper limb training protocol occupied half of the session (the other half was FES). In dose level three and four, the upper limb training protocol occupied one third of the session (together with one third FES and one third mirror therapy). Four main principles of Motor Learning (Daly et al., 2019) were applied, for example positioning that could influence task difficulty. 'Single joint movement' was executed for the scapula, shoulder, elbow, wrist and hand. 'Task component practice' and 'Full functional practice' consisted of patient specific exercises linked to their usual daily activities. More details of the upper limb training protocol can be found in the 'Appendix'.

Table 3. Upper limb training protocol: Treatment progression hierarchy for coordinated movement practice (Daly et al., 2019).

A. Muscle activation in synergy
B. Single joint movement in synergy
C. Single joint movement out of synergy
D. Alternating joint movement (Flexion and extension)
E. Task component practice
F. Full functional task practice

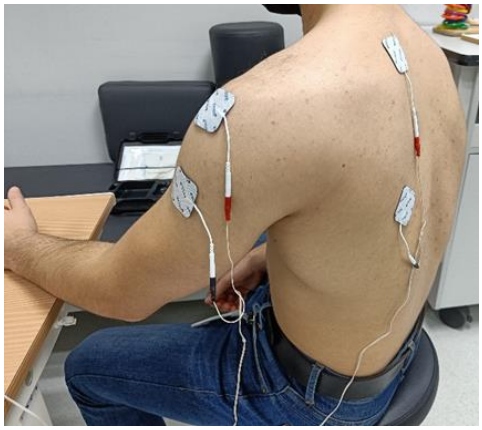
b) Functional Electrical Stimulation (FES)

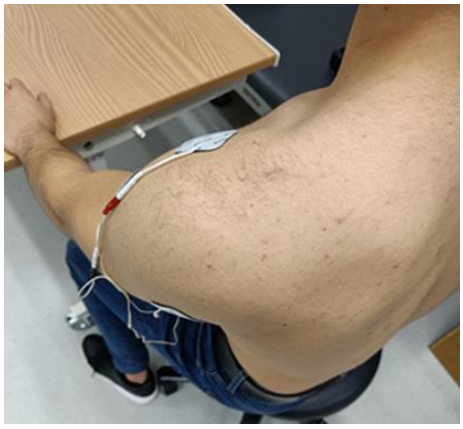
Our review demonstrated the promising evidence of FES in the acute and early subacute stage after stroke in patients with severe upper limb impairments. FES occupied half of the sessions in dose level one and two (together with the upper limb protocol) and one third of the session in dose level three and four (together with the upper limb protocol and mirror therapy). This was possible through the application of two to eight electrodes that were set synchronous or in alternation. Either the whole movement (e.g. reaching) was directed by the electrodes or only a part of the involved muscles was stimulated with two to eight electrodes (Figure 4). In this way, augmented functional training (e.g. reaching for a glass)

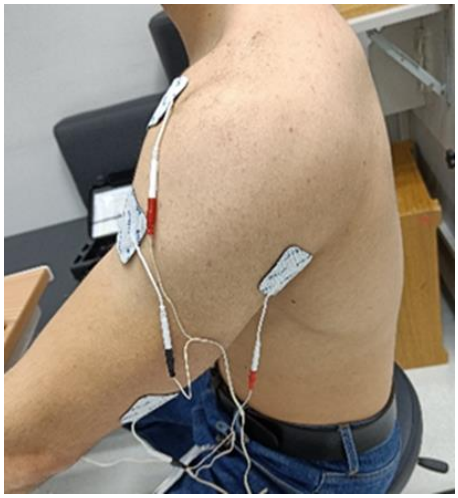
was provided. Two different stimulation programs were created and used based on the manual of the SaeboStim Pro XFT-2000 that was used as FES nerve and muscle stimulator (XFT Medical., 2000; Hofmann, H., 2021) (Table 4). Program one resulted in short muscle contractions and program two in a long contractions. Both programs were applied depending on the type and goal of the concerning exercise. When a good execution of a given exercise was not possible with these parameter settings, the frequency was raised to 60 Hertz (Hz) or another functional movement was chosen.

Table 4. Functional Electrical Stimulation (FES) parameter settings of the two used programs. Hz, Hertz; µs, micro seconds; sec, seconds.

Program	Prescription	Frequency (Hz)	Pulse width (µs)	Contraction (sec)	Relaxation (sec)	Ramp up (sec)	Ramp down (sec)
1	Short contraction	35	250	8	5	2	2
2	Long contraction	35	250	14	10	2	2







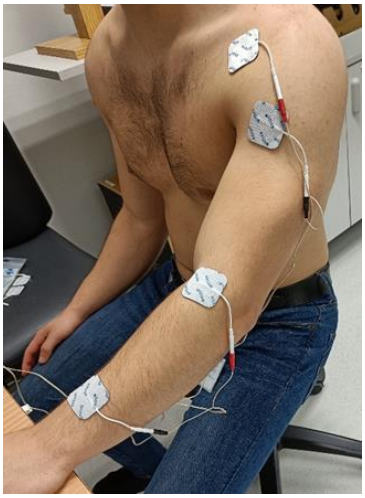


Figure 4. Some examples of FES electrodes positioning to support and augment the reaching movement of the participant.

c) Mirror Therapy

Mirror therapy was chosen as a third component to provide extra variation in the rehabilitation programme at dose level three and four, occupying one third of the sessions. Our review demonstrated that mirror therapy was equally effective as conventional exercise therapy in improving severe upper limb impairments in the acute and early subacute stage after stroke. In mirror therapy, visual feedback is provided placing a mirror box in front of the subject (Figure 5). When the participant looks in the mirror, the unaffected limb was reflected. The participant is told to move the unaffected arm while looking in the mirror. The participant was first instructed to simply watch the reflection of the unaffected hand in the mirror. Progressions were made from static to active and functional movements like rolling a ball. When possible, gentle and synchronous movements of the affected hand were encouraged behind the mirror. All analytical and functional exercises, together with the motor learning principles, of the wrist and hand from a) were implemented in the mirror therapy sessions of the multimodal upper limb rehabilitation program.

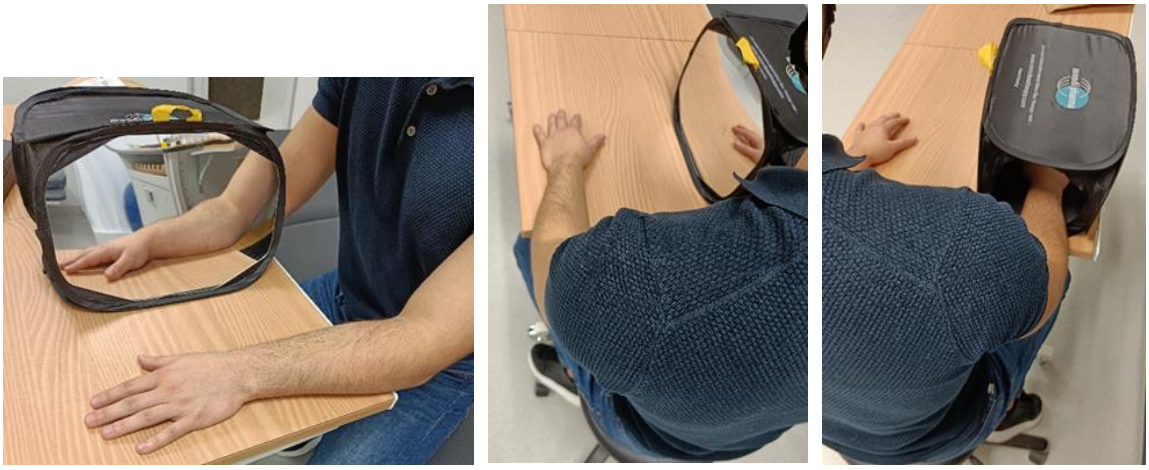


Figure 5. The mirror box needed for mirror therapy

2.6 Statistical analysis (decision tree in 'Appendix')

Statistical analyses involved using JMP software version 16.2 (2022) (Jones, B. & Sall, J., 2011). This analysis included the data of participants that completed the study.

To analyse if there was a cumulative fatigue present in participants, a difference in the before session fatigue scores between the different days was regarded, a distribution (mathematical function) for each participants' data apart was made. After checking for normality by the Shapiro-Wilk test, the signed rank test was conducted accordingly. A value of $p<0.05$ was considered statistically significant.

To analyse if there was a significant difference in fatigue change (after session outcome minus before session outcome) and absolute after session fatigue scores between the two doses, an analysis of two independent groups with continuous data was conducted by a Fit Y by X model. With either after session outcomes or fatigue difference in outcomes as the Y variable and the dose level (consisting of level one and two) as the X-variable. Normality and equality of variance were respectively checked by the Shapiro-Wilk and Brown-Forsythe test. Accordingly, the parametric Pooled t-Test or non-parametric Wilcoxon Rank Sum test were used. A value of $p<0.05$ was considered statistically significant.

The same method, as described for fatigue difference between doses, was used for the analysis of the RPE after session scores by dose and pain after therapy session scores by dose.

To see if a baseline difference between primary and secondary outcome measures was present between the participants, the baseline outcomes were compared in a distribution for one group (consisting of all five participants). After checking for normality by the Shapiro-Wilk test, the t-test or the signed rank test was conducted to see if a significant difference was present with $p<0.05$. The analyses of the baseline to post-intervention outcome changes of the FMA-UE, ARAT, and MI was conducted by using the difference of these scores (post-intervention outcome minus baseline outcome) as independent variables. To compare the difference between post-intervention and baseline scores, the same analysis as described for the baseline differences was conducted.

3. Results

The results section is divided in three parts. First, the demographics and baseline measurements of the included participants in presented. Afterwards, individual case reports for each participant are elaborated. At last, the effect of the intervention program on fatigue, rating of perceived exertion and clinical outcome measures with its statistics is presented.

3.1 Demographics and baseline measurements (Table 6)

Six participants were included in the dose escalation study, but only five completed the study. Dose level one was completed with three participants, while dose level two could be completed by two participants until now. There was one drop-out after the first full intervention session of the sixth participant. The data of this drop-out was not included in the number of patients or any analysis. The respective participant suffered from a second stroke on a different location the night after the first dose of 67 minutes. Recruitment was expanded until one month after stroke, but the five participants were all included in the acute stage after their stroke. All participants had an ischemic stroke, buy all in different brain regions (Table 6). Based on the median Fugl-Meyer Upper Extremity score of 29 points (Interquartile range, IQR) at baseline, participants had moderate upper limb impairments with a poor upper limb capacity (Table 5). This severity was confirmed through the average baseline score of 14 points on the Action Research Arm Test (ARAT) (Table 5). At baseline, there were no significant differences between all participants for all three clinical outcome measures (FMA-UE p=0.062; ARAT p=0.125; MI p=0.062). The specific content of the upper limb therapy program for each participant can be found in detail in the 'Appendix'.

Table 5. Classification of upper limb impairments based on Hoonhorst et al., 2015 and Woodbury et al., 2013

Hoonhorst et al., 2015	**No capacity** - FMA-UE: 0 - 22 - ARAT: 0 - 10	**Poor capacity** - FMA-UE: 23 - 31 - ARAT: 11 - 21	**Limited capacity** - FMA-UE: 32 - 47 - ARAT: 22 - 42
Woodbury et al., 2013	**Severe impairments** - FMA-UE: 0 - 19 ± 2	**Moderate impairments** - FMA-UE: 22 - 47 ± 2	

Table 6. Demographics and baseline measurements

Number of patients	5	
- Acute stage (1 – 7 days)	5	
- Very early subacute (7days – 1 month)	0	
- Dose level 1	3	
- Dose level 2	2	
Age (mean ± SD) (years)	59 ± 12.65 (range 38 – 70)	
Side of stroke (L/R)	2/3	
- Dominant side affected (yes/no)	3/2	
Type of stroke (Ischemic/Hemorrhagic)	5/0	
Location of stroke	• MCA R (middle cerebral artery) • R parietal – frontal prerolandic • M2 • Post nucleo-thalamocapsular • Anterior medulla oblongata	
Days since stroke (mean ± SD) (Days)	4.2 ± 1.64 (range 2 – 6)	
Gender (M/F)	3/2	
MI score at inclusion (mean ± SD)	38.2 ± 16.59 (range 11 – 55)	p = 0.062
FMA (mean ± SD)	29 ± 13.32 (range 11 – 48)	p = 0.062
ARAT (mean ± SD)	14 ± 12.38 (range 0 – 32)	p = 0.125

3.2 Case reports of all participants at the two different dose levels

Participant one: dose level one (Table 7, Appendix)

This participant was the only one included with severe upper limb impairments or no capacity based on table 5 (Hoonhorst et al., 2015; Woodbury et al., 2013). Inclusion and treatment was in the acute stage after stroke. After the three intervention sessions of dose level one, the participant did not show dose-limiting fatigue and there was no increased fatigue after the intervention sessions. Also, the rating of perceived exertion thresholds were not exceeded. The fatigue scores before each session did not increase during the course of the three-day rehabilitation program (p=0.125), which excludes a cumulative fatigue. Nevertheless, the participant did not show any notable improvements on any outcome measure of clinical effectiveness. So, dose level one can be considered as feasible, but not effective in facilitating the spontaneous recovery in this respective case.

Table 7. Individual fatigue scores of participant one

	Before session	After session	Fatigue difference
Preparation dose	6	8.5	2.5
Day 1	6	6	0
Day 2	9	7	-2
Day 3	9	7.5	-1.5
p-value	0.125		

Participant two: dose level one (Table 8, Appendix)

Participant two, included in its first week after stroke, suffered from moderate upper limb impairments (Table 5). All fatigue scores, before and after the sessions, were beneath the DLT-thresholds and no increase in fatigue due to the therapy sessions was observed. There was also no cumulative fatigue (p=0.125). The therapy sessions were perceived as heavy but tolerable. Dose level one can be considered as feasible, but not effective in improving upper limb impairments and disabilities in this respective case.

Table 8. Individual fatigue scores of participant two

	Before session	After session	Fatigue difference
Preparation dose	5	5.5	0.5
Day 1	5	7	2
Day 2	5	5.5	0.5
Day 3	4.5	1	-3.5
p-value	0.125		

Participant three: dose level one (Table 9, Appendix)

The third participant, also included in the acute stage after stroke, suffered from moderate upper limb impairments but had almost no capacity based on the ARAT (Table 5). The participant showed low levels of fatigue, no increased fatigue and perceived the therapy sessions as rather easy. No cumulative fatigue was present (p=0.125). Dose level one can be considered as feasible, but not effective in improving upper limb impairments and disabilities in this respective case. Important to note is that the participant received an upper

limb training protocol of 44 minutes without the application of Functional Electrical Stimulation (FES) because no muscle contraction could be retrieved due to obesity.

Table 9. Individual fatigue scores of participant three

	Before session	After session	Fatigue difference
Preparation dose	2.5	3.5	1
Day 1	4	3	-1
Day 2	4	4	0
Day 3	3	3.5	0.5
p-value	0.125		

Participant four: dose level two (Table 10, Appendix)

The fourth participant, the first one of dose level two, was included two days after its stroke and suffered from moderate upper limb impairments with limited capacity (Table 5). The participant showed low fatigue at all three days before the therapy sessions which eliminates a cumulative fatigue (p=0.125). The therapy sessions caused a slight increase of fatigue after the session but with fatigue scores still far beneath the DLT-thresholds. The participant improved clinically relevant on the Motricity Index with 36 points in comparison with the minimally clinically important difference of 13 points (Lin et al., 2022). For the FMA-UE and ARAT, the third participant made some notable, however not clinically relevant, improvement in upper limb impairments and disabilities. Even more, the participant evolved from moderate to mild upper limb impairments (Table 5). Dose level two of 67 minutes was therefore feasible and effective in augmenting the recovery of upper limb impairments in this respective case.

Table 10. Individual fatigue scores of participant four

	Before session	After session	Fatigue difference
Preparation dose	2	3.5	1.5
Day 1	2.5	6	3.5
Day 2	3.5	3.5	0
Day 3	3.5	3.5	0
p-value	0.125		

Participant five: dose level two (Table 11, Appendix)

The fifth participant, the second of dose level two, was included in the acute stage after stroke and suffered from moderate upper limb impairments with poor capacity (Table 5). The participant showed low fatigue scores before and after the therapy sessions with only a slight increase from the beginning to the end of the sessions. However, all scores were clearly beneath the DLT-thresholds. The respective participant improved clinically relevant on the FMA-UE (20 points in comparison with the MCID of 12.4 points established by Hiragami et al., 2019), the MI (25 points in comparison with MCID of 13 points established by Lin et al., 2022) and the ARAT (32 points in comparison with the MCID of 12 points established by Lang et al., 2008). Following table 5, the participant had only mild to moderate impairments after the intervention program. Dose level two of 67 minutes is therefore feasible and effective in improving upper limb impairments and disabilities in this respective case.

Table 11. Individual fatigue scores of participant five

	Before session	After session	Fatigue difference
Preparation dose	6	3	-3
Day 1	0	5.5	5.5
Day 2	3	6	3
Day 3	6	7	1
p-value	0.25		

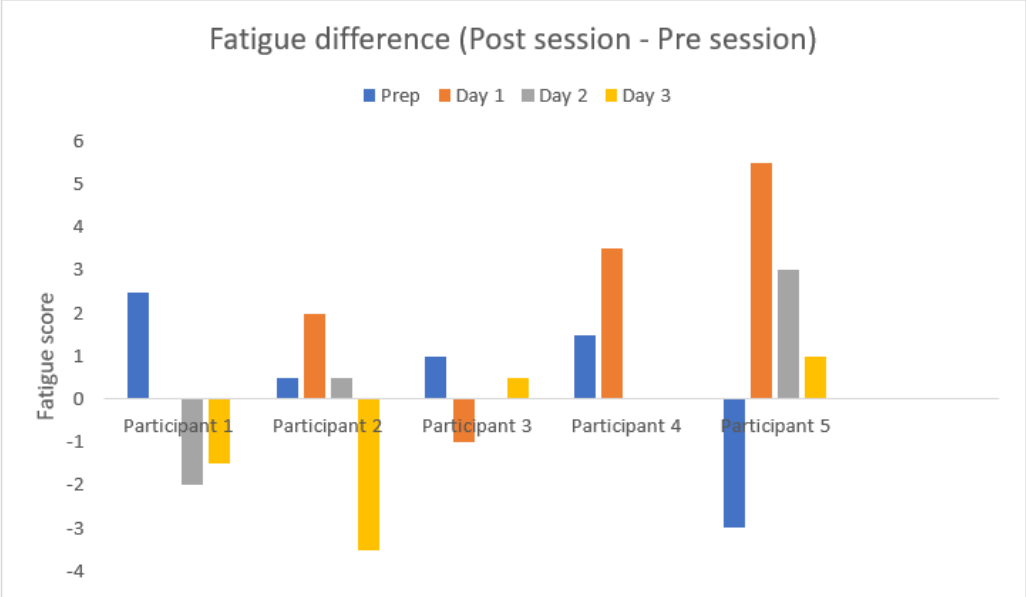
3.3 Intervention effects

Effect of intervention on fatigue (Table in 'Appendix')

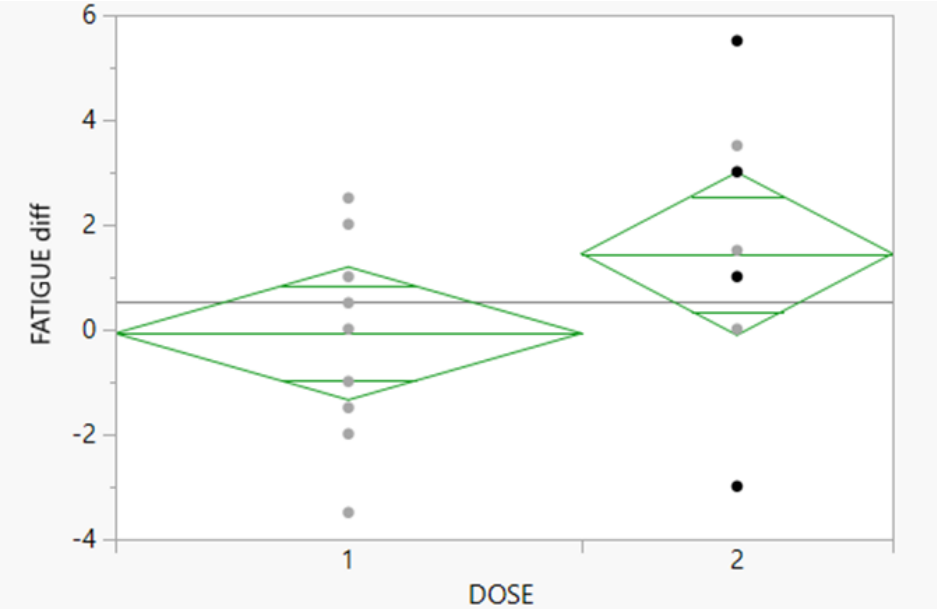
There was no significant difference in fatigue change, from the beginning to the end of the sessions, between the two dose levels (p=0.128) (Graph 4), which means that a session length of 67 minutes did not cause aggravated fatigue in comparison with a session length of 44 minutes. Furthermore, the absolute fatigue scores after the therapy sessions did not differ significantly between dose level one and two (p=0.648) (Graph 5). So, dose level two did neither cause aggravated fatigue nor did it cause absolute higher fatigue scores. The case

reports already discovered that no participants suffered from a cumulative fatigue. No Dose-Limiting Tolerance was reached during the current intervention dose levels.

Figure 4. Fatigue difference scores by participant and by dose

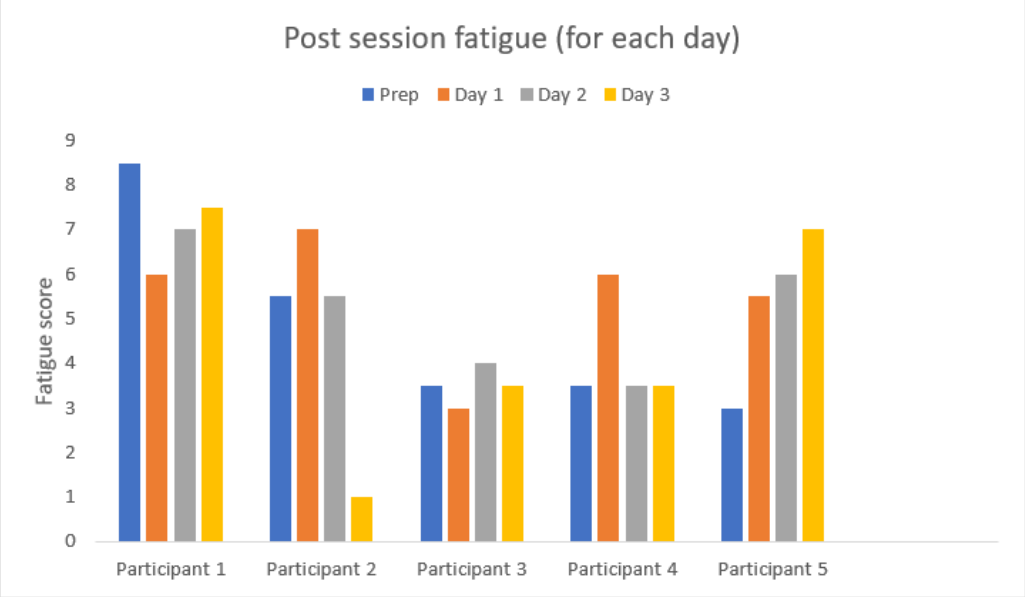


The fatigue difference from before to after session fatigue is presented for each participant on each day. Preparation dose, Prep

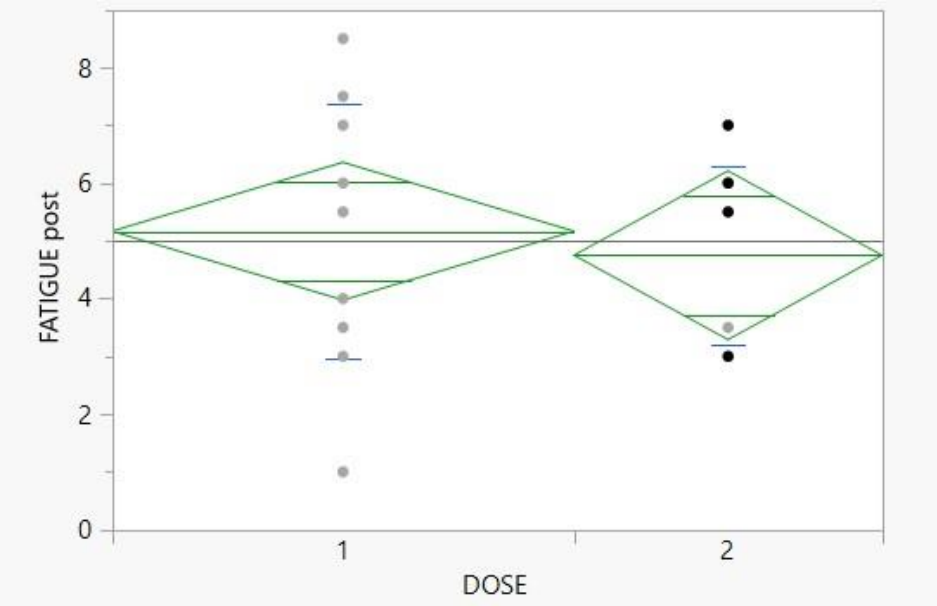


The mean fatigue difference score (from before to after the session) is presented for each dose and between doses. Fatigue difference plotted by dose; Difference, diff

Figure 5. After session fatigue scores by participant and by dose



The after session fatigue score of each participant for each day is presented. Preparation dose, Prep



The mean after session fatigue score per dose and between doses is presented. After session fatigue scores plotted by dose

Effect of intervention on Rating of Perceived Exertion (RPE) (Table in Appendix)

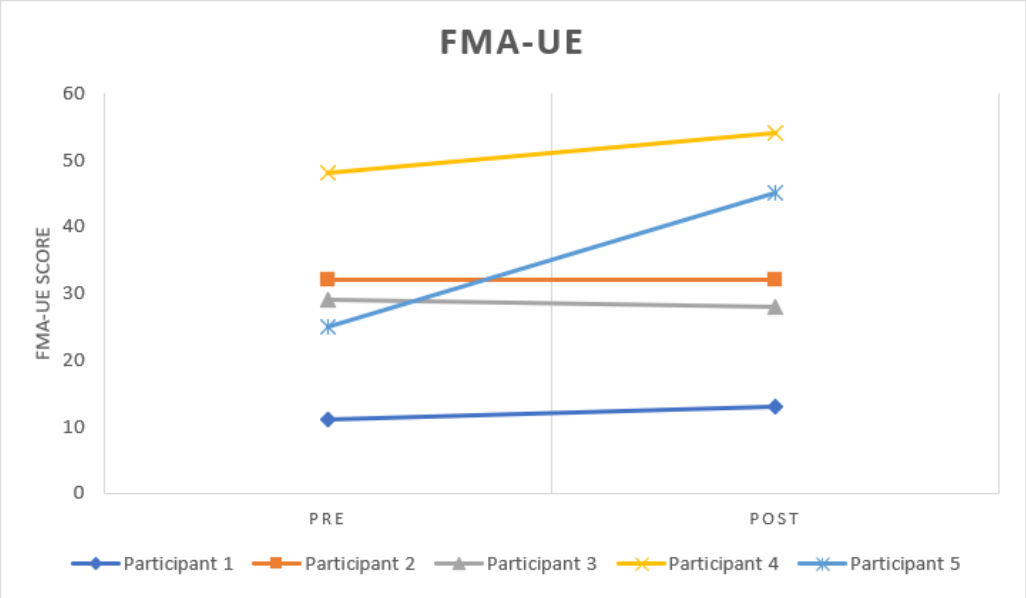
The case reports did confirm that each participant tolerated their respective intervention dose during and after the intervention. Moreover, there were no significant differences between the two dose levels in absolute Borg RPE scores at the end of the sessions (p=0.383, 'Appendix'). So, dose level two of 67 minutes was not perceived as more intensive than dose

level one of 44 minutes. No Dose-Limiting Tolerance was reached during the current intervention dose levels.

Effect of intervention on clinical outcome measures

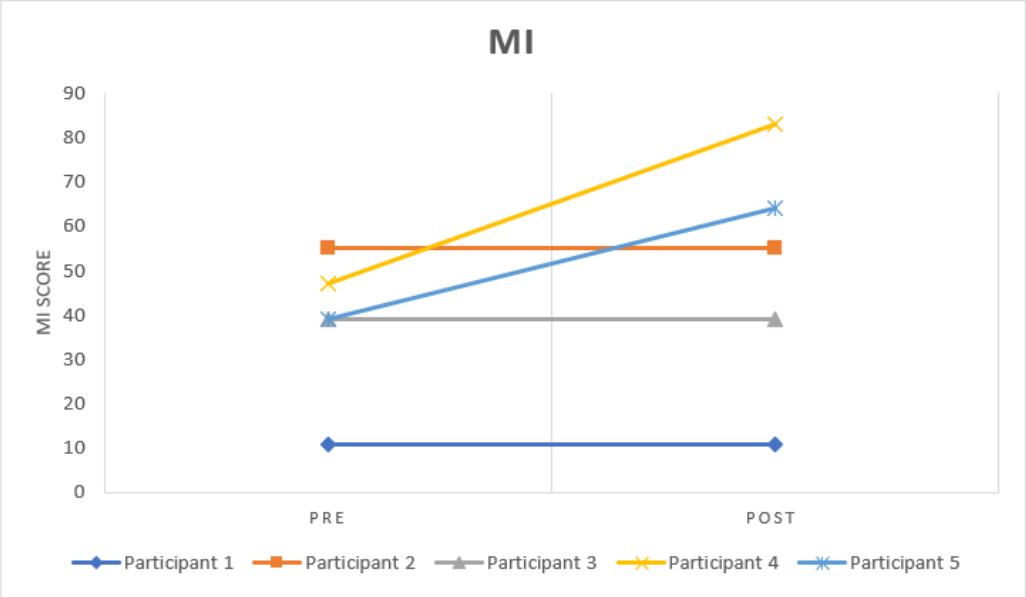
The total intervention program (dose level one plus dose level two) had no overall significant effect on FMA-UE (p=0.25) and MI (p=0.50), and ARAT (p=0.625) ('Appendix'). Due to low sample size and the incomplete dose level two, it was not possible to compare the clinical effectiveness of the two doses separately. The established power was insufficient to reliably detect differences between the two doses. Nevertheless, dose level two resulted in improvements on the FMA-UE (Graph 1), MI (Graph 2) and ARAT (Graph 3) which were higher than the minimally clinically important differences of respectively 12.4, 13 and 17 (and 12) points (Hiragami et al., 2019; Lang et al., 2008; Lin et al., 2022). Due to these clinically relevant improvements, dose level two can be considered as more effective than dose level one in improving moderate to severe upper limb impairments and disabilities after acute and very early subacute stroke.

Graph 1. Fugl-Meyer Upper Extremity (FMA-UE) from baseline (pre) to post intervention



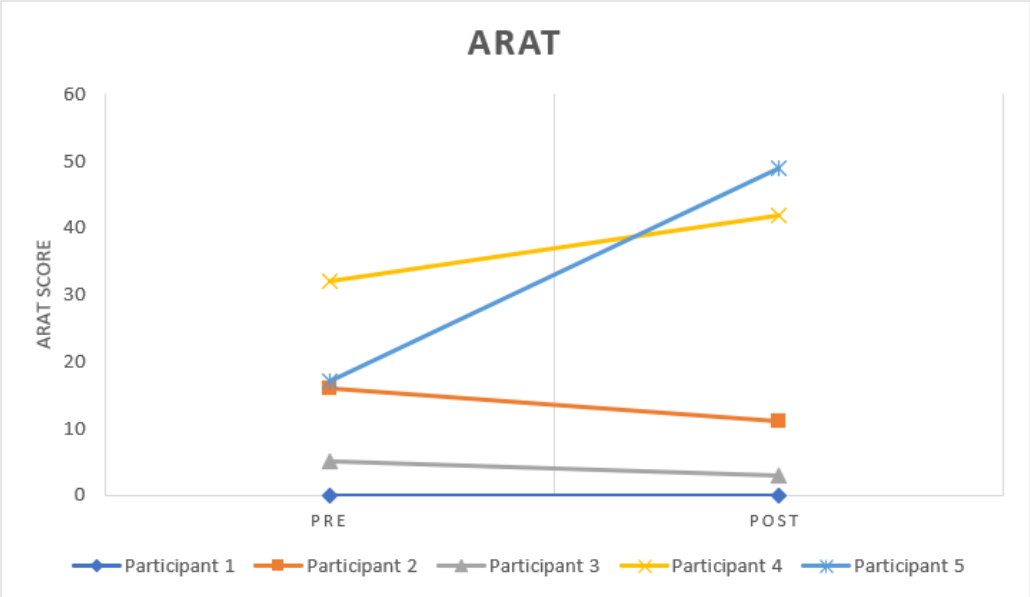
Participant 4 and 5 received dose level two.

Graph 2. Motricity Index (MI) scores from baseline (pre) to post intervention



Participant 4 and 5 received dose level two.

Graph 3. Action Research Arm Test (ARAT) scores from baseline (pre) to post intervention



Participant 4 and 5 received dose level two

4. Discussion

4.1 Interpretation of the dose escalation study

This dose escalation study aimed to identify the optimal session length of upper limb therapy for patients with moderate to severe upper limb impairments after acute (one to seven days after stroke) and very early subacute stroke (eight days to one month after stroke). To achieve this aim, the feasibility of a single-ascending dose of upper limb therapy was assessed which included safety, toxicity and tolerability measurements of an upper limb therapy program. Also, the clinical effects of the different doses were documented. Despite the low recruitment rate, some clear trends were already discovered and provide a good base to proceed the current study until Dose-Limiting Tolerance (DLT) and the Maximum Tolerated Dose (MTD) are reached or the maximum possible dose without experiencing DLT is attained.

Until now, no Dose-Limiting Tolerance (DLT) was experienced by any participant, even though every participant had their intervention in the first week after stroke. The dosages applied in the study appeared to be feasible.
There was no significant difference between dose level one and two in fatigue increase (from the beginning to the end of the sessions), which means that dose level two did not cause any aggravated fatigue. Furthermore, the average fatigue score after the sessions did not differ significantly between the two dose levels. Fatigue levels of participants in both dose levels at day one (preparation dose) did not worsen over the course of three days wherein the intervention program was executed. Thus, there was no cumulative fatigue during the intervention program. However, participants were regularly inconsistent in reporting fatigue scores with day by day oscillations. Some participants were less fatigued after their intervention session, what possibly means that this population needs activation to overcome their feeling of fatigue. This can be caused by long periods by day of not interacting at all (De Wit et al., 2005). All participants of both dose levels did tolerate the therapy sessions well in terms of intensity. The average rating of perceived exertion after the therapy sessions did not differ significantly between the two dose levels and were all beneath the DLT-thresholds. In conclusion, based on participants' and therapists' experiences, the dose of 67 minutes can be perceived as feasible and well tolerable.

The study faced one drop-out, however it was not related to the intervention program. In acute stroke care, there are some common issues therapists have to face. Mazwi et al. (2020) reported post-stroke hypoarousal, insomnia, temporary bowel and bladder incontinence, post-stroke dysphagia, mood disorders and communication difficulties as possible patient-specific barriers that hinder qualitative physical therapy. This is as well a possible explanation for the low recruitment rate our experiment faced.

The total intervention program did not provide significant effects in terms of improving moderate to severe upper limb impairments after acute and very early subacute stroke. Because of the low sample size and the incomplete dose level two, it was very difficult to establish a statistical significant difference with sufficient power which is a possible reason for not identifying any significant difference overall and the analysis of between-dose differences was not possible.

In dose level one, which included three participants in the acute stage after stroke, there were no notable improvements after the intervention on ICF level of motor function (FMA-UE, MI) or activity (ARAT). Due to low dosage of upper limb therapy, dose level one only received 44 minutes of upper limb therapy per day, the spontaneous course of stroke recovery could not be facilitated. One participant of dose level one did not receive the FES part of the intervention. In our review, FES was considered at least as effective as time-matched conventional therapy and therefore could have influenced the effect on clinical outcome measures in a positive way (Francisco et al. 1998; Obayashi et al., 2020; Shimodozono et al., 2013; Zheng et al., 2019). Nevertheless, none of the three participants of dose level one did make any notable improvements, so the influence of missing the FES part of the intervention in one participant seems to be negligible.

Dose level two did make some notable improvements over time on all outcome measures, both on ICF level of motor function (FMA-UE, MI) and activity (ARAT). Both participants were located in the acute stage after stroke. Dose level two did improve averagely with 13 points on the FMA-UE, which is higher than the minimally clinically important difference (MCID) of 12.4 points of the FMA-UE. The MCID of the MI and ARAT were exceeded as well on average by dose level two on. Even more, after the intervention the two participants were evolved from moderate to mild upper limb impairments (Table 5; Hoonhorst et al., 2015; Woodbury et al., 2013), through which the second dose of 67 minutes of upper limb therapy can be

considered to have an additional effect in comparison with the first dose of 44 minutes on improving upper limb impairments and disabilities. In this case, it's more appropriate to state that the second dose could facilitate the spontaneous stroke recovery better. These results are a trend to a positive dose-response relationship, which could not be established in our own systematic review. However, Hayward et al. (2021) stated that non-effects could be due to the low dosage of upper limb therapy, specifically with a session length from 30 to 60 minutes. Most of the included studies in our review had a therapy time per day of less than 60 minutes. It is therefore understandable that no positive dose-response relationship could be established in our systematic review because of the common low therapy dosages. This is at the same time a possible reason why the second dose level of 67 minutes may be effective. The improvements of dose level two need to be emphasized as, on average, the MCID of all clinical outcome measures were exceeded. The improvements in this trial were made within one week after their baseline assessment and within one month after stroke at the most. The MCID values referenced to in the introduction were all established at least one month (to three months) after their baseline assessments.

On the other hand, the trend to a positive dose-response relationship would confirm the findings of qualitative studies as the Queen Square Upper Limb (QSUL) Neurorehabilitation program (Ward et al., 2019) and the BOOST therapy program (Meyer et al., 2021), where higher dosages of therapy provided clinically important higher improvements in upper limb impairments in comparison with lower dosages. The QSUL program provided 30 hours of therapy per week, which is a very high dose, while the BOOST therapy program provided one hour of therapy extra per session. However, both studies did not include participants in the acute stage after stroke, although a recent study of Dromerick et al. (2021) proved the acute stage to be sensitive for intensive exercise therapy.

The observed improvements of the participants of dose level two were on ICF level of motor function (FMA-UE and MI) as well as on ICF level of activity (ARAT). It indicates a transfer from improvements in upper limb motor function to upper limb activities. This supports the findings of our own review where the transfer was already confirmed. Early studies of Chae et al. (1995) and Patel et al. (2000) stated that the level of upper limb impairment based on the FMA-UE is a predictor of physical disability in the later stages after stroke. Upper limb

motor function is considered to be the variable with the highest predictive power for self-care ability.

4.2 Strengths and weaknesses

One of the strengths of this dose escalation study is its methodology. The study design, namely the cumulative three plus three design, is a scientific underpinned method (Dite et al., 2015; Machin et al., 2011). The modified Fibonacci scheme to establish the different dose levels is proven to be feasible in earlier studies of Colucci et al. (2017), Peiris et al. (2017) and Penel et al. (2012). The applied intervention is a multimodal program that is based on the findings of our own systematic review in terms of effective strategies in the rehabilitation of moderate to severe upper limb impairments in the acute and early subacute stage after stroke. The intervention is described in detail for each day of each dose level and subdivided based on the initial FMA-UE score, these details can be found in the 'Appendix'. The intervention program was adjusted to the patient-specific level of impairments based on the initial FMA-UE score. This is a strength as a patient-specific rehabilitation is mostly overlooked in experimental studies. Our systematic review identified that scientific underpinned intervention approaches of severe upper limb impairments in the acute stage after stroke are scarce and the influence of patient-specific barriers as fatigue in this stage on rehabilitation are unknown. In accordance with our review, Hayward et al. (2021) appointed a lack of attention to interventions in the acute stage of stroke. The dose escalation study is therefore a good innovation to qualitatively elevate the literature and knowledge about rehabilitation approaches early after stroke.

The study could not yet be completed due to low recruitment rate. Nevertheless, the current obtained conclusions will be largely extended after completing the dose escalation study. The smaller sample size is a weakness because it reduced the statistical power and confidence level of the study, through which not all planned analyses could be executed. To complement the non-significant effects of the low sample size, precise individual case reports were added to discuss feasibility and effectiveness.

The inclusion of participants up to month after stroke was an attempt to promote recruitment rate. The integral first month post-stroke is a critical time for neural endogenous plasticity and responsiveness to sensorimotor experience (Biernaskie et al., 2004;

Birkenmeier et al., 2010; Krakauer et al., 2012). Doing so, the dose escalation study is not exclusively a research in the acute stage after stroke. To promote recruitment rate even more, it would be better to include another acute stroke unit other than Ziekenhuis Oost-Limburg (ZOL) Genk in the future. Recently, the first arrangements were made with Noorderhart MS centre Pelt to be added as recruitment and intervention site.
Very severe patients, who do not have a flicker in wrist extension (at least grade one at wrist extensors measured by the Medical Research Council (MRC) Scale), were excluded. The aim of the study was to provide different doses of active rehabilitation and to assess the impact of active exercise-induced fatigue on outcome measures and tolerability. This aim could not be reached when no active flicker was present.

The study did not reach dose level three, which also meant that no mirror therapy was applied in the intervention program until now. Our systematic review determined mirror therapy as an effective adjunct to conventional therapy in the rehabilitation of moderate to severe upper limb impairments in the acute and early subacute stage after stroke (Chan & Au-Yeung, 2018; Dohle et al., 2008). It is therefore possible that mirror therapy in combination with a new and longer dose (dose level three of 100 minutes) will provide an augmented effect on improvements of upper limb impairments and disabilities.

There is a possible rater bias as four different researchers performed the baseline and post-intervention clinical assessments. However, the FMA-UE is reliable both within and between raters in patients in the early stages after stroke (79-100% agreement) (Hernández et al., 2019). Van der Lee et al. (2001) and McDonnell M. (2008) confirmed the high intra- and interrater reliability of the ARAT with all Spearman's rho values being higher than 0.98 . At last, the within (ICC = 0.93, Fayazi et al., 2012) and between rater (Spearman rho = 0.88, Collin & Wade, 1990) reliability of the MI was established as well. Consequently, the rater bias has rather a negligible effect on the clinical measurements in this study.

4.3 Recommendations for future research

Mainly, future research should focus on the integral rehabilitation of moderate to severe upper limb impairments in the early stages after stroke. Obviously, it is necessary to complete the dose escalation study to identify the optimal session length in the rehabilitation of moderate and severe upper limb impairments after acute and very early

subacute stroke. In this way, a reliable dose-response relationship for this population can be demonstrated. Once, the optimal session length is determined, it can serve as a solid base for further research. The clinical effectiveness of different rehabilitation strategies can be investigated more qualitatively as session length is standardized. Also, the effect of different intensities of upper limb therapy can be investigated within the same session length. Important here is the reproducibility of dose descriptions as the dose articulation framework of Hayward et al. (2021) is a considerable option. All these elements promote the standardization of the rehabilitation of acute and very early subacute stroke patients with moderate to severe upper limb impairments. Another element to consider is the use of prognostic tools such as the proficient PREP2 model to further adjust the upper limb therapy program (Lundquist et al., 2021; Stinear et al., 2017). In doing so, a more patient-specific rehabilitation strategy can be applied, like in our dose escalation study where the initial FMA-UE scores served to specifically adjust the intervention program to each participant. Furthermore, it is important to investigate the possible barriers that therapists can face in the acute stage after stroke (Mazwi et al., 2020). This study is one of the first to investigate the influence of fatigue, tiredness and perceived exertion on the feasibility and effectiveness of an upper limb therapy program, but more research is crucial. Our study included participants with moderate or severe upper limb impairments. Based on table 5 following our own systematic review, only one participant suffered from severe upper limb impairments. This respective participant tended to be generally more fatigued than the other four participants. Nonetheless, the respective participant did not reach dose-limiting tolerance (DLT). That's why future research should also include exclusively severely impaired participants to investigate the influence of fatigue on clinical outcome measures in this specific population.

In general, a sufficient sample size is needed to obtain high-quality evidence and subanalyses on the influence of location, side and type of stroke lesion on outcome measures can be performed in addition.

5. Conclusion

The dose escalation study identified the second dose of 67 minutes as a more optimal session length, than the first dose of 44 minutes, of upper limb therapy for stroke survivors with moderate to severe upper limb impairments after acute and very early subacute stroke. The dose of 67 minutes was considered feasible as no Dose-Limiting Tolerance (DLT) thresholds were exceeded. The participants showed good tolerability as no aggravated fatigue, tiredness or perceived exertion was established. The participants of dose level two made some clinically relevant improvements on ICF level of motor function (FMA-UE, MI) and activity (ARAT), while the participants of dose level one did not make any improvements. These results indicate a trend to a positive dose-response relationship. However, the Maximum Tolerated Dose (MTD) could not yet be identified as the dose escalation study is still ongoing due to low recruitment rate. The dose escalation study is expected to proceed soon to dose level three with 100 minutes of multimodal upper limb therapy.

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Appendix

Fatigue measurements

	Participant	Day	Before session fatigue	After session fatigue	Average after session fatigue	Fatigue difference	Average fatigue difference
Dose level 1	1	Preparation	6	8.5	5.17 ± 2.10	2.5	-0.35 ± 1.61
		1	6	6		0	
		2	9	7		-2	
		3	9	7.5		-1.5	
	2	Preparation	5	5.5		0.5	
		1	5	7		2	
		2	5	5.5		0.5	
		3	4.5	1		-3.5	
	3	Preparation	2.5	3.5		1	
		1	4	3		-1	
		2	4	4		0	
		3	3	3.5		0.5	
Dose level 2	4	Preparation	2	3.5	4.75 ± 1.44	1.5	1.44 ± 2.43
		1	2.5	6		3.5	
		2	3.5	3.5		0	
		3	3.5	3.5		0	
	5	Preparation	6	3		-3	

	1	0	5.5	5.5	
	2	3	6	3	
	3	6	7	1	
p-value			p= 0.648	p= 0.128	

± Standard Deviation

Rating of Perceived Exertion (RPE) measurements

	Participant	Day	RPE after session	Average RPE after session
Dose level 1	1	Preparation	15	12.75 ± 2.59
		1	15	
		2	13	
		3	15	
	2	Preparation	13	
		1	15	
		2	17	
		3	10	
	3	Preparation	9	
		1	9	
		2	11	
		3	11	
Dose level 2	4	Preparation	11	11.75 ± 1.39
		1	13	
		2	11	
		3	11	
	5	Preparation	9	
		1	13	
		2	13	

	3	13
p-value		p= 0.383

± Standard Deviation

Fugl-Meyer Upper Extremity measurements by participant

	Participant	Baseline	Post-intervention	Difference	Average difference
Dose level 1	1	11	13	2	0.33 ± 1.25
	2	32	32	0	
	3	29	28	-1	
Dose level 2	4	48	54	6	13 ± 7
	5	25	45	20	
p- value				p= 0.25	

± Standard Deviation

Motricity Index measurements by participant

	Participant	Baseline	Post-intervention	Difference	Average difference
Dose level 1	1	11	11	0	0
	2	55	55	0	
	3	39	39	0	
Dose level 2	4	47	83	36	30.5 ± 5.5
	5	39	64	25	
p- value				p= 0.50	

± Standard Deviation

Action Research Arm Test measurements by participant

	Participant	Baseline	Post-intervention	Difference	Average difference
Dose level 1	1	0	0	0	-2.33 ± 2.05
	2	16	11	-5	
	3	5	3	-2	
Dose level 2	4	32	42	10	21 ± 11
	5	17	49	32	
p- value				p= 0.625	

Multimodal intervention program

Dose level. Day	Preparation dose	1.1	1.2	1.3	2.1	2.2	2.3
Time of session/ FMA-UE score	**20 mins**	**40 mins**	**40 mins**	**40 mins**	**67 mins**	**67 mins**	**67 mins**
0-22	10 mins: Single Joint Movement Practice in synergy: Scapula-hand (wrist fingers and thumb) 10 mins: Distal or proximal FES stimulation	20 mins: Single Joint Movement Practice in synergy: Scapula-hand (wrist fingers and thumb) 20 mins: Distal or proximal FES stimulation	20 mins: Single Joint Movement Practice in synergy: Scapula-hand (wrist fingers and thumb) 20 mins: Distal or proximal FES stimulation	20 mins: Single Joint Movement Practice in synergy: Scapula-hand (wrist fingers and thumb) 20 mins: Distal or proximal FES stimulation	33 mins: Single Joint Movement Practice in synergy: Scapula-hand (wrist fingers and thumb) 34 mins: Distal or proximal FES stimulation	33 mins: Single Joint Movement Practice in synergy: Scapula-hand (wrist fingers and thumb) 34 mins: Distal or proximal FES stimulation	33 mins: Single Joint Movement Practice in synergy: Scapula-hand (wrist fingers and thumb) 34 mins: Distal or proximal FES stimulation
23-31	10 mins: Single Joint/Alternating out of synergy: Scapula-hand (wrist fingers and thumb) 10 mins: Distal or proximal FES stimulation	20 mins: Single Joint/Alternating out of synergy: Scapula-hand (wrist fingers and thumb) 20 mins: Distal or proximal FES stimulation	20 mins: Single Joint/Alternating out of synergy: Scapula-hand (wrist fingers and thumb) 20 mins: Distal or proximal FES stimulation	20 mins: Single Joint/Alternating out of synergy: Scapula-hand (wrist fingers and thumb) 20 mins: Distal or proximal FES stimulation	33 mins: Single Joint/Alternating out of synergy: Scapula-hand (wrist fingers and thumb) 34 mins: Distal or proximal FES stimulation	33 mins: Single Joint/Alternating out of synergy: Scapula-hand (wrist fingers and thumb) 34 mins: Distal or proximal FES stimulation	33 mins: Single Joint/Alternating out of synergy: Scapula-hand (wrist fingers and thumb) 34 mins: Distal or proximal FES stimulation
32-47	10 mins: Single Joint/Alternating out of synergy/Task component practice: Scapula-hand (wrist fingers and thumb)	20 mins: Single Joint/Alternating out of synergy/Task component practice: Scapula-hand (wrist fingers and thumb)	20 mins: Single Joint/Alternating out of synergy/Task component practice: Scapula-hand (wrist fingers and thumb) 20 mins:	20 mins: Single Joint/Alternating out of synergy/Task component practice: Scapula-hand (wrist fingers and thumb)	33 mins: Single Joint/Alternating out of synergy/Task component practice: Scapula-hand (wrist fingers and thumb) 34 mins:	33 mins: Single Joint/Alternating out of synergy/Task component practice: Scapula-hand (wrist fingers and thumb)	33 mins: Single Joint/Alternating out of synergy/Task component practice: Scapula-hand (wrist fingers and thumb) 34 mins:

	10 mins: Distal or proximal FES stimulation	20 mins: Distal or proximal FES stimulation	Distal or proximal FES stimulation	20 mins: Distal or proximal FES stimulation	Distal or proximal FES stimulation	34 mins: Distal or proximal FES stimulation	Distal or proximal FES stimulation

Dose level. Day	3.1	3.2	3.3	4.1	4.2	4.3
Time of session/ FMA-UE score	**100 mins**	**100 mins**	**100 mins**	**133 mins**	**133 mins**	**133 mins**
0-22	40 mins: Single Joint Movement Practice in synergy: Scapula-hand (wrist fingers and thumb) 40 mins: Distal or proximal FES stimulation 20 mins: Motor Imagery/Mirror Therapy	40 mins: Single Joint Movement Practice in synergy: Scapula-hand (wrist fingers and thumb) 40 mins: Distal or proximal FES stimulation 20 mins: Motor Imagery/Mirror Therapy	40 mins: Single Joint Movement Practice in synergy: Scapula-hand (wrist fingers and thumb) 40 mins: Distal or proximal FES stimulation 20 mins: Motor Imagery/Mirror Therapy	45 mins: Single Joint Movement Practice in synergy: Scapula-hand (wrist fingers and thumb) 45 mins: Distal or proximal FES stimulation 43 mins: Motor imagery/mirror therapy	45 mins: Single Joint Movement Practice in synergy: Scapula-hand (wrist fingers and thumb) 45 mins: Distal or proximal FES stimulation 43 mins: Motor imagery/mirror therapy	45 mins: Single Joint Movement Practice in synergy: Scapula-hand (wrist fingers and thumb) 45 mins: Distal or proximal FES stimulation 43 mins: Motor imagery/mirror therapy
23-31	40 mins: Single Joint/Alternating out of synergy: Scapula-hand (wrist fingers and thumb) 40 mins: Distal or proximal FES stimulation 20 mins: Motor Imagery/Mirror Therapy	40 mins: Single Joint/Alternating out of synergy: Scapula-hand (wrist fingers and thumb) 40 mins: Distal or proximal FES stimulation 20 mins: Motor Imagery/Mirror Therapy	40 mins: Single Joint/Alternating out of synergy: Scapula-hand (wrist fingers and thumb) 40 mins: Distal or proximal FES stimulation 20 mins: Motor Imagery/Mirror Therapy	45 mins: Single Joint/Alternating out of synergy: Scapula-hand (wrist fingers and thumb) 45 mins: Distal or proximal FES stimulation 43 mins: Motor imagery/mirror therapy	45 mins: Single Joint/Alternating out of synergy: Scapula-hand (wrist fingers and thumb) 45 mins: Distal or proximal FES stimulation 43 mins: Motor imagery/mirror therapy	45 mins: Single Joint/Alternating out of synergy: Scapula-hand (wrist fingers and thumb) 45 mins: Distal or proximal FES stimulation 43 mins: Motor imagery/mirror therapy
32-47	35 mins:	35 mins:	35 mins:	45 mins:	45 mins:	45 mins:

	Single Joint/Alternating out of synergy/Task component practice: Scapula-hand (wrist fingers and thumb) <u>34 mins:</u> Distal or proximal FES stimulation <u>20 mins:</u> Motor Imagery/Mirror Therapy	Single Joint/Alternating out of synergy/Task component practice: Scapula-hand (wrist fingers and thumb) <u>34 mins:</u> Distal or proximal FES stimulation <u>20 mins:</u> Motor Imagery/Mirror Therapy	Single Joint/Alternating out of synergy/Task component practice: Scapula-hand (wrist fingers and thumb) <u>34 mins:</u> Distal or proximal FES stimulation <u>20 mins:</u> Motor Imagery/Mirror Therapy	Single Joint/Alternating out of synergy/Task component practice: Scapula-hand (wrist fingers and thumb) <u>45 mins:</u> Distal or proximal FES stimulation <u>43 mins:</u> Motor imagery/mirror therapy	Single Joint/Alternating out of synergy/Task component practice: Scapula-hand (wrist fingers and thumb) <u>45 mins:</u> Distal or proximal FES stimulation <u>43 mins:</u> Motor imagery/mirror therapy	Single Joint/Alternating out of synergy/Task component practice: Scapula-hand (wrist fingers and thumb) <u>45 mins:</u> Distal or proximal FES stimulation <u>43 mins:</u> Motor imagery/mirror therapy

<u>Upper limb training protocol</u>

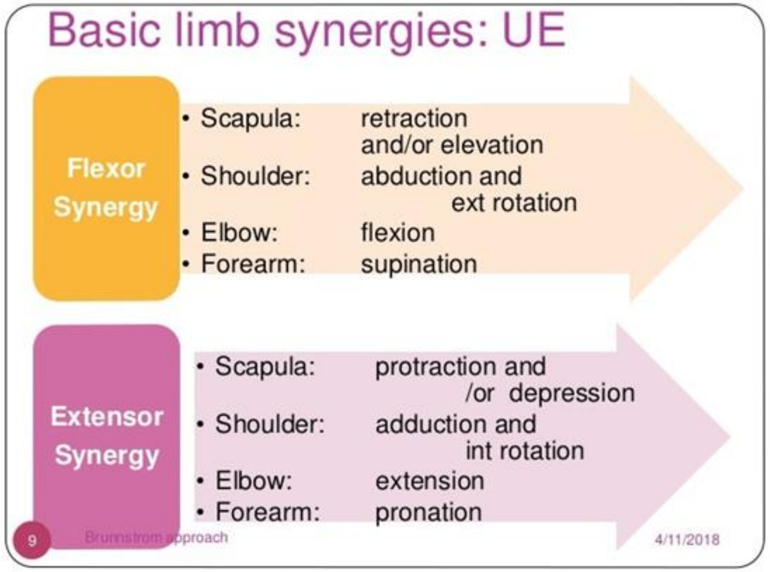
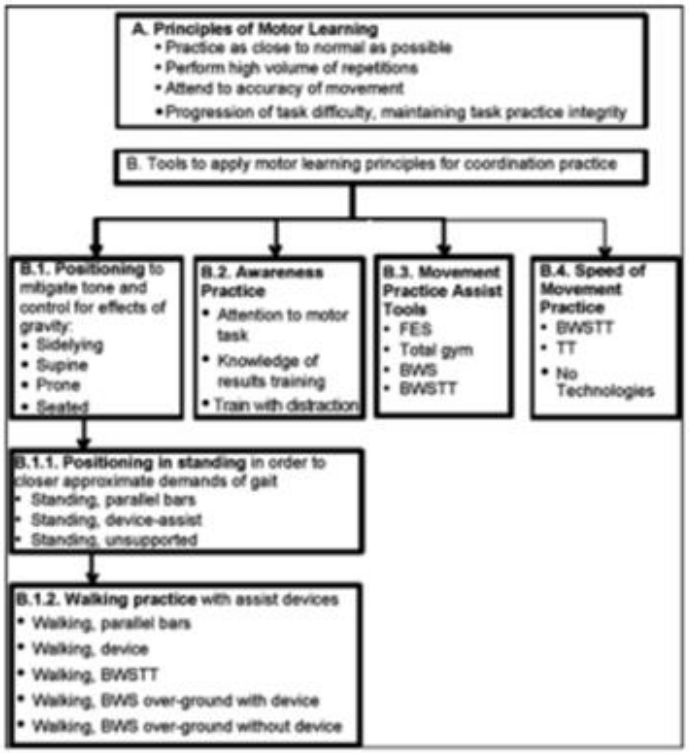


Table 1. Upper Limb Training Protocol: Treatment Progression Hierarchy for Coordinated Movement Practice.[a]

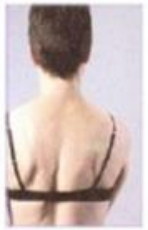
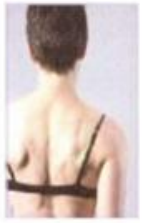
A.	Muscle activation in synergy
B.	Single joint movement in synergy
C.	Single joint movement, out of synergy * Coordination training * Speed of movement training
D.	Alternating joint movement (flexion and extension) * Coordination training * Speed of movement training
E.	Task component practice * Coordination training * *Speed of movement training*
F.	Full functional task practice * Coordination training * *Speed of movement training*

[a]Table from Daly (2012) and McCabe (2015).

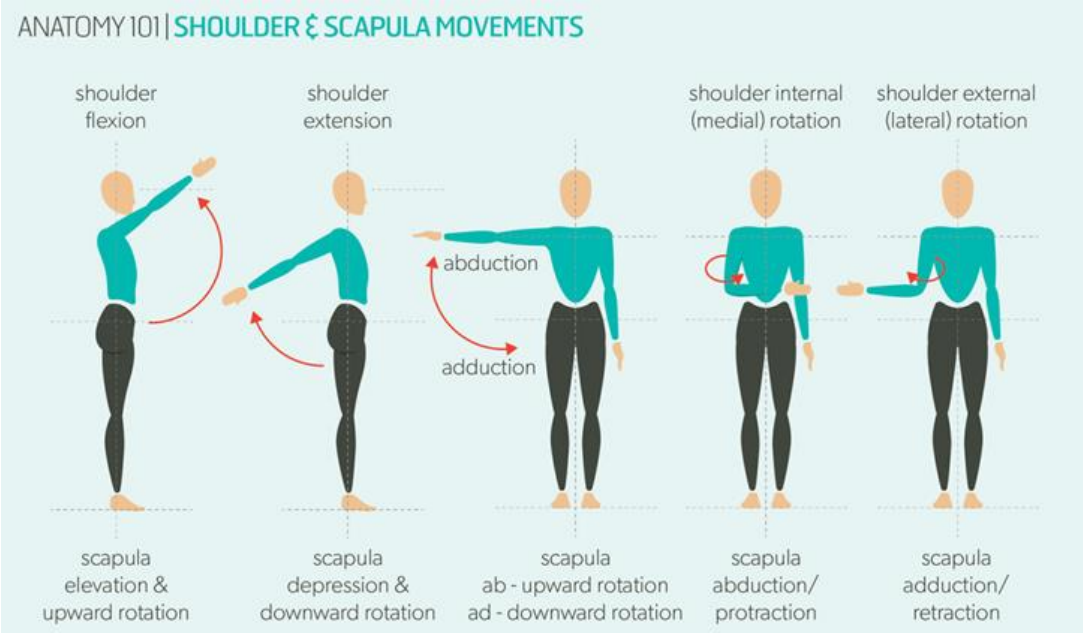


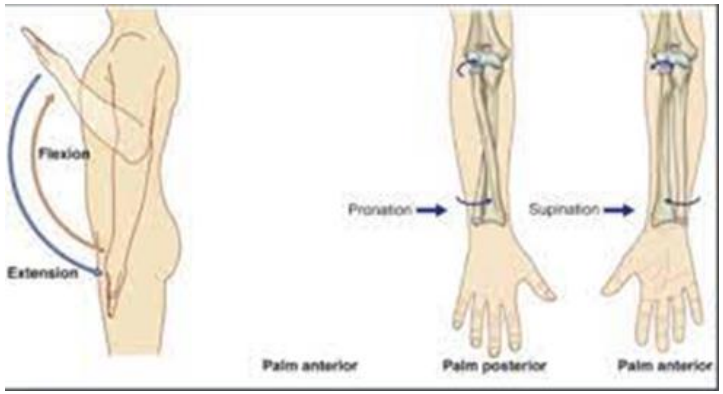
Scapula program

SYNERGISTS/ANTAGONISTS: SCAPULA

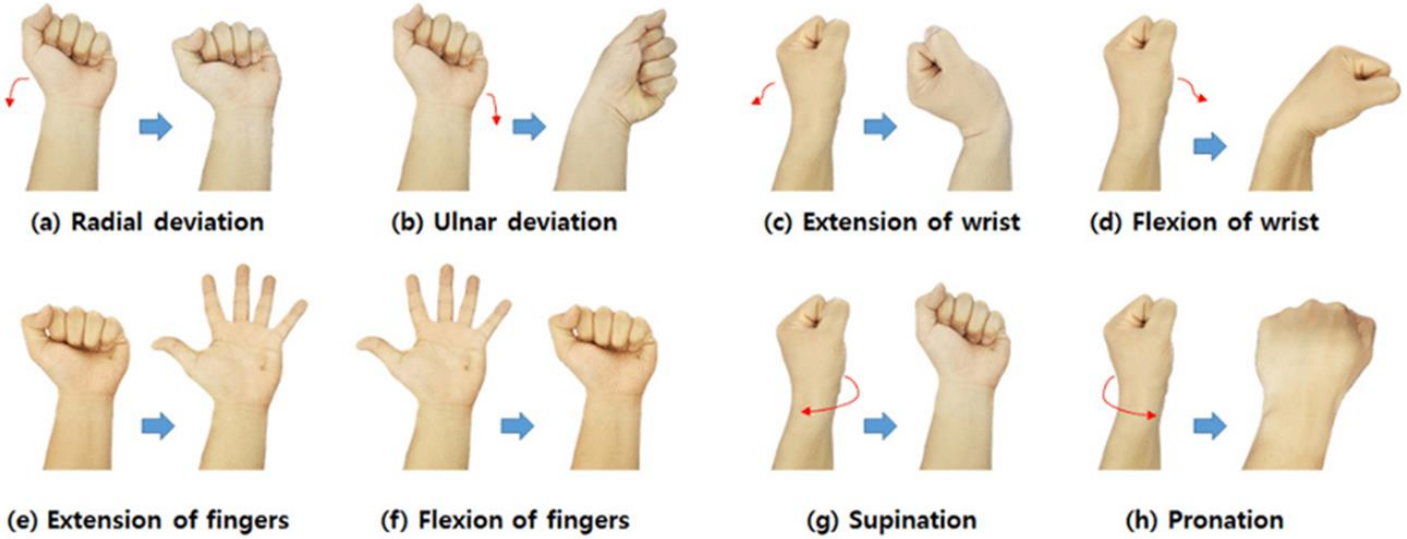
Scapular Motion		Muscles Involved	Scapular Motion		Muscles Involved
Elevation		Trapezius (upper fibers) Levator scapula Rhomboids	Depression		Trapezius (lower fibers) Pectoralis minor Serratus anterior
Retraction		Trapezius (all fibers) Rhomboids Levator scapula	Protraction		Pectoralis minor Serratus anterior
Upward Rotation		Trapezius (all fibers) Serratus anterior	Downward Rotation		Levator scapula Pectoralis minor Rhomboids

Shoulder and elbow program





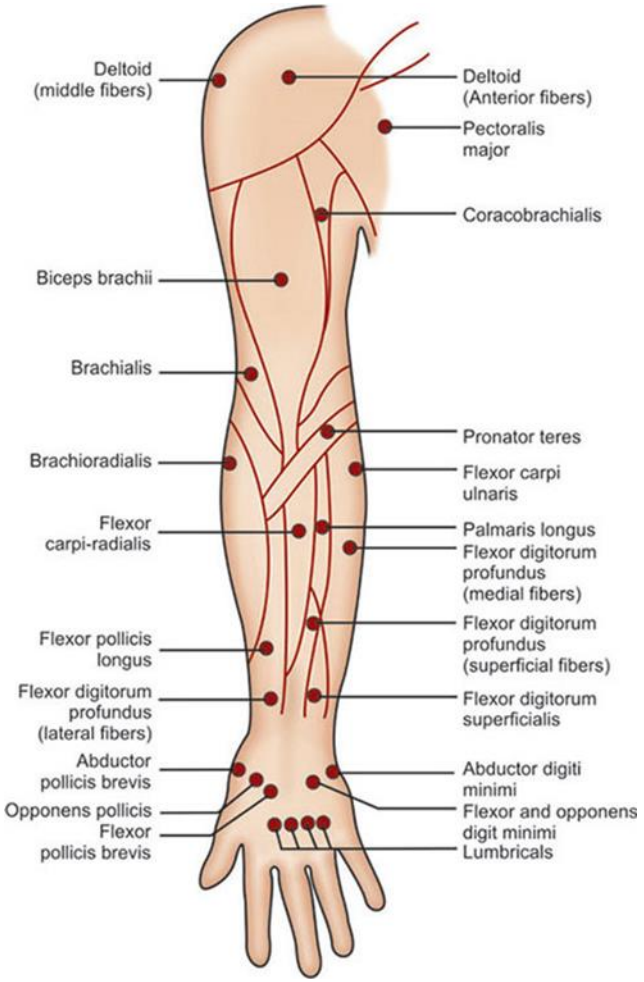
Wrist, hand and finger program

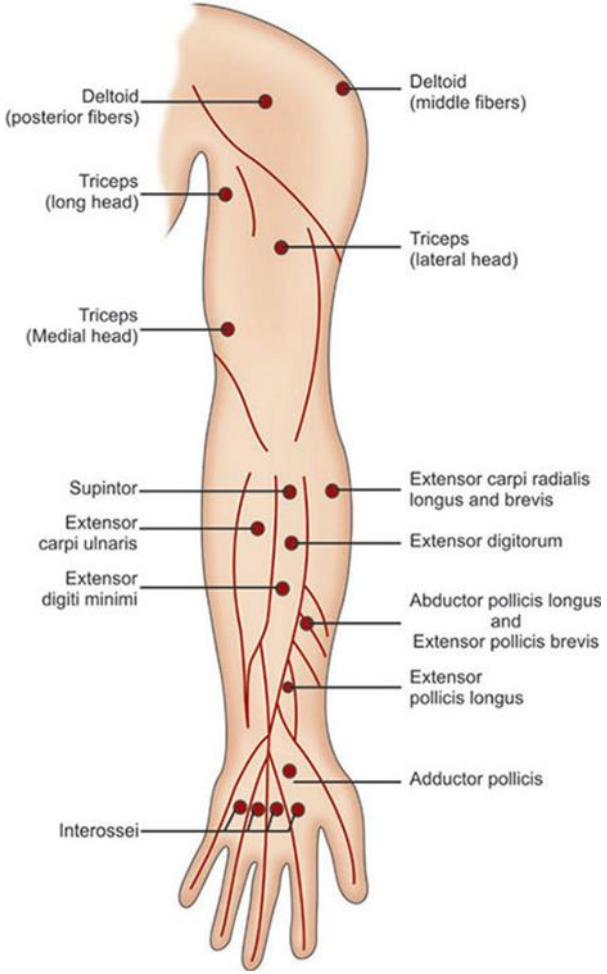


Task component practice, full functional practice; examples

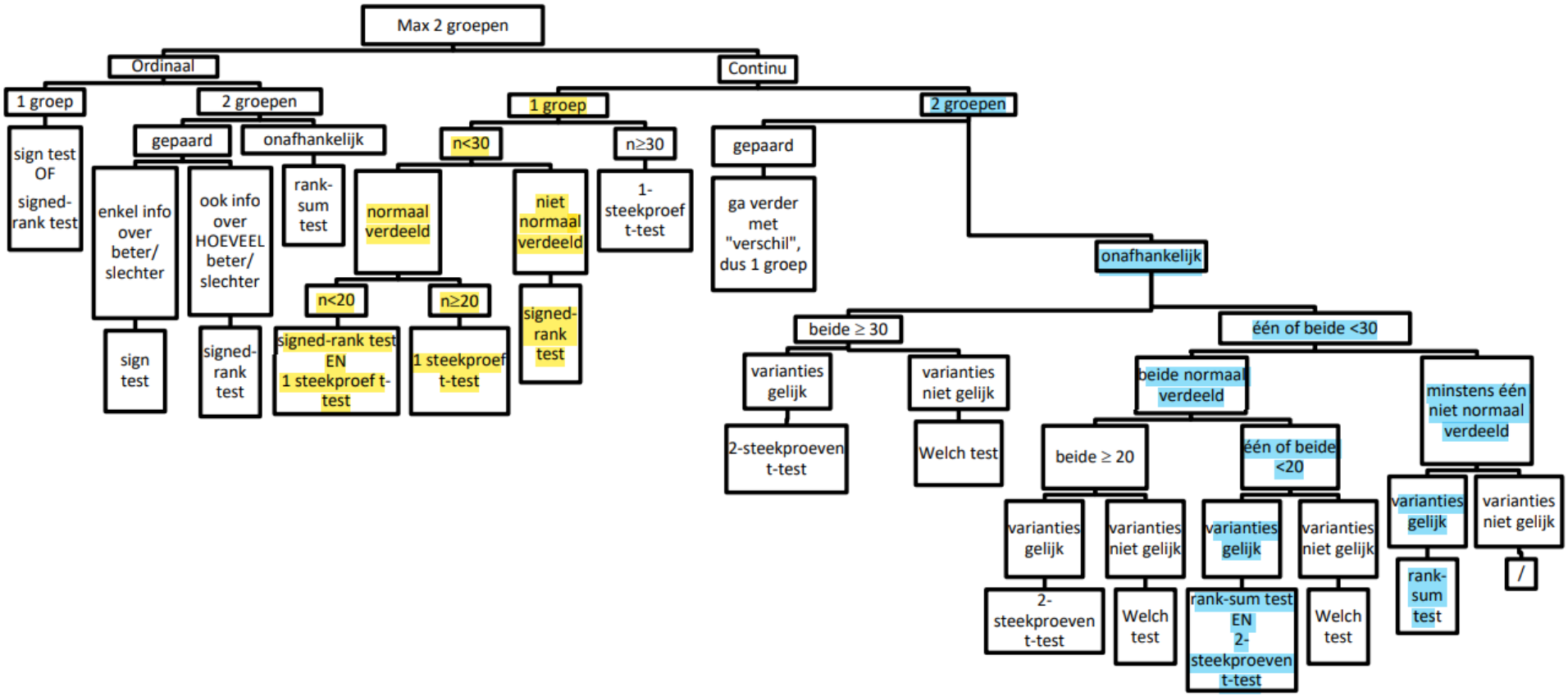
- Stir food in a bowl
- Place objects in kitchen cupboard
- Carry objects (unilateral and bilateral)
- Write with pen or pencil
- Throw ball
- Swing a golf club

Functional Electrical Stimulation





Statistical decision tree



Yellow represents the one-group statistical analyses, Blue represents the two-group statistical analyses

Outcome measures

Visual Analog Scale for Fatigue (VAS-F)

Visual Analogue Scale to Evaluate Fatigue Severity (VAS-F)

ID #_____ Date_____

Time _____a.m. _____p.m.

We are trying to find out about your level of energy before and after your night of sleep. There are 18 items we would like you to respond to. This should take less than 1 minute of your time. Thank you.

DIRECTIONS: You are asked to circle a number on each of the following lines to indicate how you are feeling RIGHT NOW.

For example, suppose you have not eaten since yesterday.
What number would you circle below?

not at all hungry 0 1 2 3 4 5 6 7 8 9 10 extremely hungry

You would probably circle a number closer to the "extremely hungry" end of the line.
This is where I put it:

not at all hungry 0 1 2 3 4 5 6 (8) 9 10 extremely hungry

NOW PLEASE COMPLETE THE FOLLOWING ITEMS:

1. not at all **tired** 0 1 2 3 4 5 6 7 8 9 10 extremely **tired**

4. not at all **fatigued** 0 1 2 3 4 5 6 7 8 9 10 extremely **fatigued**

Rating of Perceived Exertion (RPE) Borg scale

Borg RPE Scale	
Scoring	Level of Exertion
6	No Exertion
7	Extremely Light
8	
9	Very Light
10	
11	Light
12	
13	Somewhat Hard
14	
15	Hard (Heavy)
16	
17	Very Hard
18	
19	Extremely Hard
20	Maximal Exertion

Numeric Rating Scale for Pain

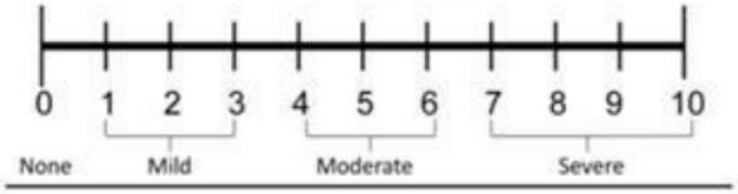
The Numeric Pain Rating Scale Instructions

General Information:

- The patient is asked to make three pain ratings, corresponding to current, best and worst pain experienced over the past 24 hours.
- The average of the 3 ratings was used to represent the patient's level of pain over the previous 24 hours.

Patient Instructions (adopted from (McCaffery, Beebe et al. 1989):

"Please indicate the intensity of current, best, and worst pain levels over the past 24 hours on a scale of 0 (no pain) to 10 (worst pain imaginable)"



Reference:
McCaffery, M., Beebe, A., et al. (1989). Pain: Clinical manual for nursing practice. Mosby St. Louis, MO.

Fugl-Meyer Upper Extremity Assessment (FMA-UE)

FMA-UE PROTOCOL — Rehabilitation Medicine, University of Gothenburg

FUGL-MEYER ASSESSMENT
UPPER EXTREMITY (FMA-UE)
Assessment of sensorimotor function

ID:
Date:
Examiner:

Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S: The post-stroke hemiplegic patient. A method for evaluation of physical performance. Scand J Rehabil Med 1975, 7:13-31.

A. UPPER EXTREMITY, sitting position					
I. Reflex activity				**none**	**can be elicited**
Flexors: biceps and finger flexors (at least one) **Extensors**: triceps				0 0	2 2
			Subtotal I (max 4)		
II. Volitional movement within synergies, without gravitational help				**none**	**partial**	**full**
Flexor synergy: Hand from contralateral knee to ipsilateral ear. From extensor synergy (shoulder adduction/ internal rotation, elbow extension, forearm pronation) to flexor synergy (shoulder abduction/ external rotation, elbow flexion, forearm supination). **Extensor synergy:** Hand from ipsilateral ear to the contralateral knee	Shoulder	retraction		0	1	2
		elevation		0	1	2
		abduction (90°)		0	1	2
		external rotation		0	1	2
	Elbow	flexion		0	1	2
	Forearm	supination		0	1	2
	Shoulder	adduction/internal rotation		0	1	2
	Elbow	extension		0	1	2
	Forearm	pronation		0	1	2
			Subtotal II (max 18)			
III. Volitional movement mixing synergies, without compensation				**none**	**partial**	**full**
Hand to lumbar spine hand on lap	cannot perform or hand in front of ant-sup iliac spine hand behind ant-sup iliac spine (without compensation) hand to lumbar spine (without compensation)			0	1	2
Shoulder flexion 0°- 90° elbow at 0° pronation-supination 0°	immediate abduction or elbow flexion abduction or elbow flexion during movement flexion 90°, no shoulder abduction or elbow flexion			0	1	2
Pronation-supination elbow at 90° shoulder at 0°	no pronation/supination, starting position impossible limited pronation/supination, maintains starting position full pronation/supination, maintains starting position			0	1	2
			Subtotal III (max 6)			
IV. Volitional movement with little or no synergy				**none**	**partial**	**full**
Shoulder abduction 0 - 90° elbow at 0° forearm pronated	immediate supination or elbow flexion supination or elbow flexion during movement abduction 90°, maintains extension and pronation			0	1	2
Shoulder flexion 90° - 180° elbow at 0° pronation-supination 0°	immediate abduction or elbow flexion abduction or elbow flexion during movement flexion 180°, no shoulder abduction or elbow flexion			0	1	2
Pronation/supination elbow at 0° shoulder at 30°- 90° flexion	no pronation/supination, starting position impossible limited pronation/supination, maintains start position full pronation/supination, maintains starting position			0	1	2
			Subtotal IV (max 6)			
V. Normal reflex activity assessed only if full score of 6 points is achieved in part IV; compare with the unaffected side				**0 (IV), hyper**	**lively**	**normal**
biceps, triceps, finger flexors	2 of 3 reflexes markedly hyperactive or 0 points in part IV 1 reflex markedly hyperactive or at least 2 reflexes lively maximum of 1 reflex lively, none hyperactive			0	1	2
			Subtotal V (max 2)			
			Total A (max 36)			

Approved by Fugl-Meyer AR 2010 — 1 — Updated 2015-03-11

B. WRIST support may be provided at the elbow to take or hold the starting position, no support at wrist, check the passive range of motion prior testing		none	partial	full
Stability at 15° dorsiflexion elbow at 90°, forearm pronated shoulder at 0°	less than 15° active dorsiflexion dorsiflexion 15°, no resistance tolerated maintains dorsiflexion against resistance	0	1	2
Repeated dorsifexion / volar flexion elbow at 90°, forearm pronated shoulder at 0°, slight finger flexion	cannot perform volitionally limited active range of motion full active range of motion, smoothly	0	1	2
Stability at 15° dorsiflexion elbow at 0°, forearm pronated slight shoulder flexion/abduction	less than 15° active dorsiflexion dorsiflexion 15°, no resistance tolerated maintains dorsiflexion against resistance	0	1	2
Repeated dorsifexion / volar flexion elbow at 0°, forearm pronated slight shoulder flexion/abduction	cannot perform volitionally limited active range of motion full active range of motion, smoothly	0	1	2
Circumduction elbow at 90°, forearm pronated shoulder at 0°	cannot perform volitionally jerky movement or incomplete complete and smooth circumduction	0	1	2
	Total B (max 10)			

C. HAND support may be provided at the elbow to keep 90° flexion, no support at the wrist, compare with unaffected hand, the objects are interposed, active grasp		none	partial	full
Mass flexion from full active or passive extension		0	1	2
Mass extension from full active or passive flexion		0	1	2
GRASP				
a. Hook grasp flexion in PIP and DIP (digits II-V), extension in MCP II-V	cannot be performed can hold position but weak maintains position against resistance	0	1	2
b. Thumb adduction 1-st CMC, MCP, IP at 0°, scrap of paper between thumb and 2-nd MCP joint	cannot be performed can hold paper but not against tug can hold paper against a tug	0	1	2
c. Pincer grasp, opposition pulpa of the thumb against the pulpa of 2-nd finger, pencil, tug upward	cannot be performed can hold pencil but not against tug can hold pencil against a tug	0	1	2
d. Cylinder grasp cylinder shaped object (small can) tug upward, opposition of thumb and fingers	cannot be performed can hold cylinder but not against tug can hold cylinder against a tug	0	1	2
e. Spherical grasp fingers in abduction/flexion, thumb opposed, tennis ball, tug away	cannot be performed can hold ball but not against tug can hold ball against a tug	0	1	2
	Total C (max 14)			

D. COORDINATION/SPEED, sitting, after one trial with both arms, eyes closed, tip of the index finger from knee to nose, 5 times as fast as possible		marked	slight	none
Tremor	at least 1 completed movement	0	1	2
Dysmetria at least 1 completed movement	pronounced or unsystematic slight and systematic no dysmetria	0	1	2
		≥ 6s	**2 - 5s**	**< 2s**
Time start and end with the hand on the knee	at least 6 seconds slower than unaffected side 2-5 seconds slower than unaffected side less than 2 seconds difference	0	1	2
	Total D (max 6)			

Motricity Index (MI)

Motricity Index

De test wordt afgenomen wanneer de patiënt zit. Gekeken wordt naar de willekeurige bewegingsactiviteit van arm en been. De gewenste beweging mag indien nodig worden voorgedaan. Bij een volledige score van de arm (99 punten) en/of been (99 punten) mag 1 punt worden opgeteld. De ernst van de hemiplegie wordt berekend door (arm+ been) te delen door 2.

Arm:	**Activiteit:**	**Beoordeling:**
_____ _____ _____ TOTAAL (1+2+3)= _____	1. Pincet greep (het vasthouden van een 2,5 cm blokje tussen duim en wijsvinger) 2. Het willekeurig flecteren van de elleboog 3. De schouder abduceren vanuit 0° stand	**Test 1:** 0 = geen beweging 11= elke willekeurige beweging van vinger en/of duim 19 = patiënt pakt het blokje maar kan het niet optillen tegen de zwaartekracht in 22 = patiënt pakt het blokje maar kan het niet stevig vasthouden 26 = patiënt pakt het blokje op maar kan het niet zo stevig vasthouden als aan de niet aangedane zijde 33= normale knijpkracht (in vergelijking met niet aangedane zijde)
[redacted]		**Beoordeling:** **Test 2 t/m 6:** 0 = geen willekeurige beweging 9 = willekeurige activiteit is palpabel 14 = willekeurige beweging is zichtbaar maar niet over de hele bewegingsrange 19 = willekeurige beweging is over de hele range mogelijk, maar niet tegen een weerstand in 25 = willekeurige beweging is tegen een weerstand in over de hele range mogelijk maar is zwakker dan aan de niet aangedane zijde 33 = normale kracht
TOTAAL (1t/m 6 / 2)	**Opmerkingen:**	

Action Research Arm Test (ARAT)

Action Research Arm Test

De Action Research Arm Test (ARAT) evalueert de handvaardigheid. De test bestaat uit 19 items, welke gescoord worden op een ordinale 4 puntsschaal (0-3 punten).

In totaal zijn 57 punten te behalen. Voor het afnemen van de test is een ARAT-koffer vereist (te verkrijgen bij het VU medisch centrum, via de link http://www.aratest.eu/Index_nederlands.htm).

Testprotocol Action Research Arm Test

Voor het afnemen van de test zijn een ARAT-koffer, stopwatch, tafel en stoel (met rugleuning, bij voorkeur zonder armleuningen) nodig.
De ARAT-koffer wordt geopend op tafel neergezet (gemiddelde tafelhoogte 76 cm), met de klep tegen de voorrand van de tafel aan. De patiënt zit midden voor de ARAT-koffer. De niet-paretische arm wordt op de schoot onder de tafel geplaatst.
De patiënt moet met zijn rug tegen de rugleuning aan blijven zitten gedurende het uitvoeren van de gevraagde items van de test. De afstand tussen patiënt en koffer moet zo zijn, dat de patiënt met zijn rug tegen de rugleuning kan blijven, terwijl zijn vingers (bij het naar voren strekken van de arm) de achterrand van de bovenzijde van de koffer aanraken.
Bij het starten moet de patiënt zijn hand naast het rode vakje op de tafel leggen. Gevraagd wordt om op eigen comfortabel tempo de handeling uit te voeren. De patiënt start nadat tot 3 is geteld en het startsein 'ja' is gegeven. Bij het loskomen van de hand van de tafel wordt tevens de stopwatch ingedrukt. De handeling wordt afgeklokt op het moment dat de hand weer terug op tafel ligt. Voor de rechterarm worden de rechter elementen van de koffer gebruikt en voor de linkerarm de linker.[6]

Voor de ARAT bestaat hiërarchische schaalindeling. Als de patiënt maximaal (= 3 punten) scoort op het eerste item, kunnen voor de daarop volgende items van dezelfde subtest ook 3 punten worden gescoord.
Desalniettemin wordt geadviseerd om bij twijfel het volgende item van de subtest te testen.
Gestart wordt met het eerste item van elke subtest. Hiervan wordt aangenomen dat deze het moeilijkst is voor de patiënt; van het tweede item wordt aangenomen dat deze het gemakkelijkst is voor de patiënt. Indien de patiënt om één of ander reden niet te testen is, wordt een score = 0 genoteerd. De maximale totaalscore die behaald kan worden is 57 punten.[6]

A. Subtest 'vijfvingergreep'
De 6 items moeten vanaf het afgebakende vierkant in het midden van het werkblad van de koffer opgepakt worden en boven op de bovenrand van de koffer geplaatst worden.
Het wetsteentje moet op de smalle lange zijkant neergezet worden op het vierkant en zo door de patiënt worden opgepakt.

B. Subtest 'cilindergreep'
Het glas moet tot de aangegeven streep gevuld worden met water (het glas is dan voor de helft gevuld).
Verstandig is om vooraf een handdoek op de benen van de patiënt te leggen. De patiënt moet het volle glas in het lege schenken.
De ring moet zo geplaatst worden op het vierkant, dat de elleboog van de patiënt vanuit pronatie start bij het oppakken van de ring en naar supinatie gaat bij het plaatsen van de ring om de bijpassende pin in de koffer.
De buis van 1 cm en van 2,5 cm moet geplaatst worden in daarbij passende uitsparing op het werkblad van de koffer. De patiënt moet hem van daaruit oppakken en over de bijpassende pin in de koffer plaatsen.

C. Subtest 'pincetgreep'
Zowel de kogeltjes als de stuiters moeten vanaf het afgebakende vierkant van het midden van het werkblad van de koffer opgepakt worden en boven in het ronde bakje op de bovenrand van de koffer geplaatst worden.

D Subtest 'grove armbewegingen'
Het is verstandig patiënten die een bril dragen deze voor het uitvoeren van de test eerst af te laten zetten.

Testformulier Action Research Arm Test

Naam patiënt: _____
Geb. datum: _____
Paretische zijde: links/rechts
Datum: _____
Naam beoordelaar: _____

0 = de patiënt kan geen enkel onderdeel van het test-item uitvoeren
1 = de patiënt voert het test-item gedeeltelijk uit
2 = de patiënt voert het test-item goed uit, maar met veel moeite/tijd
3 = de patiënt voert het test-item goed uit

A. Subtest 'vijfvingergreep'

Test	**Tijd overschrijdingswaarde* rechts/links**	**Score**
1. houten blok 10 cm (indien score = 3, dan totaal = 18 punten; ga naar subtest B)	_____4,1/4,3 seconde	_____
2. houten blok 2,5 cm (indien score = 0 dan totaal = 0 punten; ga naar subtest B)	_____3,6/3,5 seconde	_____
3. houten blok 5 cm	_____3,6/3,5 seconde	_____
4. houten blok 7,5 cm	_____3,8/3,9 seconde	_____
5. houten bal 7,5 cm	_____3,7/3,9 seconde	_____
6. wetsteentje	_____3,5/3,8 seconde	_____
	Totaal A:	_____

*Overschrijdingswaarde = gemiddelde waarde + 1,96 x standaarddeviatie

B. Subtest 'cilindergreep'

Test	Tijd overschrijdingswaarde* rechts/links	Score
1. glazen met water (indien score =3, dan totaal = 12 punten; ga naar subtest C)	..... 7,8/7,9 seconde	.....
2. buis 2,5 cm (indien score = 0 dan totaal = 0 punten; ga naar subtest C)	..... 4,1/4,2 seconde	.....
3. buis 1 cm	..... 4,1/4,4 seconde	.....
4. ring 3,5 cm	..... 3,9/4,1 seconde	.....
	Totaal B:	.....

*Overschrijdingswaarde = gemiddelde waarde + 1,96 x standaarddeviatie

C. Subtest 'pincetgreep'

Test	Tijd overschrijdingswaarde* rechts/links	Score
1. kogeltje 6 mm (duim – ringvinger) (indien score 3, dan totaal: C = 18 punten; ga naar subtest D)	..... 4,4/4,5 seconde	.....
2. stuiter 1,5 cm (duim – wijsvinger) (indien score = 0, dan totaal: C = 0 punten, da naar subtest D)	..... 3,9/3,7 seconde	.....
3. stuiter 1,5 cm (duim – middelvinger)	..... 3,8/3,9 seconde	.....
4. stuiter 1,5 cm (Duim – ringvinger)	..... 3,8/4,2 seconde	.....
5. kogeltje 6 mm (duim – wijsvinger)	..... 3,8/4,2 seconde	.....
6. kogeltje 6 mm (duim – middelvinger)	..... 4,0/4,1 seconde	.....
	Totaal C:	.....

* Overschrijdingswaarde = gemiddelde waarde + 1,96 x standaarddeviatie

D. Subtest ' grove arm bewegingen'

Test	Tijd overschrijdingswaarde* rechts/links	Score
1. hand – achterhoofd (indien score = 3, dan totaal = 9 punten; de test is klaar)	.....2,6/2,8 seconden	.....
2. hand – mond	.....2,4/2,5 seconden	.....
3. hand – bovenkant hoofd	.....2,6/2,8 seconden	.....
	Totaal D:	.....

* Overschrijdingswaarde = gemiddelde waarde + 1,96 x standaarddeviatie

Indien de linkerarm dominant is, moet de tijd bij rechts aangegeven worden aangehouden.

Totaalscore op de ARAT (maximale score = 57): _____

ARAT standardization following Yozbatiran et al. (2008)

POSITIONING

Positioning of the Subject

Appropriate body posture for ARAT testing has the subject seated upright in a standard chair that has a firm back and no armrests. The assessor may provide foam padding to the back of the chair to ensure that upright position is maintained. The trunk must remain in contact with the back of the chair throughout testing. In this regard, the subject is instructed and regularly reminded not to lean forward, stand up, or move sideways, although we do not recommend that the subject's trunk be strapped to the chair. The head is held in a neutral upright position. The subject's legs are in front of the chair, with feet in contact with floor throughout testing.

All ARAT tasks are performed unilaterally. To promote this and keep the nontested hand in view, the subject is always asked to start with both hands in pronated position on the table, except for the "gross movement" subscale, which requires starting with both hands pronated on the lap. Suggested chair and testing-table dimensions are provided in Table A2. The testing-table level should approximate the subject's midabdomen, with the difference in chair-table height of about 30 cm considered optimal.

Positioning of the Materials for Each Task

The subject sits close to the table, with a 15-cm distance from the anterior torso to the front edge of table. In our experience, this distance allows enough upper-extremity mobility for the subject to be able to reach the top of the shelf, but maintains emphasis on the required body posture during testing. The use of a nonslip mat that is placed over the table is highly recommended. We have found it useful to draw prestated positions for each test object on this mat (Figure 2).

Further specifications for position of testing materials are specified under the instructions for each subscale.

Declarations of honour

UHASSELT

Verklaring op Eer

Ondergetekende, student aan de Universiteit Hasselt (UHasselt), faculteit **Revalidatiewetenschappen en Kinesitherapie** aanvaardt de volgende voorwaarden en bepalingen van deze verklaring:

1. Ik ben ingeschreven als student aan de UHasselt in de opleiding **Revalidatiewetenschappen en Kinesitherapie** waarbij ik de kans krijg om **in het kader van mijn opleiding** mee te werken aan onderzoek van de faculteit **Revalidatiewetenschappen en Kinesitherapie** aan de UHasselt. Dit onderzoek wordt beleid door **Prof. Dr. Peter Feys en Dr. Lisa Tedesco Triccas** en kadert binnen **het opleidingsonderdeel wetenschappelijke stage/ masterproef Deel 2** zal in het kader van dit onderzoek creaties, schetsen, ontwerpen, prototypes en/of onderzoeksresultaten tot stand brengen in het domein van **de neurologische revalidatie van het bovenste lidmaat na CVA** (hierna: "De Onderzoeksresultaten").

2. Bij de creatie van De Onderzoeksresultaten doe ik beroep op de achtergrondkennis, vertrouwelijke informatie[1], universitaire middelen en faciliteiten van UHasselt (hierna: de "Expertise").

3. Ik zal de Expertise, met inbegrip van vertrouwelijke informatie, uitsluitend aanwenden voor het uitvoeren van hogergenoemd onderzoek binnen UHasselt. Ik zal hierbij steeds de toepasselijke regelgeving, in het bijzonder de Algemene Verordening Gegevensbescherming (EU 2016-679), in acht nemen.

4. Ik zal de Expertise (i) voor geen enkele andere doelstelling gebruiken, en (ii) niet zonder voorafgaande schriftelijke toestemming van UHasselt op directe of indirecte wijze publiek maken.

5. Aangezien ik in het kader van mijn onderzoek beroep doe op de Expertise van de UHasselt, draag ik hierbij alle bestaande en toekomstige intellectuele eigendomsrechten op De Onderzoeksresultaten over aan de UHasselt. Deze overdracht omvat alle vormen van intellectuele eigendomsrechten, zoals onder meer – zonder daartoe beperkt te zijn – het auteursrecht, octrooirecht, merkenrecht, modellenrecht en knowhow. De overdracht geschiedt in de meest volledige omvang, voor de gehele wereld en voor de gehele beschermingsduur van de betrokken rechten.

6. In zoverre De Onderzoeksresultaten auteursrechtelijk beschermd zijn, omvat bovenstaande overdracht onder meer de volgende exploitatiewijzen, en dit steeds voor de hele beschermingsduur, voor de gehele wereld en zonder vergoeding:

[1] Vertrouwelijke informatie betekent alle informatie en data door de UHasselt meegedeeld aan de student voor de uitvoering van deze overeenkomst, inclusief alle persoonsgegevens in de zin van de Algemene Verordening Gegevensbescherming (EU 2016/679), met uitzondering van de informatie die (a) reeds algemeen bekend is; (b) reeds in het bezit was van de student voor de mededeling ervan door de UHasselt; (c) de student verkregen heeft van een derde zonder enige geheimhoudingsplicht; (d) de student onafhankelijk heeft ontwikkeld zonder gebruik te maken van de vertrouwelijke informatie van de UHasselt; (e) wettelijk of als gevolg van een rechterlijke beslissing moet worden bekendgemaakt, op voorwaarde dat de student de UHasselt hiervan schriftelijk en zo snel mogelijk op de hoogte brengt.

1

- het recht om De Onderzoeksresultaten vast te (laten) leggen door alle technieken en op alle dragers;
- het recht om De Onderzoeksresultaten geheel of gedeeltelijk te (laten) reproduceren, openbaar te (laten) maken, uit te (laten) geven, te (laten) exploiteren en te (laten) verspreiden in eender welke vorm, in een onbeperkt aantal exemplaren;
- het recht om De Onderzoeksresultaten te (laten) verspreiden en mee te (laten) delen aan het publiek door alle technieken met inbegrip van de kabel, de satelliet, het internet en alle vormen van computernetwerken;
- het recht De Onderzoeksresultaten geheel of gedeeltelijk te (laten) bewerken of te (laten) vertalen en het (laten) reproduceren van die bewerkingen of vertalingen;
- het recht De Onderzoeksresultaten te (laten) bewerken of (laten) wijzigen, onder meer door het reproduceren van bepaalde elementen door alle technieken en/of door het wijzigen van bepaalde parameters (zoals de kleuren en de afmetingen).

De overdracht van rechten voor deze exploitatiewijzen heeft ook betrekking op toekomstige onderzoeksresultaten tot stand gekomen tijdens het onderzoek aan UHasselt, eveneens voor de hele beschermingsduur, voor de gehele wereld en zonder vergoeding.

Ik behoud daarbij steeds het recht op naamvermelding als (mede)auteur van de betreffende Onderzoeksresultaten.

7. Ik zal alle onderzoeksdata, ideeën en uitvoeringen neerschrijven in een "laboratory notebook" en deze gegevens niet vrijgeven, tenzij met uitdrukkelijke toestemming van mijn UHasseltbegeleider **Prof. Dr. Peter Feys en Dr. Lisa Tedesco Triccas**

8. Na de eindevaluatie van mijn onderzoek aan de UHasselt zal ik alle verkregen vertrouwelijke informatie, materialen, en kopieën daarvan, die nog in mijn bezit zouden zijn, aan UHasselt terugbezorgen.

Gelezen voor akkoord en goedgekeurd,

Naam: DOUMEN STEFF

Adres: VENNENDIJK 3, 3680 MAASEIK

Geboortedatum en -plaats : 05 APRIL 1999, GENK

Datum: 01/03/2022

Handtekening:

UHASSELT

Verklaring op Eer

Ondergetekende, student aan de Universiteit Hasselt (UHasselt), faculteit **Revalidatiewetenschappen en Kinesitherapie** aanvaardt de volgende voorwaarden en bepalingen van deze verklaring:

1. Ik ben ingeschreven als student aan de UHasselt in de opleiding **Revalidatiewetenschappen en Kinesitherapie** waarbij ik de kans krijg om **in het kader van mijn opleiding** mee te werken aan onderzoek van de faculteit **Revalidatiewetenschappen en Kinesitherapie** aan de UHasselt. Dit onderzoek wordt beleid door **Prof. Dr. Peter Feys en Dr. Lisa Tedesco Triccas** en kadert binnen **het opleidingsonderdeel wetenschappelijke stage/ masterproef Deel 2** zal in het kader van dit onderzoek creaties, schetsen, ontwerpen, prototypes en/of onderzoeksresultaten tot stand brengen in het domein van **de neurologische revalidatie van het bovenste lidmaat na CVA** (hierna: "De Onderzoeksresultaten").

2. Bij de creatie van De Onderzoeksresultaten doe ik beroep op de achtergrondkennis, vertrouwelijke informatie[1], universitaire middelen en faciliteiten van UHasselt (hierna: de "Expertise").

3. Ik zal de Expertise, met inbegrip van vertrouwelijke informatie, uitsluitend aanwenden voor het uitvoeren van hogergenoemd onderzoek binnen UHasselt. Ik zal hierbij steeds de toepasselijke regelgeving, in het bijzonder de Algemene Verordening Gegevensbescherming (EU 2016-679), in acht nemen.

4. Ik zal de Expertise (i) voor geen enkele andere doelstelling gebruiken, en (ii) niet zonder voorafgaande schriftelijke toestemming van UHasselt op directe of indirecte wijze publiek maken.

5. Aangezien ik in het kader van mijn onderzoek beroep doe op de Expertise van de UHasselt, draag ik hierbij alle bestaande en toekomstige intellectuele eigendomsrechten op De Onderzoeksresultaten over aan de UHasselt. Deze overdracht omvat alle vormen van intellectuele eigendomsrechten, zoals onder meer – zonder daartoe beperkt te zijn – het auteursrecht, octrooirecht, merkenrecht, modellenrecht en knowhow. De overdracht geschiedt in de meest volledige omvang, voor de gehele wereld en voor de gehele beschermingsduur van de betrokken rechten.

6. In zoverre De Onderzoeksresultaten auteursrechtelijk beschermd zijn, omvat bovenstaande overdracht onder meer de volgende exploitatiewijzen, en dit steeds voor de hele beschermingsduur, voor de gehele wereld en zonder vergoeding:

   - het recht om De Onderzoeksresultaten vast te (laten) leggen door alle technieken en op alle dragers;

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[1] Vertrouwelijke informatie betekent alle informatie en data door de UHasselt meegedeeld aan de student voor de uitvoering van deze overeenkomst, inclusief alle persoonsgegevens in de zin van de Algemene Verordening Gegevensbescherming (EU 2016/679), met uitzondering van de informatie die (a) reeds algemeen bekend is; (b) reeds in het bezit was van de student voor de mededeling ervan door de UHasselt; (c) de student verkregen heeft van een derde zonder enige geheimhoudingsplicht; (d) de student onafhankelijk heeft ontwikkeld zonder gebruik te maken van de vertrouwelijke informatie van de UHasselt; (e) wettelijk of als gevolg van een rechterlijke beslissing moet worden bekendgemaakt, op voorwaarde dat de student de UHasselt hiervan schriftelijk en zo snel mogelijk op de hoogte brengt.

- het recht om De Onderzoeksresultaten geheel of gedeeltelijk te (laten) reproduceren, openbaar te (laten) maken, uit te (laten) geven, te (laten) exploiteren en te (laten) verspreiden in eender welke vorm, in een onbeperkt aantal exemplaren;
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De overdracht van rechten voor deze exploitatiewijzen heeft ook betrekking op toekomstige onderzoeksresultaten tot stand gekomen tijdens het onderzoek aan UHasselt, eveneens voor de hele beschermingsduur, voor de gehele wereld en zonder vergoeding.

Ik behoud daarbij steeds het recht op naamvermelding als (mede)auteur van de betreffende Onderzoeksresultaten.

7. Ik zal alle onderzoeksdata, ideeën en uitvoeringen neerschrijven in een "laboratory notebook" en deze gegevens niet vrijgeven, tenzij met uitdrukkelijke toestemming van mijn UHasseltbegeleider **Prof. Dr. Peter Feys en Dr. Lisa Tedesco Triccas**

8. Na de eindevaluatie van mijn onderzoek aan de UHasselt zal ik alle verkregen vertrouwelijke informatie, materialen, en kopieën daarvan, die nog in mijn bezit zouden zijn, aan UHasselt terugbezorgen.

Gelezen voor akkoord en goedgekeurd,

Naam: Socba Luca

Adres: Boterbloemstraat 5, 3600 Genk

Geboortedatum en -plaats : 3600 Genk, 20/02/1999

Datum: 25/05/'22

Handtekening:

Timeline meetings

www.uhasselt.be
Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Campus Diepenbeek | Agoralaan gebouw D | BE-3590 Diepenbeek
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UHASSELT
KNOWLEDGE IN ACTION

INVENTARISATIEFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
29/08/2021	Discussing protocol and writing booklet for intervention and data collection	Promotor: Prof. Dr. Peter Feys Copromotor/Begeleider: Dr. Lisa Tedesco Triccas Studenten: Doumen Steff, Sorba Luca
10/09/2021	Meeting with ZOL + finishing protocol and booklet	Promotor: Prof. Dr. Peter Feys Copromotor/Begeleider: Dr. Lisa Tedesco Triccas Studenten: Doumen Steff, Sorba Luca
12/10/2021	CTA approval, start dose escalation study, planning availability to collect data in 2021	Promotor: Prof. Dr. Peter Feys Copromotor/Begeleider: Dr. Lisa Tedesco Triccas Studenten: Doumen Steff, Sorba Luca
13/11/2021	Discussing the course of the dose escalation study, feedback writing methodology section	Promotor: Prof. Dr. Peter Feys Copromotor/Begeleider: Dr. Lisa Tedesco Triccas Studenten: Doumen Steff, Sorba Luca
29/11/2021	Discussing second version methodology and first version introduction section	Promotor: Prof. Dr. Peter Feys Copromotor/Begeleider: Dr. Lisa Tedesco Triccas Studenten: Doumen Steff, Sorba Luca
03/12/2021	Discussing second version introduction and planning data analysis and statistics	Promotor: Prof. Dr. Peter Feys Copromotor/Begeleider: Dr. Lisa Tedesco Triccas Studenten: Doumen Steff, Sorba Luca
10/12/2021	Planning availability to collect data in 2022	Promotor: Prof. Dr. Peter Feys Copromotor/Begeleider: Dr. Lisa Tedesco Triccas Studenten: Doumen Steff, Sorba Luca
21/03/2022	Presentation provisional data analysis and statistics, discussing course of the dose escalation study (postponing end of data collection)	Promotor: Prof. Dr. Peter Feys Copromotor/Begeleider: Dr. Lisa Tedesco Triccas Studenten: Doumen Steff, Sorba Luca
28/04/2022	Presentation data analysis and statistics	Promotor: Prof. Dr. Peter Feys Copromotor/Begeleider: Dr. Lisa Tedesco Triccas Studenten: Doumen Steff, Sorba Luca

12/05/2022	Presentation results and first version of discussion section	Promotor: Prof. Dr. Peter Feys Copromotor/Begeleider: Dr. Lisa Tedesco Triccas Studenten: Doumen Steff, Sorba Luca
23/05/2022	First draft master's thesis part 2	Promotor: Prof. Dr. Peter Feys Copromotor/Begeleider: Dr. Lisa Tedesco Triccas Studenten: Doumen Steff, Sorba Luca
26/05/2022	Feedback first draft master's thesis part 2	Promotor: Prof. Dr. Peter Feys Copromotor/Begeleider: Dr. Lisa Tedesco Triccas Studenten: Doumen Steff, Sorba Luca

Datum en handtekening
Studenten

26/05/2022

Datum en handtekening
Promotor(en) en/of Co-promotor(en)

30.05.22