

Dose in stroke rehabilitation trials

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A thesis submitted for the Degree of Doctor of Philosophy

UNIVERSITY OF EAST ANGLIA

School of Health Science

February 2017

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Abstract

Background: the dose and the length of rehabilitative interventions for optimal motor recovery after stroke are unknown. Dose optimization studies are required as precursors to efficacy trials, but are rarely conducted in stroke rehabilitation research.

Objective: to overcome the knowledge gap on appropriate dose and length of rehabilitative interventions guiding the implementation of novel effective approaches to dose optimization in stroke rehabilitation research.

Method: two systematic reviews on dose optimization in exercise-based training and pharmaceutical clinical research guided the development of a new approach to dose-finding suitable for physical interventions. The feasibility of a novel phase I 3+3 rule-based, outcome-adaptive dose-finding design was assessed with stroke survivors with moderate upper limb paresis. Moreover, the feasibility of a repetitive assessment procedure to identify the appropriate length of motor interventions was explored in stroke rehabilitation research.

Results: the first literature review showed a lack of reliable approaches to dose optimization in exercise-based training. The review of pharmaceutical research highlighted dose optimization “gold” standard approaches, and helped in devising the dose-finding study for physical intervention. The dose-finding study was feasible using the applied model-task intervention. Preliminary explorations on the dose-response relationship were possible indicating a maximum tolerable dose and a potential recommended dose of 209 and 162 repetitions respectively of the applied intervention-task. The repetitive assessment procedure was found feasible in a clinical efficacy stroke rehabilitative trial. The repetitive assessment procedure provided relevant data on the therapy effect over-time showing that more than six weeks of the applied upper limb intervention may be necessary to reach maximal therapy

effects. Whereas, five weeks of intervention appeared enough to exploit therapy effects for the lower limb.

Conclusions: results are promising on identifying relevant dose and protocol endpoints implementing dose-finding and repetitive assessments approaches in stroke rehabilitation. Further confirmative data are needed to validate these findings.

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List of abbreviations

ADL= Activities of Daily Living
APB= Abductor Pollicis Brevis
ARAT= Action Research Arm Test
BB= Biceps Brachii Muscle
CI= Confidence Interval
CNS= Central Nervous System
CT= Controlled Trial
DLT= Dose Limiting Toxicity
ECT= Extensor Carpi Radialis
FAC= Functional Ambulatory Category
FMA= Fugl-Meyer Assessment
FST= Functional Strength Training
IC= Informed Consent
LL= Lower Limb
M1= Primary Motor Cortex
mBBT= Modified Box and Clock Test
MCIC= Minimally Clinical Important Change
mCRM= Modified Continual Reassessment Method
MEPS= Motor Evoked Potential
mFBS= Modified Fibonacci Scheme
MinED= Minimal Effective Dose
MoveExLab= Movement and Exercise Laboratory
MT= Motor Threshold
MTD= Maximal Tolerable Dose
OD= Optimal Dose
OTD= Optimal Therapeutic Dose
PIS= Participant Information Sheet
RCT= Randomised Controlled Trial
RD= Recommended Dose
RMT= Resting Motor Threshold
RPTD= Recommended Phase 2 Dose
RT= Randomised Trial
SD= Standard Deviation
TMS= Transcranial Magnetic Stimulation
UL= Upper Limb

Acknowledgments

I express my gratitude to my first supervisor Prof Valerie Pomeroy for her valuable guidance and advice as a PhD student. I would also like to thank Dr Allan Clark and Prof Catherine Lang for their longstanding support.

My appreciation goes to my parents who taught me the value of hard work, my friends who have been annoyed by listening to my PhD obsession, and my son who has made this journey even more challenging, but surely more fun.

Above all my gratitude goes to my husband and partner in life, without whom I would never have started nor finished this amazing journey.

Declarations

The present thesis is the result of my original research work. This thesis was composed entirely by myself and my contributions to each reported study were as follows. I was the primary researcher in the two literature reviews. In the dose-finding trial I acted as principal researcher playing a major role in: planning and organizing the trial; ethical approval processes; participants' recruitment procedures; delivery of the trial intervention; and data analyses. In the FeSTivALS trial, the second trial reported in this thesis, I participated as one of the research therapists delivering the trial intervention programme. I also played a major role in the design, planning, organization and data analyses of the repetitive assessment procedure embedded in the main clinical trial.

Wherever contributions of others were involved, every effort was made to indicate this clearly, with due reference to the literature, and acknowledgement of collaborative research and discussions. The work was done under the longstanding and valuable guidance of Prof Valerie Pomeroy, Dr Allan Clark at the University of East Anglia, United Kingdom and Prof Catherine Lang at the Washington University School of Medicine in St. Louis, United States.

The two literature reviews were made with the collaboration of Liz Chandler, a member of our research group, and Prof Valerie Pomeroy as second and third reviewers respectively. The dose-finding trial saw the collaboration of two members of the research team, Katy Collins and Jessica Smith as blinded outcome assessors. Katy Collins also acted as the expert in undertaking TMS measurements.

Posters presentations have been held at national conferences (e.g. UEA Postgraduate Research Showcase in 2012 and the UK Stroke Forum 2013). I wish also to thank participants for helpful comments and discussions at the UEA Postgraduate Research Faculty of Medicine and Health Science Conference and at the 2015 First International Congress on Neurorehabilitation and Neural Repair, Maastricht, the Netherlands (title of the oral presentations: "Identification of the Optimal Therapeutic Dose of repetitive upper limb exercise after stroke").

An article, based on the dose-finding study (chapter 5), has been published in the scientific journal *Physiotherapy* "A rule-based, dose-finding for use in stroke rehabilitation research: methodological development" (available online at: <http://dx.doi.org/10.1016/j.physio.2016.10.393>)

Two further publications are foreseen from the systematic review on dose optimization in exercise-based training (chapter 2) and on the feasibility of a repetitive assessment procedure in stroke rehabilitation research (chapter 6).

The use of the Cando DIGI-EXTEND® finger exerciser (chapter 5) did not imply any affiliation between the researcher or the University of East Anglia and the manufacturer or endorsement by them.

Chapter 1:

Introduction

1.1 Stroke syndrome: definition and statistics

According to the World Health Organisation (WHO), stroke is a clinical syndrome that occurs when the blood flow to the brain is interrupted with no apparent cause other than a vascular origin. It results in a damage to the brain tissue that is often serious and disabling. In the UK, stroke is the fourth largest cause of death after cancer, heart and respiratory diseases [1]. However, thanks to advances in medicine and rehabilitation, the majority of people survive after their first stroke, with an increasing number of hospital admissions¹.

Approximately half of people surviving a stroke make an incomplete recovery. In the UK, it has been estimated that around 33% of stroke survivors remain moderately or severely disabled [2], requiring assistance in their daily activities and long-term rehabilitation, on many occasions, for the rest of their life [3,4]. The impact of stroke for the healthcare system, patients and families is significant and likely to increase with the growth of the ageing population.

¹ <http://www.england.nhs.uk/statistics/statistical-work-areas/integrated-performance-measures-monitoring/stroke-data/> (Accessed July 2014).

1.2 Effects of stroke: motor impairment

Stroke is typified by a rapid development of signs of focal or global disturbance of cerebral functions, which last more than 24 hours or lead to death [5]. Stroke can result in a variety of signs and symptoms depending on the extent and site of the brain lesion. The greatest long-term effect of stroke is the development of physical and psychological impairments. These impairments often lead to limitations of activities and disabilities, which, in turn, reduce life participation of stroke survivors [6]. The most common and wide recognised impairment caused by stroke is motor impairment affecting about 80% of stroke survivors [7]. Other common areas of impairment are speech and language (about 42%), vision (about 18%), swallowing (about 45%), sensation (about 19%) and cognition (about 32%) [8,9,10].

Motor impairments after stroke result from the interruption or disruption of descending signals from the motor cortex, premotor cortex, or cerebellum to the spinal moto-neurons [11]. Motor impairment is typified by a loss or limitation of muscle function and motor control commonly affecting the face, arm and leg of the opposite side of the brain damage. This limitation is called contralesional hemiparesis [12]. Complete loss of motor functions in one side of the body is called hemi-paralysis.

The coexistence of ipsilesional motor deficits (same side of the lesion) after stroke have been reported from animal [13] and human studies [14,15]. But, these are milder than on the contralesional side.

1.3 Functional motor recovery

Recovery after stroke is heterogeneous in its nature and is influenced by many factors. Functional motor recovery refers to improvements in mobility and activities of daily living. It is a complex process linked to the ability of the injured brain to change [16]. These neural changes, called functional neuroplasticity, are possible because of the brain ability to reorganise itself by

the redundant connectivity within the central nervous system (CNS) and the ability of new circuits to form [17,18,19,20].

Functional motor recovery often follows stereotyped patterns and is said to be predictable in the first days after the brain injury [21,22]. A combination of *spontaneous* and *training-induced recovery* processes have been found in the motor recovery processes [23,24]. These include:

- i. restitution of functionality of injured neural tissue;
- ii. substitution and reorganization of spared or partly injured neural pathways to relearn lost functions;
- iii. compensation processes, often resulting as patients' adaptation between motor impairments and the environment demands [25,26].

The spontaneous recovery typically plateaus three months after the brain injury whereas, training-induced recovery has been observed long after the injury [27,28,29].

Faster motor improvements are seen on the initial stage followed by slower changes after the first few weeks. In the period from 12 hours to seven days after ischemic stroke onset, many patients who are without complications experience moderate but steady improvement in neurologic impairments [21]. The greatest proportion of recovery after stroke occurs in the first 3 to 6 months and evidence supports the "six months window" as the gold standard timeframe for post-stroke care worldwide [30,31]. However, evidence has shown that patients can improve in later stage [32,33].

1.4 Rehabilitation after stroke

Stroke rehabilitation is a multidisciplinary intervention which comprised of several interactive procedures. Its main aim is to reduce the disabilities and participation restriction following a stroke [24]. Its favourable effects in enhancing functional motor recovery is widely recognised by researchers [34,35,36,37,38,39] and stroke survivors [40].

In the last decades, many novel rehabilitation interventions have been developed, based on advances in neuroscience, to assist the natural pattern of functional motor recovery after stroke [24,39,41,42,43]. However, what is commonly referred to as the “black box” of therapy has not yet fully understood [44].

The debate on which components of the rehabilitative intervention are more effective to enhance individual’s treatment responsiveness and functional motor recovery is far from being closed [42,45,46,47]. It is still unclear whether it is the content of a specific therapy or the therapy dose which matter more to enhance stroke motor recovery. Besides, there are still uncertainties whether it is the same therapy dose beneficial for all patients at any stage of stroke, or some patients and stages of recovery benefit more from a specific dose.

Literature converged on the importance of characterizing what components of these interventions were key to support motor recovery [7,45,48]. Identifying the appropriate dose of rehabilitative interventions is thought to be pivotal to exploit training effects and enhance stroke survivors’ functional recovery [24,46,49,50,51,52,53]. However, the multifactorial and complex nature of stroke rehabilitation brings several challenges in fulfilling these gaps of knowledge and on conducting rigorous evaluation [54].

1.5 Neuroimaging and experience-dependent principles

Effective therapeutic interventions following stroke depend on an understanding of brain changes, their time frame from the injury and their relationship with behavioural stimulus (training-induced changes in neural function) [20,26,55,56,57].

In the last two decades, non-invasive neuroimaging studies have successfully contributed to investigate the dynamics of adaptive reorganization of the injured brain associated with functional recovery [33,55,58,59,60,61]. Among them, Transcranial Magnetic Stimulation (TMS), which uses magnetic fields to depolarize nerves cells in the brain, has been widely applied and has proven

to be a valuable and safe tool to better understand motor dysfunctions and recovery after brain injury. However, even with the use of non-invasive neuroimaging tools, the precise mechanisms of the brain reorganization underpinning functional recovery and the key active ingredients to maximise rehabilitative interventions outcomes after stroke remain topical and still unclear [24,26,33,62].

1.6 The dose of training

In an injured brain, the amount of skilled practice is thought to be crucial to support the training-induced neuroplasticity and, consequently, the improvement of motor function [63,64]. The amount of skilled task-specific training provided after stroke is crucial to enhance improvements of functional outcomes [24,31,39,65,66,67,68,69]. Evidence converged on the assumption that the extent to which an intervention can be effective inherently depends on the delivered dose [67]. It seems that the brain reorganization is more influenced by the amount of training, rather than the type of intervention delivered [70,71,72]. Dobkin, for example, stressed the relevance of identifying at which dose of intervention it is possible to reach the *“peak behavioural effects of training [to enhance patients’ outcomes and] for how long a physical intervention needs to be prescribed till a diminished therapy effect is seen”* [73,74]. Hornby and colleagues reviewed the relevant literature on the key dose parameters of stroke rehabilitative interventions to improve lower limb functions. They highlighted that the amount and intensity of the locomotor practice² have a prominent role to enhance motor recovery [50]. The dose of training is also linked with important factors influencing the functional motor recovery such as, the motor learning processes (or re-learning ability) of the brain and the time since the brain injury [43,63,75,76].

² These parameters of the training were defined as the time or number of steps undertaken and the effort needed to pursue the training.

Regardless the presence of an injured brain, all motor learning processes in the brain are based on: functional skills acquisition, motor adaptations -or motor control-, and decision making processes. It is known that these processes are strictly linked with the dose of skilled practice [76] and can be conditioned by training [63,77].

The functional neural plasticity following stroke is a process which sees a cascade of several events influenced by a variety of possible factors, rather than a standardised single event. The type of plasticity observed and its suitability to further change is likely to depend on the time point of the observation after the brain injury. How much therapy should be delivered to maximise functional recovery preserving patients' safety is therefore linked with the time since the brain injury. Despite a general consensus that early initiation of rehabilitative intervention could enhance recovery [24,78,79], how early [80] and how much therapy should be provided given the risks of a vulnerable brain early after the injury [81] is still debated. Recently, the AVERT trial challenged the assumption that higher dose of therapy are always better, in particular in the early stage of the recovery [82].

Identifying the appropriate dose at which the intervention produces optimal outcomes is therefore of paramount importance in enhancing stroke survivors' motor recovery at any stage of recovery and it is seen as a research priority.

1.7 Recommendations for training dose after stroke

Although there is growing interest on the appropriate dose and protocols of rehabilitative interventions after stroke, current evidence is sparse and inconclusive [83].

In 2005, the American Health Association AHA/ASA-Endorsed Practice Guidelines reported the difficulty in generating guidelines on the appropriate dose of rehabilitative interventions after stroke due to the lack of information

on important dose thresholds for efficacy. The dose level below which the intervention is not effective and the dose level above which a marginal improvement is seen are still under investigation [84].

In 2012, the Intercollegiate Stroke Working Party (ICSWP)[31] recommended a minimum threshold of 45 minutes of stroke rehabilitation therapy, for any patient able to sustain it, for a minimum of five days per week. This recommendation was the result of an experts' consensus summit, rather than a guideline grounded on scientific evidence. They recognised, however, that in this context of uncertainty about appropriate dose and protocols of rehabilitative interventions after stroke, the recommendation was as specific as it could possibly be.

The threshold of 45 minutes of therapy a day for 5 days a week was subsequently advocated by the National Institute for Health and Care Excellence (NICE) in their 2013 Stroke Rehabilitation guidelines [68].

One of the first challenges faced by stroke rehabilitation research when addressing dose optimization is the multifactorial aspects of the training protocol and training dose. In rehabilitation the training protocol is commonly shaped by three parameters: the *dose*, the *frequency*, and the *total length* (often in weeks) of the training period. In turn, the dose of training is often shaped by two: the *intensity* and the *amount* of training.

The impact of these training parameters able to maximize stroke survivors' motor recovery is still under investigation. Whether it is the time that patients spend engaging in therapy, the number of task-repetitions accomplished, the intensity of the rehabilitative sessions or the total length of the intervention that matter most to induce positive lasting brain changes is unknown.

1.8 The optimal therapeutic dose

In medicine and in pharmaceutical research in particular, the *optimal dose* (OD) or *optimal therapeutic dose* (OTD) is defined as the dose at which the

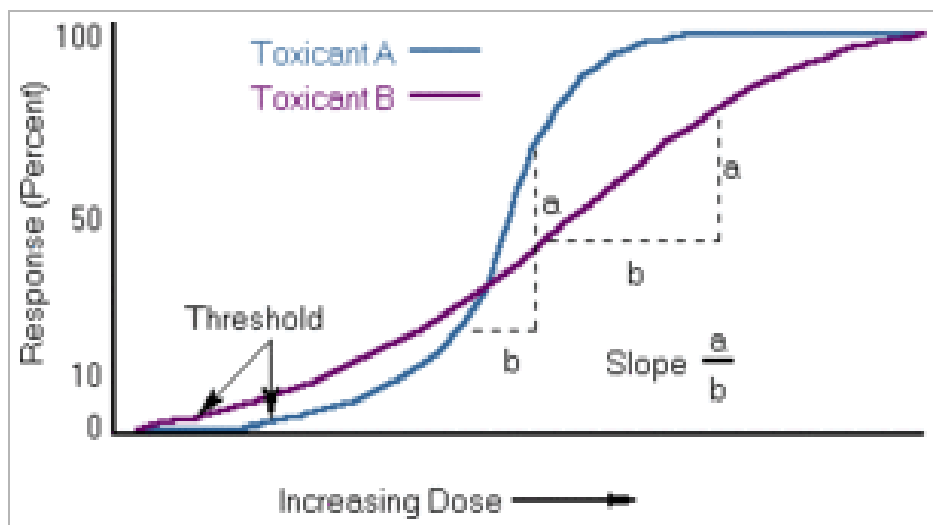
drug is able to provide the best possible outcomes with a tolerable onset of adverse events for the majority of patients. Translating this definition to rehabilitative interventions, the OTD of a physical intervention is the dose at which the applied intervention is likely to be feasible, tolerable and safe with the best observed outcomes for the majority of patients.

Identify the OTD is not a straightforward task for complex motor interventions such as stroke rehabilitation. This can partially explain why these doses of motor intervention which are proven to be feasible, safe and able to maximise motor recovery after stroke are still not identified [50,74,83].

The clinical process of studying the dose-response relationship of the applied intervention to identify the OTDs is commonly defined as the dose optimization process. The dose-response relationship describes how marginal changes (increases or decreases) in the dose affect the outcome of interest. Dose-response data are typically graphed with a bi-dimensional graph, with the dose on the x-axis and the measured effect (response) on the y-axis.

Figure 1 provides an example of two toxicant compounds (A and B) with different dose-response relationships. In this example it is possible to see that the dose-response of pharmaceutical compounds (drug element) normally takes the form of a sigmoid curve. The compound dose at which response (or toxicity) first appear is known as threshold. From this point the curve shows the increased observed benefits associated with higher doses. The slope of the curve represents the rapidity of the compound to reach effect (or toxicity). The compounds reached a dose beyond which no further benefit is observed, often defined as plateau stage. In this example, toxicant compound A shows a higher threshold and a steeper slope than toxicant compound B.

Figure 1-1: Example of the dose-response relationships of two pharmaceutical toxicant compounds



Notes: Toxicant A and Toxicant B represents the dose-response relationships of the two studied compounds (drug elements); the x-axis reports the individual's response to the applied compound; y-axis reports the dose applied. Source: National Library of Medicine, The Encyclopedia of Earth Toxicology webpage³.

1.9 Evidence on training dose after stroke: is more therapy always better?

Animal models with damaged motor cortex suggested that high dose of rehabilitative interventions after stroke enhanced motor recovery. In these studies, rats or primates, after induced brain damage, were trained on a repetitive motor task involving the retrieval of food pellets for an extensive amount of time per day, five days per week. Animals that were able to reach around 300/400 task repetitions per session had significant neural changes compared with those observed with lower dose [85,86,87,88,89,90,91]. Luke et al. found that animals exposed to low dose (60 reaching a day, five days a week) did not show any neural changes [53]. A recent study suggested the possible presence of a lower threshold in the number of repetitions performed

³ <http://www.eoearth.org/view/article/151784/>

(around 240 task repetitions), below which motor recovery was not seen [92]. Animal studies, however, often failed to identify a strong correlation between plasticity changes and acquisition of functional motor skills rather than adaptation and compensatory behavioural strategies [16,93].

Translating results from animal model studies to human clinical research, and eventually clinical practice, is not straightforward. This is particularly challenging in regard to the dose of motor interventions for several reasons. First, some morphological structures of the nervous system greatly differ. Among others, the rubrospinal tract⁴ differs in humans compared with rats and monkeys. The rubrospinal tract is an alternative pathway by which voluntary motor commands can be sent to the spinal cord. Although it is a major pathway in many animals, it is relatively minor in humans.

Second, although the feasibility of high intensive protocols in sub-group of stroke survivors has been suggested [94,95], it is almost impossible to mimic among humans the same conditions in animal models.

Finally, results from animal studies cannot be used to suggest what number of task-repetitions should be delivered in humans to see similar –or to some extent, proportional- neuroplasticity enhancement.

The beneficial effect of high dose of rehabilitative interventions have also been questioned by other evidence that highlighted the vulnerability of the animals' brain when engaged in intensive training early after the brain injury [96,97,98,99].

Despite the above-mentioned limitations and concerns emerging from pre-clinical studies, the hypothesis that higher dose could maximise rehabilitative benefits after stroke is now well-accepted among clinicians and research. A wide-spread consensus is emerging from research and clinical practice on the

⁴ The rubrospinal tract is an axon tract originating in the red nucleus of the midbrain. After leaving the red nucleus, axons cross to the contralateral side and descend into the spinal cord, where they terminate in the ventral horns. The red nucleus is innervated by axons from the motor-cortices and the cerebellum. The rubrospinal pathway is an extrapyramidal route to the spinal cord. Source: Farlex Partner Medical Dictionary © Farlex 2012.

efficacy of high-intensive task-specific training protocols in enhancing stroke survivors' motor recovery [29,95,100,101,102,103]. As a result, there is a proliferation of clinical studies assessing the effectiveness of these intensive protocols against routinely practice or lower dose [e.g., 27,29,49,52,70,100,104,105,106,107,108,109,110,111,112,113].

In the majority of these studies high dose protocols were associated with better motor outcomes for patients regardless the stage of stroke.

Few clinical studies reported no or limited evidence to support these intensive protocols. Di Lauro et al. investigated the efficacy of intensive rehabilitation, over standard rehabilitation. They showed that high intensity training may not always be required to produce positive motor changes in people early after stroke [114]. In 2009, the VECTORS' study⁵ found that high intensity constraint-induced movement therapy was detrimental when delivered within 28 days after stroke[115]. Detrimental effects on upper limb strength early after stroke have been reported from other studies [116,117]. Thus, it seems that more therapy may not always produce a better recovery [118,119].

The quality of some of the cited studies supporting the effectiveness of high dose protocols is another matter of concern. Appropriate trial design and dose optimization approaches were important to validate results on dose. For instance, results from observational studies could be confounded by the lack of random allocation procedure. Studies applying retrospective analyses could suffer from limitation brought by the specificity of the a posteriori analysis [120]. In Randomised Controlled Trials (RCTs) the small number of doses tested could limit the relevance of the study on investigating the dose-response relationship and thus, on the OTD [29,49]. Information on dose efficacy is only available for the tested dose and inference on the efficacy of other doses is not advisable.

Variations in the training protocol between intervention groups (or across multiple research sites) was thought to be another important issue on dose

⁵ "Very early constraint-induced movement study during stroke rehabilitation" study.

optimization in clinical trials. These variations could obfuscate the true effect of different doses confounding results on dose [100,108] and decreasing the reliability of the results on doses [42,50,83,121].

When clinical trials were aggregate in quantitative analyses they seemed to suggest a positive dose-response relationship between intervention dose and motor recovery after stroke [22,39,72,122,123,124,125]. This positive therapy effect for intensive (repetitive) task-specific protocols was particularly evident in studies with higher treatment contrast [124] and it was suggested irrespectively to either, upper and lower limbs motor functions and stage of stroke [39]. However, caution is needed in interpreting results on appropriate doses and protocols coming from quantitative analyses which synthesize studies with heterogeneity across included studies and among study groups [46]. In the available literature syntheses [83,125,126], heterogeneity has been found with respect to:

- i)* training protocols and dose characteristics;
- ii)* patients' characteristics and time since stroke;
- iii)* trials designs; and
- iv)* trial outcome measures.

Two systematic reviews, which included studies assessing the effect of different doses of the same intervention, were able to collate seven and fourteen studies respectively [125,126]. With this restriction, both reviews concluded that evidence on the enhanced benefit of higher dose are limited. They argued that the differences in therapy effect size found among included studies is likely to reflect the difference in the protocols and in the dose-matching across studies. They concluded that definitive evidence on how much therapy is needed to maximise recovery after stroke is still not available. Besides, the efficacy and safety of high intensive protocols were not yet supported by strong evidence.

1.10 The optimal length of training

Alongside with the relevance on identify the OTD, another key aspect of the training protocol is to know for how long the selected intervention dose should be delivered. Information on the time course of rehabilitative interventions outcome are indispensable to identify the appropriate length of treatment able to maximise rehabilitative intervention outcomes and thus, plan cost-effective interventions.

In stroke rehabilitation research longitudinal studies were rare. Few studies investigated the time course effect of interventions [127,128] or added a mid-point measure [129] between the more common pre- to post-intervention assessment points. As a result, the length of treatment is often left to arbitrary choice [130,131] decreasing the chance to maximise therapy benefit.

1.11 Making advances in dose optimization approaches

Gathering early information on appropriate dose to test in subsequent efficacy phase II trials could improve the stroke rehabilitation research pathway in a cost-effective manner. In other words, if more information on appropriate dose were available from early phase I studies then, the efficacy of phase II trial in targeting the OTD increases, reducing the likelihood to test sub-optimal or dangerous doses. This approach, which is supported by the scientific community [50,73,132,133,134], and advocated by the Stroke Progress Review Group (2012)⁶ and the UK Medical Research Council (MRC)⁷, stresses on the relevance to improve knowledge on the OTDs of stroke rehabilitation by implementing rigorous pilot phase I designs, prior to phase II clinical trial.

⁶ http://www.ninds.nih.gov/about_ninds/groups/stroke_prg/2012-stroke-prg-full-report.htm#RR (last visited April 2015).

⁷ <http://www.mrc.ac.uk/documents/pdf/complex-interventions-guidance/> (last visited April 2015).

This pathway, rarely conducted in stroke rehabilitation research [49,51,74,75,135,136,137], is common in other fields of medicine [138].

Similarly, information on the appropriate length of therapy able to maximise training effect in a cost effective manner are rare in stroke rehabilitative interventions. To investigate the appropriate length of rehabilitative interventions and thus, to investigate the therapy effect over time, within-patient variations of the selected outcome at different time points were required. These longitudinal approaches are not yet common in stroke rehabilitation research [127,130], but promising to fill this knowledge gap on appropriate training protocols [95].

Despite this call for dose optimization studies, rigorous methodological works which focus on how to identify the optimal dose and length of motor interventions in general, and for stroke rehabilitation intervention in particular are still absent.

1.12 Overall research focus and statement of aims

The main aim of this thesis was to serve the complex and challenging field of dose optimization in motor interventions by developing effective and rigorous methods of dose optimization suitable for stroke rehabilitation research. These new dose optimization methods will be able to provide evidence on the appropriate 1) dose and 2) length of motor interventions. In doing so, in this research project it was planned to:

1. devise an innovative approach to dose optimization for motor interventions;
2. test the feasibility and informative nature of the novel dose optimization design in stroke rehabilitative research;
3. test the feasibility and informative nature of a multiple assessment procedure to identify the optimal length of a rehabilitative intervention in a stroke clinical research setting.

To ground with evidence the devising of the new dose optimization study (point 1), the dose optimization designs and approaches currently applied in two health research fields, the exercise-based training⁸ and the pharmaceutical clinical research were investigated.

The rationale to explore dose optimization in exercise-based training literature was the direct relevance of this field to stroke rehabilitation research. Both fields, in fact, applied motor interventions to achieve their goals. Furthermore, in exercise-based training several guidelines and recommendations on appropriate training dose and protocols were available by leading health agency. Whereas, pharmaceutical research was investigated because assumed to apply the “gold” standard designs and approaches in dose optimization processes [139].

To fulfill this research breakthrough, the following specific aims and objectives were set and addressed in the remaining chapters of this PhD thesis.

Aims 1: to identify dose optimization approaches that were suitable for use in stroke rehabilitation research. The specific objectives were to:

- a. identify the dose optimization approaches that have been applied in exercise-based training research (study 1, chapter 2);
- b. identify the pharmaceutical industry standard procedures of dose optimization used in clinical trials (study 2, chapter 3);
- c. use the information gathered from addressing objectives 1a. and 1b. to devise a dose optimization trial design suitable for use in stroke rehabilitation research (study 3, chapter 4).

⁸ The term exercise-based training was used, in all this thesis, to collate all the terminologies which refer to physical activity, exercise trainings and physical therapy programs.

Aims 2: to test the feasibility of a novel phase I dose optimization trial design for motor interventions after stroke (study 4, chapter 5). Specific objectives of this feasibility study were to:

- a. assess whether all the features of the new protocol to dose optimization were feasible for motor interventions after stroke;
- b. explore on the sample size in dose optimization trials of motor interventions;
- c. explore the informative nature to stroke rehabilitation of the dose optimization data provided;
- d. explore the feasibility of using the data generated from this design to dose optimization;
- e. investigate how results on dose could be used and shown;
- f. assess feasibility of the recruitment procedure and retention rate;
- g. identify any further refinements that could enhance the appropriateness of this design.

Aims 3: to assess the feasibility and acceptability of undertaking repetitive assessments to identify the appropriate length of stroke rehabilitative interventions in a clinical efficacy trial (study 5, chapter 6). Specific objectives of this feasibility study were to:

- a. assess the feasibility of the repetitive assessment procedure
- b. explore the feasibility of using the data generated from this design to help determine the appropriate length of the trial intervention;
- c. explore the relevance of data collection on the intervention therapy effect over time and thus, on the intervention appropriate duration;
- d. explore the appropriateness of undertaking weekly measure points;

- e. determine if there were additional requirements to implement the new trial design.

The following chapter 2 was set to identify dose optimization methods and approaches applied in exercise-based training. This background of knowledge was then used to devise a newly dose optimization approach for stroke rehabilitation research.

Chapter 2:

Dose optimization approaches in exercise-based training research: a Systematic Review

2.1 Introduction

Stroke rehabilitation research does not apply dose optimization approaches to identify the optimal therapeutic doses. Stroke rehabilitation is a relatively young scientific discipline [37] and its complex nature could explain, in part, the challenge in addressing efficaciously the issue of appropriate doses of training. To ameliorate this research gap, it appeared useful to investigate dose optimization approaches in the broad field of exercise-based training (ExBT)⁹. ExBT literature includes all research applying exercises and motor interventions to achieve performance and health related goals. This field of research has a longstanding research history on the study of the optimal doses and protocols of training. The first speculation that the right dose of physical exercise was a critical component to preserve or improve individuals' health was made by Hippocrates (460–377 B.C.). He believed that *“if we could give every individual the*

⁹ The term exercise-based training collated all the terminologies which refer to physical activities, exercise trainings, motor and rehabilitative interventions.

right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health” [140].

Nowadays recommendations and guidelines on the appropriate training dose and protocols were issued by scientific and regulatory bodies including the WHO¹⁰, the American College of Sports Medicine (ACSM), the American Heart Association (AHA), and the US Department of Health and Human Service¹¹. These agencies represent the main source of information for sport and health professionals to shape training programmes.

The first recognised evidence-based recommendations on physical activity and exercise was published by the Centre for Disease Control and Prevention (CDC) and the ACSM in 1995 [141]. Since then, new recommendations and guidelines, based on updating evidence, have been regularly published on the appropriate dose to improve performance and health.

Guidelines indications on appropriate training doses derive from the evidence upon which they were based. Therefore, the quality and validity of these primary studies are important to assess the strength of guidelines in providing reliable results on dose. The implementation of inadequate methodological approaches in primary studies to identify the dose and protocols could seriously distort results on dose and thus, it could invalidate the guidelines and recommendations outcomes. Despite the key role of studies upon which guidelines and recommendation were based, an assessment on their dose optimization approaches have not been done yet. Assessing the current dose optimization procedures of guidelines primary studies can guide in devising reliable method to dose optimization for motor interventions in general and stroke rehabilitation in particular.

¹⁰ WHO global health recommendations
(http://apps.who.int/iris/bitstream/10665/44399/1/9789241599979_eng.pdf) Accessed 14 Dec 2012

¹¹ Department of Health and Human Service online physical activity guidelines for Americans 2008 <http://www.health.gov/paguidelines/pdf/paguide.pdf>. Accessed 25 Jun 2012

The main aim of this systematic review was to identify dose optimization approaches that were suitable for use in stroke rehabilitation research investigating dose optimization designs applied in exercise-based training literature (*Overall Aim 1; objective 1.a*) In addition, a taxonomic study on the definition of the training dose and its components towards dose optimization was conducted. The knowledge gathered from this review guided the devising a new dose optimization approach for use in physical interventions.

2.2 Methods

2.2.1 Design

A systematic review of published data on dose optimization approaches applied to ExBT was conducted following the recommendations of the Cochrane Collaboration¹². The PRISMA guidelines¹³ were used to report findings.

2.2.2 Search strategy

In ExBT guidelines and recommendations are considered the main sources of information on appropriate dose and protocols. Consequently, for this systematic review the search for relevant studies was based on the three latest guidelines published by the two leading public health agencies in ExBT, the ACSM and the AHA [142,143,144]. All the studies upon which these guidelines and recommendations were based were assessed for inclusion.

These guidelines, however, were based on studies published between 1982 and 2007. To update these searches a systematic search on relevant publications published between 2007 and 2011 was conducted in November 2011 and, subsequently, updated in September 2015.

¹² <http://www.cochrane-handbook.org/>, last visit on July 2012.

¹³ <http://www.prisma-statement.org/> last visit on October 2012

The electronic searches were made in the following databases: Medline, Embase, CINHAI Plus, and CENTRAL. No language restriction was applied to the searches. The Medline search was implemented with the collaboration of the librarian at the University of East Anglia (UEA) and subsequently modified for each database search. The primary researcher (EC) performed all electronic searches. The complete electronic search strategies were provided in Appendix A.

Lead authors¹⁴ were contacted to screen for unpublished (grey) relevant research and ongoing research.

Main search terms included a combination of the following subject headings and keywords:

(exercise or therapy or training or motor activity or physical activity) AND

(dose or dose relationship or dose-response or dose-finding or intensity or frequency or duration or time or amount or power or how much or repetition or set or load or volume or work) AND

(training or therapy or protocol or activity or program or schedule).

2.2.3 Inclusion criteria

Studies were included in this review if:

- 1) they were dose optimization studies reporting empirical data. To be identified as a dose optimization a study should:
 - investigated the same intervention among groups apart from the dose or the training protocol. As the largest sport medicine and exercise science organisation in the world, the ACSM¹⁵ classification of different physical activities was used to assess the training programme characteristics [145];

¹⁴ Lead author on the field was defined as any author who published at least three relevant studies.

¹⁵ <http://www.acsm.org/>

- involved more than one intervention group among which the different doses were applied.
- 2) the training dose or training protocol was specified (i.e.: training intensity, amount, duration, volume of training, time spent exercising, frequency or length of training);
 - 3) assessed functional abilities (i.e.: activity of daily living (ADL), balance, walking, climbing steps) or muscular functions (i.e.: muscular strength, power, torque, endurance, force). Occurrences of adverse events (AEs) was considered when reported in the study.

To be consistent with the inclusion criteria set by the guidelines used to identify relevant studies, papers were included if:

- 4) involved healthy adults (18+ years) or, adults with chronic conditions¹⁶ aged 50+ years;

Translations were available for studies published in Italian, Spanish and French languages.

2.2.4 Exclusion criteria

Studies were excluded from this review if they included as a primary population:

- athletes;
- pregnant women or women who were in a post-partum period;
- people in their pre or post-operative period.

Only primary studies with empirical data were included so, literature reviews were excluded.

¹⁶ A chronic condition was defined as any condition requiring regular medical treatment or a condition which causes any physical functional limitation. Therefore, the acute stages of chronic conditions were included. This inclusion criterion was consistent with the inclusion criteria applied in the reviewed guidelines.

2.2.5 Identification of studies

The primary researcher downloaded all citations on EndNote X6 programme¹⁷ where the electronic de-duplication of papers was made.

After de-duplication, the primary researcher and an additional reviewer (LC) independently screened all articles by title, abstract and full-text for inclusion. Reviewers met after each screening step checking selection results for agreement. If any inconsistent selection has arisen, reviewers went back to the original source and consensus was sought by discussion. If disagreement persisted between the two reviewers (EC and LC) a third person (VP) was available to make the final decisions.

The study selection procedure was consistent for studies retrieved from guidelines and electronic searches.

2.2.6 Data Extraction

Data extraction was undertaken by the primary researcher. A predesigned data extraction sheet (see Table 2-1) was used to record information for each study on:

- authors and date of publication;
- trial design characteristics;
- target population and sample size;
- type of exercise-based training applied;
- training schedule (frequency and length of the training);
- training dose characteristics (number of dose applied, dose manipulation process and characteristic of the dose studied);
- outcome measurements;
- assessments and follow-up time points.

Data from multiple reports of the same study were extracted from each report directly into a single data collection form.

¹⁷ See <http://endnote.com/> for more details on the reference programme tool.

If any relevant data was missing from the study report an attempt was made to obtain it by contacting the lead authors by email.

Table 2-1: Data extraction sheet

Study	Trial design charact.			Population	ExBT	Scheduling					Dose			Outcomes		Assessments & follows-up
	Design Characteristics	R	C gr			Length ExBT	Freq d/wk	nr of dose	Manipulation applied	Studied dose characteristic	V const	type	method			
1																
2																

2.2.7 Risk of potential bias assessment

A methodological quality score was developed with items recommended by the Cochrane Collaboration¹⁸ tool for methodological quality assessment.

Because not all the Cochrane Collaboration items were considered appropriate for dose optimization studies, a modification was made as used by Kwakkel and colleagues in a previous review investigating the effect of different intensities of training after stroke [53]. Focus of this review were the elements of the trial design and training protocol which could bias the dose optimization results. To validate the strength of the studies, trial designs and approaches used to dose optimization, five items were added. These scores assessed key variables of the study design and therapy protocol which could modify the intervention effect size biasing results on dose. In detail, a control on the presence of co-interventions and on the adherence to the training protocol were added. These are important factors to increase reliability on the information on dose and on the methodological quality of the study. In a systematic review investigating the quality of reporting the training dose on stroke rehabilitation research using the FITT components (Frequency, Intensity, Time and Type of exercise), authors claimed that, without a detailed information on the prescribed and actually

¹⁸ See: Cochrane Handbook, Part:2, chapter 8.5 (http://handbook.cochrane.org/chapter_8/figure_8_6_a_example_of_a_risk_of_bias_table_for_a_single.htm).

received dose and type of exercise training, results on dose were difficult to discern [45].

The presence of baseline balanced group procedure and sample-size calculation was assessed to validate the strength of results on the intervention effect size and dose.

The onset of AEs was an important indicators of the feasibility and safety of the applied dose.

As a result, the following nine items were evaluated for each included study: 1) presence of randomization sequence procedure; 2) presence of allocation concealment procedure; 3) presence of blinding outcome assessor procedure; 4) baseline balanced groups procedure; 5) sample-size calculation; 6) control for co-intervention; 7) adherence to the protocol; 8) consistency on outcome assessments; and, 9) recording of AEs.

The risk of potential bias was assessed by the first reviewer based on a summary assessment of the risk of bias for each items.

2.3 Analysis

The aim of this review was not to test the effectiveness of any intervention dose, nor protocol but rather, to explore the designs and approaches applied to dose optimization. Thus, a meta-analysis was not planned for this review. Instead, narrative descriptions were undertaken on:

- the dose optimization designs and approaches applied in ExBT;
- the definition and manipulation of the training dose and training protocol towards optimization.

Studies were grouped primarily according to the trial design. Sub-groups were made on the characteristics of the dose optimization approach implemented and on the applied definition and manipulation of the dose and training protocol.

2.4 Results

2.4.1 Identification of relevant studies: flow of references

Fifty-nine studies met the inclusion criteria of this review (reference list of included studies can be found in Appendix B). The flowchart of the review search and selection process following PRISMA recommendations¹⁹ is reported in Figure 2-1.

In detail, 431 potential citations were identified from the three guidelines and recommendations of reference and, 1,223 citations were identified from the electronic searches. Articles were collated in one database and 1,623 potential studies were retrieved after electronic de-duplication. From the first screening on study titles, 962 citations were excluded because they were clearly not relevant for this review. 556 studies were then excluded based on their abstracts. Of the remaining 105 studies, the full texts were assessed for inclusion and 53 studies were further excluded. A list of excluded studies, with justification for exclusion is available in Appendix C). Major reasons for exclusions were: study not identified as a dose optimization study; different training modalities applied between groups or within the group; full text not available; populations and measures not compliant with the inclusion criteria. The update electronic search, performed in September 2015, identified 591 further potential studies. Of them, 511 were excluded by title, 54 by abstract and 19 by their full text.

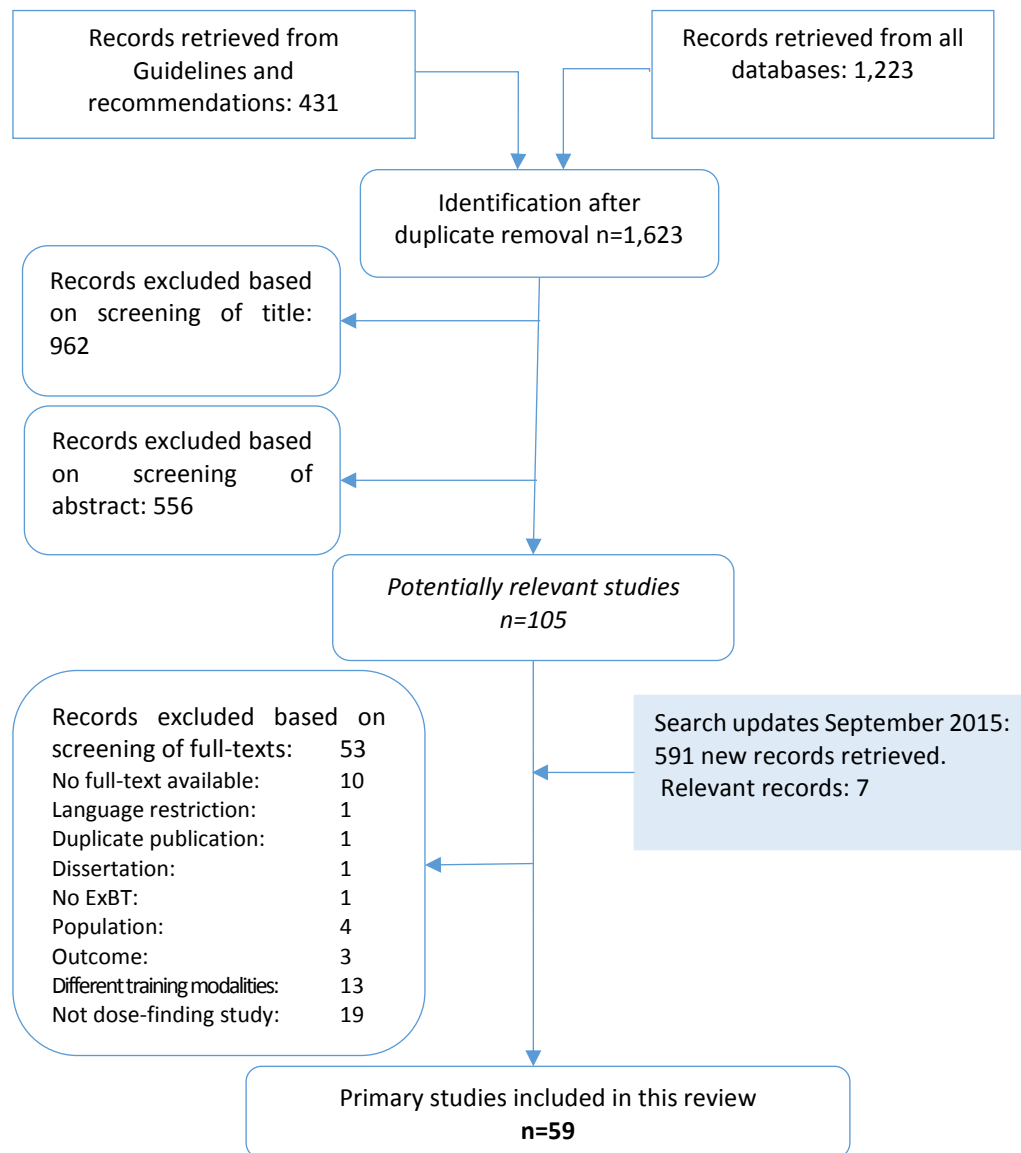
A test to assess the two reviewers understanding of inclusion criteria was made for the first one hundred titles in the reference list. The agreement between the two authors was considered excellent, with a kappa statistic value [146] equal to 0.78.

Persistent disagreement between the two reviewers (EC and LC) arose for two studies at the full-text stage. The disagreement was on the inclusion (or not) of two studies involving well-trained subjects. The two reviewers had different

¹⁹ See: <http://www.prisma-statement.org/statement.htm>, last visited on 07/2012

opinion on considering these subjects as athletes or well fit subjects. The third party (VP) made the final decisions including the two studies in the review.

Figure 2-1: Flowchart of the review search and selection process on dose-finding approaches in exercise-based training



2.4.2 Characteristics of studies

Table 2-2 summarises all the relevant characteristics of the fifty-nine studies included in this review, grouped by trial design and by the characteristics of the studied dose. Table 2-3 condenses the review’s key results reported on Table 2-2.

Table 2-2: Characteristic of included studies by trial design

STUDY	TRIAL DESIGN CHARACT.				POPULATION	EXBT	SCHEDULING			DOSE		OUTCOMES		ASSESSMENTS & FOLLOW-UP	
	DESIGN	R	C GR	LENGT H EXBT			FREQ D/WK	NR OF DOSE	MANIPULATION APPLIED	STUDIED DOSE CHARACTERISTIC	V CON ST	TYPE	METHOD		
<i>Controlled Trial (CT)</i>															
1	Ahtiainen, 2005	cross-over group	N	N	13 healthy adults recreationally trained men (22-35y),	RT	24 weeks	2	2	HI/less sets vs. LI/more sets/	Intensity & amount	N	muscle strength	1RM	pre- 3 - 6 months tests
2	Berger, 1962a	parallel group	N	N	177 healthy sportive university students;	RT	12 weeks	3	9	1Set 2RM vs. 1Set 6RM vs. 1Set 10RM vs. 2Set 2RM vs. 2Set 6RM vs. 2Set 10RM vs. 3Set 2RM vs. 3Set 6RM vs. 3Set 10RM	Intensity & amount	Y	muscle strength	1RM	pre- 3 - 6 - 9 and 12 weeks
3	Berger, 1962b	parallel group	N	N	199 healthy sportive university students;	RT	12 weeks	3	6	2RM vs. 4RM vs. 6RM vs. 8RM vs. 10RM vs. 12RM	Intensity & amount	Y	muscle strength	1RM	pre/post training test
4	Signorile, 2004	parallel group	N	N	17 old (61-75y) untrained women	RT	12 weeks	3	2	10reps, low resistance vs. 6reps, high resistance	Intensity & amount	N	Average muscle power; peak torque	dynamometer	pre /weekly /post training test
5	Borst SE, 2001	parallel group	N	Y	31 healthy subjects (25-50y)	RT	25 weeks	3	2	1-set vs. multiple-set	Amount	N	muscle strength	1RM	pre/ 13 - 25 weeks
6	Goto, 2004	parallel group	N	N	17 recreational active healthy young subjects (19-22y)	RT	(10 wks) 4 weeks	2	2	HI/low reps vs. HI/low reps+1 additional set(LI/high)	Amount	N	muscular strength and endurance	1RM	pre/post training test
7	McBride, 2003	parallel group	N	Y	28 untrained young men and women	RT	12 weeks	2	2	1 Set vs. 6 and 3 Sets	Amount	N	muscular strength	1RM= dynamic test	pre - 6 - 12 weeks
8	Hunter,1988	parallel group	N	N	44 young healthy subjects (20-28y)	RT	7 weeks	VAR	2	3d/wk, 3 sets vs. 4d/wk,	Frequency	Y	Muscular strength and endurance;	1RM free-weight; endurance=max reps at 50%RM	pre/post training test

STUDY	TRIAL DESIGN CHARACT.			POPULATION	EXBT	SCHEDULING			DOSE			OUTCOMES		ASSESSMENTS & FOLLOW-UP	
	DESIGN	R	C GR			LENGT H EXBT	FREQ D/WK	NR OF DOSE	MANIPULATION APPLIED	STUDIED DOSE CHARACTERISTIC	V CON ST	TYPE	METHOD		
9	Capen, 1956	parallel group	N	N	159 healthy university men	RT	12 weeks	VAR	4	3d/wk, 8-15RM vs. 5d/wk, 8-15RM vs. 3d/wk, 5RMx3 vs. 5d/wk, 5RMx3	Frequency	N	muscle strength	1RM free weight and machines	pre/post training test
10	Jigami H, 2012	parallel group	N	N	36 women with hip osteoarthritis (42-79y)	Land and aquatic exerc.	10 sessions	VAR	2	1/week vs. 1/fortnightly	Frequency	Y	muscle strength; functional activity; questionnaire.	Peak force dynamometer; Timed up to go; Time of one-leg standing with open eyes; Harris Hip Score; SF-36	pre/post training test
11	Nakamura, 2006	parallel group	N	Y	45 healthy sedentary women (60-75y)	Recreat. activity + RT	12 weeks	VAR	3	90min 1d/wk vs. 90min 2d/wk vs. 90min 3d/wk	Frequency	N	functional fitness test	IADL	pre/post training test
Randomized Controlled Trial (RCT)															
12	Humburg H, 2007	cross-over	Y	Y	21 untrained men and women (18-35y)	RT	9 weeks X2	3	2	1-Set vs. 3-Set	Amount	N	muscle strength	1RM	pre - middle and post training test
13	Kemmler, 2004	cross-over	Y	N	71 well-trained postmenopausal women (50-60y)	RT	29 weeks (12wks x2)	2 + 2	2	single-set vs. multiple-set	Amount	Y	muscle strength	1RM free-weight	pre/post training test
14	Anderson, 1982	parallel group	Y	N	43 healthy untrained young subject (18-24y)	RT	9 weeks	3	3	HI-Lrep (6-8RM) vs. LI-Hrep (100-150RM) vs. MI-Mrep (30-40RM)	Intensity & amount	Y	muscle strength; absolute and relative endurance	1RM	pre/post training test
15	Campos, 2002	parallel group	Y	Y	27 healthy fit untrained young male plus 5 control (18-30y)	RT	8 weeks	2 (4 wks); 3 (4 wks)	3	LowR vs. IntR vs. HighR	Intensity & amount	Y	muscular strength and endurance	1RM= free weight; endurance= max. nr of reps at 60%RM	pre-post intervention
16	Ewing J, 1990	parallel group	Y	N	21 young healthy men (20-26y)	RT	10 weeks	3	2	8RM vs. 20 RM	Intensity & amount	N	isokinetic strength	dynamometer	pre/post training test

STUDY	TRIAL DESIGN CHARACT.			POPULATION	EXBT	SCHEDULING			DOSE		STUDIED DOSE CHARACTERISTIC	V CON ST	OUTCOMES		ASSESSMENTS & FOLLOW S-UP
	DESIGN	R	C GR			LENGT H EXBT	FREQ D/WK	NR OF DOSE	MANIPULATION APPLIED	TYPE			METHOD		
17	Holm, 2008	parallel group	Y	N	12 sedentary healthy young men (20-25y)	RT	12 weeks	3	2	70%RM x 8reps vs. 15.5%RM x 3reps	Intensity & amount	Y	muscle strength, peak torque	1RM= isokinetic dynamometer;	pre, 10th, 20th, 30th session and post-tests
18	Hsieh, 2011	parallel group	Y	Y	18 chronic stroke (45-70y)	RT	4 weeks	5	2	HI vs. Low I	Intensity & amount	N	muscle strength; functional activity	strength= MRC; function= FMA and motor activity log	pre/post training test
19	Kalapotharakos, 2004	parallel group	Y	Y	33 inactive participants (60-74 y)	RT	12 weeks	3	2	High-RT 8 reps 80%RM vs. Moderate-RT 15reps 60%RM,	Intensity & amount	N	strength; peak torque; functional perform.	1RM	pre/post training tests
20	Kraemer, 2004	parallel group	Y	Y	85 physical active college aged women	RT	24 weeks	3	4	total-body 3-5RM vs. 8-12RM; up-body 3-5RM vs. 8-12RM	Intensity & amount	Y	muscle strength and power	1RM, power= Jump squat and ballistic press	pre - 12 weeks - post training
21	Nemoto, 2007	parallel group	Y	Y	246 healthy middle-age/ old subsj	Walkin g train.	20 weeks	4	2	moderate-Int continuous vs. HI interval walking	Intensity & amount	N	muscle strength	1RM= isokinetic dynamometer;	pre/post tests
22	O'Shea, 1963	parallel group	Y	N	30 healthy young subjects	RT	6 weeks	3	3	9-10RM vs. 5-6RM vs. 2-3RM	Intensity & amount	Y	dynamic and static strength	1RM free-weight and dynamometer	pre- 2 -4 -6 weeks
23	Paulsen, 2003	parallel group	Y	N	18 untrained young healthy male subjects	RT	6 weeks	3	2	3set LL-1set UL gr vs. 1set LL-3set UL	Intensity & amount	N	muscle isometric and dynamic strength	1RM free-weight and isokinetic	pre/post training test
24	Rana, 2008	parallel group	Y	Y	34 healthy young females (18-23y)	RT	6 weeks	3	2	TS: 6-10RM vs. TE: 20-30RM	Intensity & amount	Y	muscular endurance, strength, power	1RM free-weight; endurance= max reps at 60%RM	pre/post tests
25	Stone, 1994	parallel group	Y	N	50 college-age women with no formal RT experience	RT	9 weeks	3	3	HI/LowReps vs. MedI/MedReps vs. LI/LowReps	Intensity & amount	Y	muscle strength; absolute and relative endurance	1RM free weight; absolute endurance, relative endurance	pre/post training test
26	Vincent, 2002	parallel group	Y	Y	62 healthy old adults (60-85y)	RT	6 months	3	2	50%RM, 13reps vs. 80% RM, 8reps	Intensity & amount	Y	muscular strength;	1RM free weight;	pre/post training test

STUDY	TRIAL DESIGN CHARACT.			POPULATION	EXBT	SCHEDULING			DOSE		STUDIED DOSE CHARACTERISTIC	V CON ST	OUTCOMES		ASSESSMENTS & FOLLOW-UP
	DESIGN	R	C GR			LENGT H EXBT	FREQ D/WK	NR OF DOSE	MANIPULATION APPLIED	TYPE			METHOD		
27	Harris, 2004	parallel group	Y	Y	61 older untrained adults (70-90y)	RT	18 weeks	2	3	2sets, 15RM vs. 3sets, 9RM vs. 4sets 6RM	Intensity & amount	Y	muscle strength	1RM free weight and machines	pre- 6- 12 weeks post treatment
28	Fatouros, 2006	parallel group	Y	Y	58 healthy, inactive older men (65- 78 y)	RT	24 weeks	3	3	LI 40-45%RM vs. MI 60-65%RM vs. HI 80-85%RM	Intensity & amount	Y	muscle strength	1RM= weight machines	pre/post training test
29	Weiss, 1999	parallel group	Y	Y	38 untrained young men (18-30y)	RT	7 weeks	3	2	3-5RM vs. 13-15RM vs. 23-25RM;	Intensity & amount	Y	muscle strength, and peak torque	1RM= dynamic RT machine; Peak torque	pre/post training test
30	Van Roie, 2013	parallel group	Y	N	56 community-dwelling old subjects (60+y)	RT	12 weeks	3	2	2 x 10-1* 20RM vs. 1 x 80-100* 40RM	Intensity & amount	Y	muscle strength, & volume, dynamic force	dynamic peak torque, CT-scan, 1RM	pre/post training test
31	Abrahin, 2014	parallel group	Y	N	30 elderly woman (65-71y)	RT	24 training sessions	2	2	1 set vs. 3 sets	Amount	N	muscle strength, & performance	1RM, sit-to-stand test	pre/post training test
32	Baker, 2013	parallel group	Y	Y	20 recreationally trained young men (18-21y)	RT	8 weeks	3	2	1 set vs. 3 sets	Amount	N	muscle strength	1RM free weight	pre/post training test
33	Galvão, 2005	parallel group	Y	N	28 healthy old subjects (65-78y)	RT	20 weeks	2	2	1-Set vs. 3-Set	Amount	N	muscular strength, endurance and physical tests		pre/post training test
34	Han, 2013	parallel group	Y	Y	32 acute stroke (35-80y)	MRP	6 weeks	5	3	1hour vs. 2hours vs. 3hours	Amount	N	functional activities and ADL	FMA, ARAT, BI	Pre- 2- 4 weeks and post training
35	Hass, 2000	parallel group	Y	N	49 adults weight recreational weightlifter (20-50y)	RT	13 weeks	3	2	single set vs. Multiple sets (3)	Amount	N	isometric strength, endurance;	isometric strength, endurance	pre- 7weeks- post training
36	Kelly, 2007	parallel group	Y	Y	40 healthy recreational trained students	RT	8 weeks	2	2	single sets vs. 3 sets	Amount	N	muscle strength	1RM= isokinetic dynamometer;	pre/ 4 -8 weeks;
37	Marzolini, 2008	parallel group	Y	N	72 old subjs with CD (55-65y)	AT+RT	24 weeks	3 + 2 AT/RT	2	single sets vs. 3 sets	Amount	N	muscle strength; isokinetic, endurance	1RM= isokinetic dynamometer; endurance	pre/post tests

STUDY	TRIAL DESIGN CHARACT.			POPULATION	EXBT	SCHEDULING			DOSE		STUDIED DOSE CHARACTERISTIC	V CON ST	OUTCOMES		ASSESSMENTS & FOLLOW S-UP
	DESIGN	R	C GR			LENGT H EXBT	FREQ D/WK	NR OF DOSE	MANIPULATION APPLIED	TYPE			METHOD		
38	Munn, 2005	parallel group	Y	Y	115 untrained young healthy subjects (18-30y)	RT	6 weeks	3	4	1setFast vs. 3setFast vs. 1setSlow vs. 3setSlow	Amount	N	muscular strength;	1RM free weight;	pre/post training test
39	Rhea, 2002	parallel group	Y	N	16 recreationally trained men (19-23y)	RT	12 weeks	3	2	single-set vs. multiple-set	Amount	N	muscle strength	1RM free weight and machines	pre/post training test
40	Ronnestad, 2007	parallel group	Y	N	21 untrained young men (25-30y)	RT	11 weeks	3	2	3set LL-1set UL gr vs. 1set LL-3set UL	Amount	N	muscle strength; peak torque	1RM free weight and machines; Peak torque	pre/ 3, 6, 9 weeks
41	Schlumberger, 2001	parallel group	Y	Y	27 young active women (20-40y)	RT	6 weeks	2	2	single-set vs. 3-set	Amount	N	muscle strength	1RM machines;	pre/post training test
42	Starkey, 1995	parallel group	Y	Y	59 untrained healthy subjects (18-50y)	RT	14 weeks	3	2	single set vs. multiple sets	Amount	N	maximal isometric strength;	Isometric torque= dynamic ergometer	pre/post training test
43	da Silva, 2014	parallel group	Y	N	20 stroke survivors (60-80y)	task oriented training (TOT)	6 weeks	2	2	TOT with vs. without load	Intensity	N	functional tests	upper extremity performance, FMA, strength	pre/post training test
44	Hunter, 2001	parallel group	Y	Y	15 sedentary old women and fifteen men (60-70y)	RT	25 weeks	3	2	High-RT 80%RM vs. Variable-RT 50-65-60%RM,	Intensity	N	muscle strength; isometric strength; daily tasks		pre- every 25days /post tests
45	de Paleville, 2009	parallel group	Y	N	32 active healthy old subj (55-83y)	Body RecT	8 weeks	3	2	with vs. Without load	Intensity	N	muscle isometric strength;	dynamometer; functional ability tests	pre/post training test
46	Dromerick, 2009	parallel group	Y	N	52 Stroke survivors (50-80y)	CIMT	2 weeks	5	2	standard CIMT vs. HI CIMT	Intensity	N	functional ability; Independence; pain	NIH stroke scale; ARAT test; FIM; Stroke Impact Scale	pre/post training + 90 days follow-up
47	Miszko, 2003	parallel group	Y	Y	50 old subjects with low level of physical function (65-90y)	RT	8 weeks	3	2	80%RM vs. 40%RM	Intensity	N	muscular strength; physical function test	1RM free-weight; physical function test= CS-PFP	pre/post training test
48	Neils, 2005	parallel group	Y	N	19 healthy young with RT experience (18-30y)	RT	8 weeks	3	2	80%RM vs. 50%RM	Intensity	N	muscular strength; peak power	1RM free-weight; peak power	pre/post training test

STUDY	TRIAL DESIGN CHARACT.			POPULATION	EXBT	SCHEDULING			DOSE		STUDIED DOSE CHARACTERISTIC	V CON ST	OUTCOMES		ASSESSMENTS & FOLLOW S-UP
	DESIGN	R	C GR			LENGT H EXBT	FREQ D/WK	NR OF DOSE	MANIPULATION APPLIED	TYPE			METHOD		
49	de Souza, 2010	parallel group	Y	N	20 recreationally trained men	RT	6 weeks	6	2	constant vs. decreasing rest intervals and intensity	Intensity	N	muscle strength; peak torque	1RM free-weight ; peak torque	pre/post training test
50	de Vos, 2005	parallel group	Y	Y	112 untrained healthy old subjects (≥ 60y)	RT	12 weeks	2	2	20%RM vs. 50%RM vs. 80%RM	Intensity	N	muscular strength, endurance and power	1RM, and Watt	week 0 -8 -12
51	Pollock, 1993	parallel group	Y	Y	50 men + 28 women; young with no RT experience (18-35y)	RT	12 weeks	VAR	4	1d/w 1set vs. 2d/w 1set vs. 1d/w vs. 2d/w;	Frequency	N	isometric and dynamic muscle strength	CERVICAL Extensor machine	pre/post training test
52	Henwood, 2008	parallel group	Y	Y	67 old healthy subjects (65-84y)	RT	24 weeks	2	2	75%RM vs. varied load (45%, 60%, 75%RM)	Intensity	N	muscle strength, endurance, power, functional perform. and balance	1RM, endurance, power, physical perform. tests	pre/ 8- 24 week
53	Cauraugh, 2009	parallel group	Y	Y	30 chronic stroke (55-80y)	CBT	2 weeks	4	2	with vs. Without load	Intensity	N	muscle strength, functional ability and dexterity level	isometric and isotonic muscle contraction; Box and Blocks, functional and dexterity tests	pre/post training test
54	Onambélé-Pearson, 2010	parallel group	Y	N	34 healthy old active subjects (60-79y)	RT	12 weeks	3	2	80%RM vs.40%RM	Intensity	N	muscle strength, max isometric force and functional ability;	1RM, functional ability tests dynamometer; Cybex machine;	pre/post tests
55	DiFrancisco-Donoghue, 2007	parallel group	Y	N	18 healthy old subjects (65-79y)	RT	9 weeks	VAR	2	1d/w vs. 2d/wk	Frequency	N	muscle strength	1RM free-weight	pre/post training test
56	Candow, 2007	parallel group	Y	N	29 untrained people (27-58 y)	RT	6 weeks	VAR	2	3d/wk, 2 sets vs. 2d/wk, 3sets	Frequency	Y	muscle strength	1RM	pre/post training test
57	Farinatti, 2013	parallel group	Y	Y	48 active woman (60-78y)	RT	16 weeks	VAR	3	1d/wk vs. 2 vs. 3d/wk	Frequency	N	functional performance and strength	1RM, functional ability tests	pre/post training test
58	Sato, 2009	parallel group	Y	N	22 frail elderly subjects (75-85y)	water ex.	2 years	VAR	2	1d/w vs. 2d/wk	Frequency	N	muscle strength; functional ability	strength= dynamometer; ADL ability=FIM	pre/ 6months; 1 and 2 years

STUDY	TRIAL DESIGN CHARACT.			POPULATION	EXBT	SCHEDULING			MANIPULATION APPLIED	DOSE	STUDIED DOSE CHARACTERISTIC	V CON ST	OUTCOMES		ASSESSMENTS & FOLLOW S-UP	
	DESIGN	R	C GR			LENGT H EXBT	FREQ D/WK	NR OF DOSE					TYPE	METHOD		
Other Trial Design																
59	McDermott, 2006	categori zed groups	X	X	417 old subjects with PAD (≥ 55y)	Walkin g train.	3 years	VAR	3		≥3d/wk (90min) vs. 1 or 2d/wk(< 90 min) vs. <1d/wk	Frequency	N	functional tests	Functional tests	pre/post training test

Notes

RCT= Randomized controlled Trials
R= Randomization procedure
CT= Controlled Trials
C gr= Control Group
RT= Resistance training
AT= Aerobic training
CBT= Coupled Bilateral load training
Body RecT= Body recall training
CIMT= Constraint-Induced Movement
MRP= Motor-relearning program

Wks= Weeks
V= volume
HI= High Intensity
LI= Low Intensity
MI= Median Intensity
reps= repetitions
RM= Repetition maximum
rpm= repetition per minute
PDA= Peripheral Arterial Disease
CD= Coronary disease

FMA=Fugl-Meyer Assessment
MRC= Medical Research Council scale
ADL= Activity of Daily Living
IADL= Instrumental Activity of Daily Living
FIM= Functional independence measure
CS-PFP= Continuous scale physical functional performance test
ARAT= Action Research Arm test
SF-36= Medical Outcomes Survey Short Form-36

Table 2-3: Summary table on characteristic of included studies by trial design

DESIGN	NR OF STUDIES	STUDIED DOSE CHARACTERISTIC			
		INTENSITY & AMOUNT	AMOUNT	INTENSITY	FREQUENCY
RCT	47	17	14	11	5
CT	11	4	3		4
other	1				1

Notes

RCT= Randomized controlled Trials
 CT= Controlled Trials

Sample characteristics

A sample of 3,294 people were involved in the included studies. The smallest study was an RCT including 12 sedentary healthy men [147]. The largest study was a longitudinal observation study including 417 older adults with peripheral arterial disease [148].

Forty-nine studies (83%) included healthy people from sedentary to physically active. Ten studies included people with chronic conditions [101,111,148,149,150,151,152,153,154,155].

Study designs

Forty-seven (79.7%) of the included studies were randomised controlled trials (RCTs). Eleven studies (18.6%) applied a quasi-experimental design being classified as non-randomized controlled trials (CTs). One study was a longitudinal observational study with more than one group [148].

Approaches to dose optimization

All studies, apart from the observational study, implemented a set of predefined dose levels or protocols towards dose optimization. This approach, called *dose-ranging*, investigates only a pre-specified number and levels of dose

(or protocols). Among studies applying a dose-ranging design fifty-five studies (94.8%) implemented a parallel group design²⁰; and three studies implemented a cross-over design to investigate the training optimal dose [156,157,158].

The observational study categorized participants into three groups depending on their (reported) weekly amount of exercise to investigate the optimal training dose.

Characteristics of the training protocol and dose

The mean number of doses considered per study was 2.5 with a maximum of 9 doses investigated in one study [159]. Forty-five studies (76.3%) made a comparison between two doses.

In fifty-seven studies (96.6%) the dose of training was defined as being composed by two characteristics: intensity and amount of training. Among them, forty-nine studies (86% of the fifty-seven studies) defined the intensity of the training as “the load applied to the exercise” and the amount of training as “the number of task repetitions undertaken during a training session” [147,149,151,152,153,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198]. In the remaining eight studies (14% of the fifty-seven studies) the amount of the training was consistently defined as “the time spent exercising” whereas, the definition for intensity was heterogeneous, including:

- the load applied to the exercise in two studies [199,200];
- the subject’s perceived exertion in two studies [154,201];
- the number of repetition tasks undertaken during a training session in two studies [101,202];
- the percentage of the peak oxygen uptake (% of VO₂ peak) in one study [203];

²⁰ A dose-ranging parallel design involves two or more intervention groups of individuals allocated to different intervention dosages.

- the product of frequency of the training and the time spent exercising in one study [127].

Two studies (3.4%) defined the dose of training using only one parameter: the time spent exercising in one session. Dromerick referred to it as the intensity of training session [115] whereas, McDermott as the weekly amount of training undertaken [148].

The volume of training was defined in nineteen (32.2%) of the included studies with heterogeneity. In detail:

- fifteen studies (78.9% of the nineteen studies that defined the volume of training) defined the volume as the product of the intensity and the amount of training undertaken in one training session [147,156,157,163,167,169,176,177,188,189,192,193,195,196,199];
- three studies (15.8%) defined the volume as the product of total work and training sessions[181,194,202];
- one study defined the volume as the product of the intensity and amount undertaken in one training week [179].

The definition of the parameters of the training protocol was found more consistent than the definition of the dose components. Specifically, all studies defined the training protocol as composed by the dose, the frequency and the total length of the training. The frequency and total length of training were also referred as the training schedule. All the studies defined the frequency of the training as the number of training days per week. All studies, but two²¹, defined the length of the study as the total duration of the training protocol, often, in weeks.

²¹ Jigami et al. (2012) and Abrahin et al (2014) defined the total length of the study training as the number of sessions delivered.

Manipulation of the training dose and the training protocol

The most studied parameter among included studies was the impact of the training dose investigated in forty-nine studies (83.3%). In detail:

- Twenty-one studies (42.9% of studies investigating dose characteristics) manipulated both characteristics of the training dose, amount and intensity, to target the desired outcome. Among which, fourteen studies held the volume of the training constant between groups [147,159,163,164,165,167,176,182,186,196,197,198,199,204]. The remaining seven studies varied the volume of training between groups [101,156,172,188,194,202,203];
- Ten studies (20.4% of studies investigating dose characteristics) investigated the effect of varying the intensity but keeping constant the amount of training [149,153,155,169,170,178,179,185,187,200]. In these studies the total volume of training varied between groups;
- Eighteen studies (36.7% of studies investigating dose characteristics) investigated the effect of varying the amount but keeping constant the intensity of training [111,115,152,157,158,160,161,166,174,175,177,181,183,184,191,192, 193,195]. In these studies the total volume of training varied between groups.

The impact of different frequencies of the training sessions was assessed in ten studies (16.9%). Three studies investigated the effect of different frequencies of training holding the same total volume of training between groups [151,179,199]. Seven studies applied different total volumes of training among groups [148,154,162,168,171,189,201]. Consequently, in these seven studies, the optimization of the training frequency depended on two parameters (frequency and volume of training).

The efficacy of different lengths of training was not investigated among any of the included studies. The mean total length of the studies protocols was 15.5

weeks with a minimum of two weeks [115,149] to a maximum of 3 years for the longitudinal study [148].

Forty-two studies (71.2%) applied a pre and post treatment assessments procedure to evaluate treatment effects. Seventeen studies (31.5%) investigated the treatment effect over time applying a multiple assessment procedure

[111,147,154,156,157,159,166,170,176,177,178,180,181,182,183,186,192,194].

2.5 Risk of potential bias assessment

Table 2-4 summarises the results from the modification of the Cochrane Collaboration tool for risk of bias used in this review. In detail: eight studies (13.6%) were evaluated as having a low risk of bias [101,111,115,152,155,162,170,176], and nine studies (15%) as having a moderate risk of bias. Whereas, forty-two studies (71.2%) were classified as potentially having high risk of bias.

The major observed issues for risk of bias were identified in the following procedures: (1) insufficient reporting or lack of randomization procedure and allocation concealment (87% and 88.9%); (2) lack on balancing baseline groups (57.4%); (3) omission of sample-size calculation (88.9%); (4) no control for co-interventions or possible confounders (54.5%); (5) lack of adherence or control on the treatment protocol (14.5%); and (6) insufficient reporting or control on onset of adverse events (80%).

Table 2-4: Summary of the risk of potential bias assessment of included studies

Study	Randomization	Allocation concealment	Blinding assessment	Balanced baseline groups	Sample-size calculation	Co-intervention	Adherence to the protocol	Consistency assessment	Adverse events reported
1 Abrahin, 2014	U	U	U	N	U	Y	Y	Y	N
2 Ahtiainen, 2005	N	U	N	N	U	U	N	Y	N
3 Anderson, 1982	U	U	U	Y	U	U	Y	Y	N
4 Baker, 2013	U	U	Y	U	U	Y	Y	Y	N
5 Berger, 1962a	N	U	U	N	U	N	Y	Y	N
6 Berger, 1962b	N	U	U	N	U	U	Y	Y	N
7 Borst, 2001	N	U	U	Y	U	Y	U	Y	N
8 Campos, 2002	U	U	Y	N	U	U	Y	Y	N
9 Candow, 2007	U	U	Y	Y	Y	U	Y	Y	N
10 Capen, 1956	N	U	U	N	U	U	Y	Y	N
11 Cauraugh, 2009	U	U	U	N	U	U	Y	Y	N
12 Han, 2013	Y	Y	Y	Y	N	U	Y	N	N
13 de Paleville, 2009	U	U	U	N	U	U	Y	Y	Y
14 de Silva, 2014	Y	Y	Y	Y	U	U	Y	Y	N
15 de Souza, 2010	U	U	U	Y	U	U	Y	Y	N
16 de Vos, 2005	U	U	N	Y	U	Y	Y	Y	Y
17 DiFrancisco-Donoghue, 2007	Y	U	U	N	Y	U	U	Y	N
18 Dromerick, 2009	Y	U	Y	Y	Y	Y	Y	Y	Y
19 Ewing J, 1990	U	U	U	N	U	Y	Y	Y	N
20 Farinatti, 2013	Y	Y	U	Y	U	Y	Y	Y	N
21 Fatouros, 2006	U	U	U	N	U	U	Y	Y	Y
22 Goto, 2004	N	U	U	N	U	Y	Y	Y	N
23 Galvao, 2005	U	U	U	Y	U	U	Y	Y	N
24 Harris, 2004	U	U	U	Y	Y	Y	Y	Y	Y
25 Hass, 2000	U	U	U	Y	U	N	Y	Y	Y
26 Henwood, 2008	U	U	U	Y	U	U	Y	Y	Y
27 Holm, 2008	U	U	U	N	U	U	Y	Y	N
28 Humburg, 2007	U	U	U	X	U	U	Y	Y	N
29 Hunter, 1985	N	U	U	N	U	U	Y	Y	N
30 Hunter, 2001	U	U	U	N	U	Y	Y	Y	N
31 Hsieh, 2011	Y	Y	Y	Y	U	Y	Y	Y	Y
32 Kalapoth 2005	U	U	U	Y	U	U	Y	Y	N
33 Kelly, 2007	U	U	U	N	U	Y	Y	Y	N
34 Jigami H, 2012	N	N	Y	Y	N	Y	Y	Y	N
35 Kemmler, 2004	U	U	U	Y	Y	Y	Y	Y	N
36 Kraemer, 2004	U	U	U	N	U	Y	Y	Y	N
37 McBride, 2003	N	U	U	N	U	U	Y	Y	N
38 McDermot, 2006	X	X	Y	Y	X	N	N	Y	N
39 Miszka, 2003	U	U	U	N	U	Y	U	Y	N
40 Manzolini, 2008	Y	Y	Y	Y	U	Y	Y	Y	Y
41 Munn, 2005	U	U	U	N	Y	Y	Y	Y	Y
42 Nakamura, 2007	N	U	U	N	U	U	U	Y	N
43 Neils, 2005	U	U	U	N	U	U	Y	Y	Y
44 Nemoto, 2007	N	N	U	N	U	U	N	Y	N
45 O'Shea, 1996	U	U	U	Y	U	U	Y	Y	N
46 Onambélé-Pearson, 2010	U	U	U	N	U	U	Y	Y	N
47 Paulsen, 2003	U	U	U	N	U	U	Y	Y	N
48 Pollok, 1993	U	U	U	N	U	U	Y	Y	N
49 Rana, 2008	U	U	U	N	U	Y	Y	Y	N
50 Rhea, 2002	U	U	U	Y	U	N	Y	Y	N
51 Ronnestad, 2007	U	U	U	Y	U	Y	Y	Y	N
52 Sato, 2009	U	Y	N	Y	U	U	Y	Y	N
53 Schlumber, 2001	U	U	U	N	U	Y	Y	Y	N
54 Starkey, 1995	U	U	U	N	U	Y	Y	Y	N
55 Signorile, 2004	N	U	U	N	U	U	Y	Y	N
56 Stone, 1994	U	U	U	N	U	U	Y	Y	Y
57 Van Roie, 2013	U	U	U	N	U	U	Y	Y	N
58 Vincent, 2003	Y	U	U	N	U	U	Y	Y	Y
59 Weiss, 1999	U	U	U	N	U	U	Y	Y	N

Notes: N= criterion not verified; Y= criterion verified; Green= criterion satisfied; Yellow= Not known/partially satisfied; Red= criterion not satisfied; X= n/a; U= not known.

2.6 Interpretation

This review highlighted standard dose optimisation designs and approaches used in exercise-based training clinical research since the middle of the twentieth century.

The choice of the trial design itself plays a key role on the appropriateness of the study to answer specific questions on the optimal dose of training and on the dose-response relationships.

All included studies identified the OTD or the optimal protocol of training by means of dose-ranging designs with a defined sample size, rather than more sophisticated optimization design such as, dose-finding designs.²²

Dose-ranging designs allowed the investigation of only pre-defined numbers and levels of dose. In these designs adjustments of the dose were not allowed. Ideally, when dealing with uncertainty on the efficacy and safety of the intervention dose-ranging study should cover a wide range of dose from low to high, reducing the efficiency of the study since it requires an ample number of cohorts (large sample-size). In these designs the likelihood of identifying the OTD can decline significantly as the appropriateness on investigating the dose-response relationships crucially depends on the relevance of the tested doses and on the previous research upon which these doses were based. In pharmaceutical research, often, the main objective of an early dose-ranging study was to investigate the efficacy and safety responses at the given training dose, rather than targeting the OTDs [139,205,206,207].

Although advocated as the more appropriate designs for dose optimization purposes [139], the implementation of dose-finding designs in exercise-based training literature was still limited. This could be mainly due to the complexity of their use in clinical settings. Dose-finding trial designs, also known as adaptive design for their adaptive (flexible) nature, are able to make changes on the dose levels, based on the results of interim analyses. This characteristic

²² See chapter 5 for details on dose-finding designs.

feature increases the study efficacy and accuracy on targeting the OTD but preserving patients' safety [208,209,210,211]²³.

Among included studies the majority applied a parallel-group design (94.8%) with a mean number of 2.5 dose per study. Thus, the majority of studies (76.3%) made a single comparison between two dose levels. This approach limited the information retrieved on the dose-response relationship. When data were available only for two dose levels it was not possible to derive a dose-response curve. Furthermore, using this approach, the importance of the spacing (gap) between two doses increases. For instance, if two doses were chosen too close they may not suggest any difference in the intervention effect. On the other hand, if the two doses were chose too far apart the shape of the curve could be mistaken.

The implementation of multiple assessment procedures was not common among included studies. Common practice was the implementation of two assessment points, at the beginning and at the end of the intervention. As a result, the data derived from pre and post intervention assessments cannot be used to speculate on the training effect over time and on the appropriate length of the training protocol. Consequently, the selection of the length of the training programme was often left to arbitrary or pragmatic decisions. This was in line with the literature which advocated longitudinal procedure as needed but uncommon in exercise based training research [73,111,136].

This review highlighted that the multifactorial aspects of the training dose could, often, complicate the dose optimization in exercise based training. This issue was even more relevant when data were synthetized across studies.

High variability was found on the definition of the training dose and its characteristics across included studies. The ambiguity in the definition of dose could complicate the interpretation of data synthesis across studies and it could preclude the effective communication among practitioners and rehabilitative teams [37]. However the variability found on this review on the terminology

²³ For a more detailed discussion, see chapters 5 and 6.

concerning dose could be, in part, explained by the inclusion of different fields applying exercise-based training.

On the other hand, more consistency was found in the definition of the components of the training protocol, often shaped by the dose, frequency and length of the training.

To identify the OTD, more than one characteristic of the dose was manipulated at a time in several studies (42.9% of studies investigating dose characteristics). This approach produced blurred results, given the impossibility to identify which characteristic of the dose was responsible for the outcome (therapy effect).

Similar approach was often used across studies when investigating the optimal schedule (frequency) of training. Often, a different total volume of training was applied among groups (in seven studies out of ten), introducing further complexity on the understanding of the optimal frequency capable to maintain the level of stimulus delivered by the optimal dose of training over time.

The studies' quality assessment was classified as potentially high risk of bias for 71.2% of the included studies. Risk of potential bias in dose optimization study protocols included: lack of reporting of randomization; lack of balancing baseline group characteristics; limited control over possible co-interventions and confounders and lack of adherence or control on the treatment protocol. As detailed before, the lack of control for co-interventions and protocol adherence could negatively influence the confidence on the results on dose. To improve the quality of dose optimization in exercise-based training it seemed crucial to plan and report in sufficient detail the training protocol, its adherence and any deviation from it. This approach will allow intervention replication and better result interpretation. Furthermore, detailed reporting of the training dose prescribed and received by participants will provide information on the tolerability and safety of the intervention. Ideally, a standard and consistent method, such as the so-called FITT components [212], should be used in reporting training protocols and dose characteristics.

2.7 Conclusion

Despite a large number of studies pooled by guidelines and recommendations for training dose, this review has shown that only a small number of them investigated dose optimization and the associated dose-response relationships. Even the studies that claimed to investigate the optimal training dose or protocol very often applied sub-optimal designs. Inadequate trial design, with respect to dose optimization, the use of inefficient dose selection procedure, a poor definition of the training dose, and inefficient dose manipulation were often found among included studies. These issues could have a role in the lack of evidence-based knowledge on the appropriate dose and protocols experienced in many field of medicine applying exercise-based training [25,37,45,131,136,213] and in the constant need for updating once new evidence becomes available.

To our knowledge, this review was the first that explored the methodological aspects of dose optimization in the primary trials upon which the recommendations on appropriate dose of exercise-based training were based. Understanding the designs and the approaches applied to dose optimization, the definitions and use of the training dose and protocol towards dose optimization gave indication on the strength of the results on dose, as well as providing indication for further research trajectories. The assessment on the risk of bias, tailored to the dose optimization protocols, gave further indications on the lack of strong evidence on the OTDs and optimal protocols in exercise-based training research providing the basis for future good quality research.

In ExBT in general, and stroke rehabilitation in particular, the development of a structured and standardised pathway towards the identification of the OTD and appropriate protocols could enhance research further. This procedure is in line with the view advocated by the American Congress of Rehabilitation Medicine Stroke Movement Interventions Subcommittee [37] and other scholars [45].

2.8 Review limits

This review had some limitations. Some dose optimization studies may have not been included due to the broad or vague terminology used to address physical activity, exercise and the dose of training. However, the systematic approach implemented in this review and the use of multiple electronic databases should have minimized this risk of bias.

As any other review, this study may be subjected of publishing and reporting bias. However, the effort of contacting leader authors on the field looking for grey literature may have reduced this bias.

Reviewers, in applying eligibility criteria, were not blinded to authors, institutions, journals, and study results. Blinding of the (two) reviewers was not considered to be feasible given their prior considerable knowledge of some of the studies included in this review.

Only one researcher (myself) was involved in the data extraction and qualitative assessment procedure. However, the high level of standardization in both procedures should have reduced the likelihood of possible bias.

To be consistent with the guidelines of reference, only included studies that dealt with healthy adults (18+ years) or, adults with chronic conditions aged 50+ years have been involved. These criteria could have restricted the number of studies included in this review. Given the specific focus on the methodological design it is unlikely that the applied restriction criteria could have had an impact on the understanding of the designs and approaches applied to dose optimization in exercise-based training.

Finally, the paucity of trial designs and approaches to dose optimization found among included studies made considerations and comparisons limited. However, this reflected the current dose optimization standards in exercise-based training research.

2.9 Clinical and research implication

This systematic review highlighted the importance of finding a meaningful and standardised definition of the “training dose”, which accounted for its multifactorial aspects when targeting optimal doses in exercise-based training. The need to use a systematic and consistent terminology on dose emerged as a way to avoid the existing heterogeneity on the way key concepts were defined.

This review also helped in understanding how the different components of the training dose and protocol were manipulated in the existing practice of dose optimization in exercise-based training research.

These considerations were relevant to guide the devising of a novel dose optimization approach for stroke rehabilitation. However, concerning approaches applied in exercise-based training to dose optimization, some methodological limitations were found that could hampered progresses towards an answer-search process. Main limitations were on the implementation of trial designs not purposely made to identify optimal dose; inappropriate dose selection; and improper use of dose manipulation [74,137,214,215].

For these reasons a review of dose optimization approaches applied in other fields of medicine was advisable. The following chapter reported a review on dose optimization in pharmaceutical research.

Chapter 3:

What can we learn from dose optimization approaches in pharmaceutical studies? A Narrative Systematic Review.

3.1 Introduction

Commercialized drugs are delivered in a precise dose, frequency, and for a known period of time to maximise their therapeutic effect while limiting side effects.

The dose and schedule of drugs were identified by dose optimization studies that characterise the drug dose-response relationships for efficacy and safety. The pharmaceutical dose optimization processes were among the more strictly regulated procedures to guarantee participants' safety minimizing possible health risks since the early nineties.

Currently, the scientific community agrees on the implementation of this research approach to ameliorate complex interventions such as stroke rehabilitation research [73,132,134,216]. To follow these indications a

narrative review on dose optimization approaches applied in pharmaceutical clinical literature was undertaken to inform on appropriate dose optimization approaches for stroke rehabilitation research.

A narrative systematic review was chosen to investigate the trial designs and approaches applied in pharmaceutical research from both, a quantitative and qualitative point of view [217]. Narrative reviews allow extensive investigations and discussions on a specific topic from a theoretical and contextual point of view [218].

The following part of this paragraph reports a brief overview of the pharmaceutical drug development stages with a specific focus on dose optimization processes.

Pre-clinical trials are the first stages of the drug development. It is at this stage that a compound (drug element) is identified due to its potential for efficacy against the desired target. Pre-clinical studies involve first in vitro tests, outside a living organism, and, subsequent, in vivo tests on living organisms to identify the compound's actions and reactions to and with biological systems. At this stage the compound starts to be investigated in term of efficacy, potency and safety. The compound action on the target, the kinetics of absorption, distribution, metabolism and extraction in the biological systems, the onset, persistency and gravity of adverse events are widely investigated at this stage [139,219,220,221]. All these information are used to characterise the first dose-response relationships on efficacy and toxicity which will be used to set the first dose regimen to bring forward in the following phases of the research pathway. This is in contrast with the practice in exercise-based training in general, and motor intervention research in particular, where pre-clinical data are not commonly available to guide the selection of potentially efficacious and safe dose.

About 64% of the tested compounds will pass the pre-clinical studies and be moved into phase I clinical trials [222], as "first in humans trials". Phase I trials

often involve a small number of healthy volunteers²⁴ used to establish key dose and schedule to use in subsequent phase II clinical evaluation trials [207,223]. Specifically, phase I trials often allow the estimation of four important dose endpoints:

- the *maximum tolerable dose* (MTD), defined as the highest dose at which the toxicity is still considered acceptable for patients;
- the *minimum effective dose* (MinED), defined as the first dose at which a clinical relevant effect is found to be statistically significant superior from placebo;
- the *dose limiting toxicity* (DLT), defined as the toxicity level that is considered unacceptable and limits further dose escalation; and
- the recommended phase II dose (RPTD)²⁵ is the dose found to be recommendable for further efficacy studies.

About 48% of the compound which passed phase I moves into phase II clinical trial [222]. The main objective of a subsequent phase II trial is to assess the compound effectiveness, coupled with the confirmation of the optimal dose [224,225]. If the appropriate dose is not confirmed, the compound is brought back to a phase I and further efficacy trials are planned.

It is known that only the minority of promising compound reach successfully the final phase III stage. In fact, according to the FDA's research, nine out of ten drugs deemed successful in pre-clinical trials fails in clinical trials²⁶. This third phase assesses, in a larger scale, the compound effectiveness and identifies intra-patients response variability. If the efficacy and safety of a specific dose is confirmed in this phase, the compound is ready to be submitted to appropriate regulatory authorities [219,226]. Otherwise, the compound is either brought back in the research pathways or failed.

²⁴ Cancer therapy or therapies for other life-threatening illnesses are an exception to this involving patients with the target disease since the early stages [214].

²⁵ The RPTD is often called as OD for phase II trials or, simply, the recommended dose (RD).

²⁶ <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108576.htm>

This brief summary of the drug development pathway has highlighted how structured and regulated a dose optimization process should be.

The aim of the remaining parts of this chapter was to identify dose optimization approaches that were suitable for use in stroke rehabilitation research investigating pharmaceutical industry standard procedures of dose optimization used in clinical trials (*Overall aims 1; Objectives 1.b*). This, together with the results coming from the review on dose optimization in ExBT, helped in devising a novel dose optimization study suitable for stroke rehabilitation research.

3.2 Methods

3.2.1 Design

A narrative systematic review was undertaken to identify dose optimization designs and approaches applied in pharmaceutical clinical research.

With respect to a systematic review less prescriptive rules on study inclusion criteria were applied to this review to allow a broader inclusion of studies [217].

3.2.2 Search strategy

Studies for this review were retrieved from the two main medical electronic databases: Medline and Embase. Databases were searched from 1946 up to March 2012. An updating search is not planned because significant changes were not expected on the methodological aspects of the dose optimization within the time frame of this research project.

The search terms included a combination of subject headings and keywords related to the clinical phases of the pharmaceutical research pathway and the dose optimization procedure. Language and date restrictions were not applied to the searches.

The complete search strategy is reported in Table 3-1.

Table 3-1: Electronic search strategy on dose optimization procedures

Search terms	
1	(phase adj I).ab,ti.
2	(phase adj II).ab,ti.
3	(phase adj III).ab,ti.
4	(seamless adj phase).ab,ti.
5	1 or 2 or 3 or 4
6	(clinical adj trial).mp.
7	5 and 6
8	dose-ranging*.ab,ti.
9	dose-finding*.ab,ti.
10	(optimal adj2 dos*).ab,ti.
11	(dos* adj2 optimization).mp.
12	12. 8 or 9 or 10 or 11
13	7 and 12

All electronic searches results were downloaded into the EndNote X6 program.

3.2.3 Inclusion criteria

Only original published articles on dose optimization procedure from pharmaceutical clinical research were included. Included studies were those that investigated dose optimization of a single or multiple compounds among adults aged 18+ years. To be identified as dose optimization, a study should [139]:

- assess the same compound(s) among groups apart from dose;
- apply the same administration protocol between groups;
- involve more than one intervention group;
- co-intervention(s), if present, should not differ among groups.

In line with the objectives of this review, any kind of trial design and approach applied to dose optimization was accepted.

Studies published in English, Italian, Spanish or French language were assessed for inclusion.

3.2.4 Identification of studies

The primary researcher (EC) performed the searches and examined studies for inclusion. Electronic de-duplication of papers was detected by using EndNote X6 immediately after all titles were downloaded.

Citations were initially screened accordingly their titles and abstracts to exclude studies that clearly did not meet the review inclusion criteria. Full-texts were obtained and reviewed for the studies that were included after the abstract screening stage. If the researcher was unsure whether or not a study should be included, a second researcher (LC) was available for discussion to reach consensus.

3.2.5 Data extraction

The primary researcher extracted the following data from included studies:

- 1) study author(s) and year of publication,
- 2) study design characteristics towards dose optimization;
- 3) presence of random allocation procedure;
- 4) use of blinding procedure toward intervention group(s);
- 5) study sample size;
- 6) study clinical research phase;
- 7) procedure applied to select tested dose;
- 8) study dose endpoints.

When studies investigated more than one compound, data extracted referred only on the compound where dose optimization was applied.

Studies were primarily grouped according to the applied trial design. Sub-groups were subsequently generated according the features of the dose optimization approaches and the clinical phase of the study.

3.3 Analysis

Descriptive analyses were planned to identify dose optimization designs and approaches applied in pharmacological clinical trials to inform stroke rehabilitation research. Trial designs, looking specifically at dose optimization, were explored in relation to dose optimization approaches, dose escalation procedures, and phase of pharmaceutical research in use.

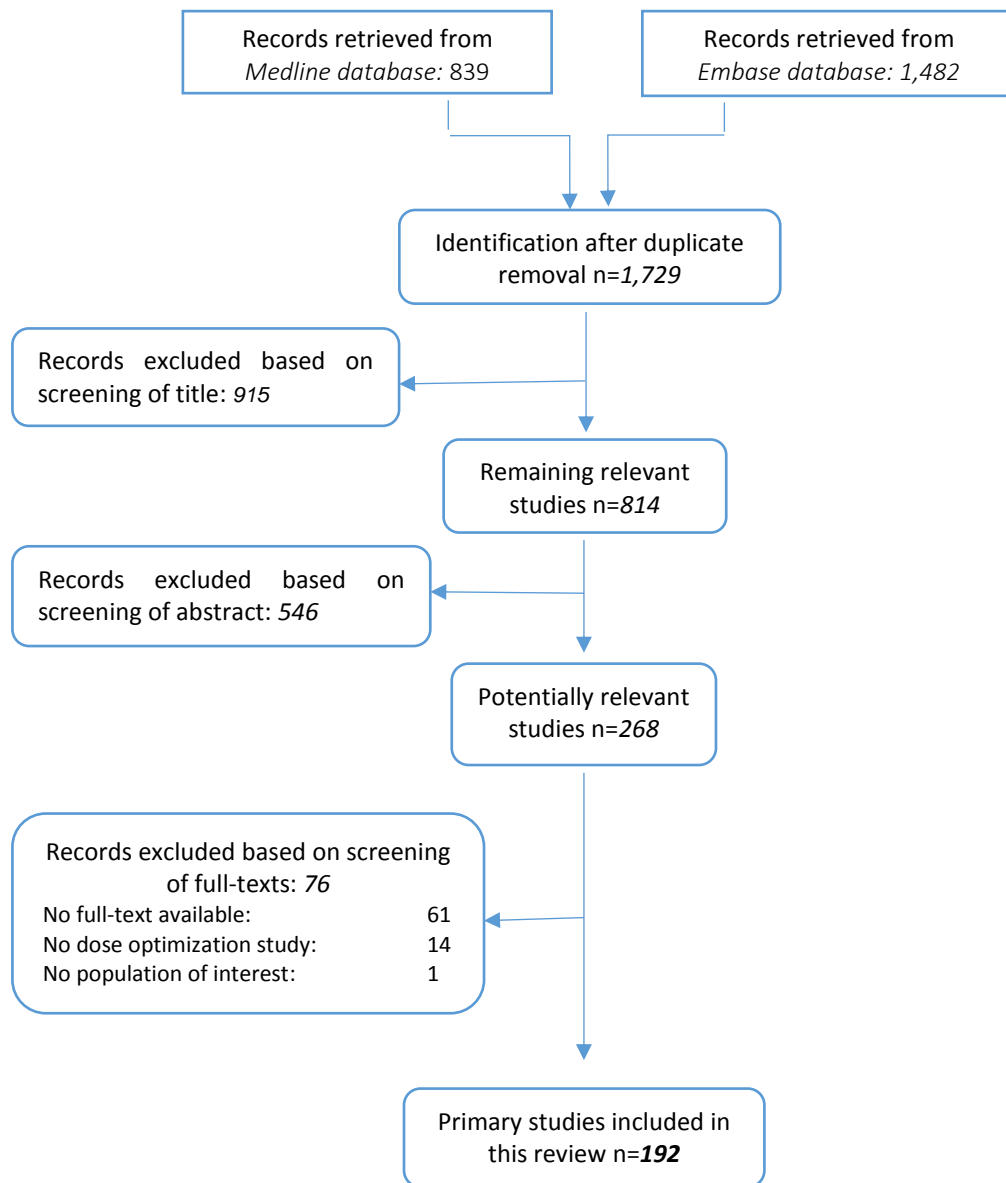
3.4 Results

3.4.1 Identification of studies

Reporting of search and selection processes followed PRISMA recommendations²⁷. Figure 3-1 summarises the review search and selection processes applied. After electronic deduplication, 1,729 references were identified as potentially eligible for this review. Of them, 915 studies were excluded by title because they clearly did not meet the review inclusion criteria. From the remaining 814 studies, 546 were excluded by abstracts and 76 by full-texts review. The remaining 192 studies were included in this review. The full list of excluded studies at the full-text stage, together with justifications for exclusion, are confined in Appendix D.

²⁷ See: <http://www.prisma-statement.org/statement.htm>, last visited on 07/2012

Figure 3-1: Flowchart of pharmaceutical drug development review search and the selection process



3.4.2 Studies characteristics

Table 3-2 lists included studies by their trial design characteristics, dose optimization approach and clinical research phase. Table 3-3 condenses the review’s key results reported on Table 3-2.

Table 3-2: Characteristics of included studies of dose optimization in pharmacological clinical literature by trial design

	Reference	Trial design characteristics	R	B	Sample Size	Clinical Phase	Dose setting procedure			Trial Endpoints	
Rule-based design											
1	Bajetta E, et al. (2009)	3+3 dose-finding	NA	N	21	I	Escalation sequence)	procedure	(predefined	numerical	MTD & DLT
2	Gibbs DD, et al. (2002)	3+3 dose-finding	NA	N	31	I	Escalation sequence)	procedure	(predefined	numerical	DLT; dose-response
3	Frasci G, et al. (1999)	3+3 dose-finding	NA	N	44	I	Escalation sequence)	procedure	(predefined	numerical	MTD;
4	Fabi A, et al. (2008)	3+3 dose-finding	NA	N	10	I	Escalation sequence)	procedure	(predefined	numerical	MTD; DLT & survival rate
5	Guarino MJ, et al. (2002)	3+3 dose-finding	NA	N	30	I	Escalation sequence)	procedure	(predefined	numerical	efficacy & safety study; OTD; DLT & MTD
6	Boven E, et al. (2010)	6+6 dose-finding	NA	N	21	I	Escalation sequence)	procedure	(predefined	numerical	safety; DLT; PK & MTD
7	Briasoulis E, et al. (2004)	3+3 dose-finding	NA	N	44	I	Escalation sequence)	procedure	(predefined	numerical	toxicity spectrum; DLT; MTD; OTD
8	Fornier MN, et al. (2007)	3+3 dose-finding	NA	N	30	I	Escalation sequence)	procedure	(predefined	numerical	PK, safety and DLT
9	Castellano D, et al. (2003)	3+3 dose-finding	NA	N	19	I	Escalation sequence)	procedure	(predefined	numerical	DLT; MTD
10	Comella P, et al. (2002)	3+3 dose-finding	NA	N	46	I	Escalation sequence)	procedure	(predefined	numerical	MTD; DLT & OTD
11	Di Costanzo F, et al. (2006)	3+3 dose-finding	NA	N	32	I	Escalation sequence)	procedure	(predefined	numerical	MTD; DLT
12	Elkas JC et al. (2007)	3+3 dose-finding	NA	N	13	I	Escalation sequence)	procedure	(predefined	numerical	OTD; DLT
13	JJonker D J, et al. (2011)	3+3 dose-finding (A)	NA	N	18	I	Escalation sequence)	procedure	(predefined	numerical	safety; PK; PD; MTD; DLT; lowest biologically active dose; OTD
14	Lin J, et al. (2009)	3+3 dose-finding	NA	N	28	I	Escalation sequence)	procedure	(predefined	numerical	MinED; MTD & OTD
15	Maenpaa J. and A. Leminen (2009)	3+3 dose-finding	NA	N	8	I	Escalation sequence)	procedure	(predefined	numerical	MTD
16	Masuda N, et al. (2008)	3+3 dose-finding	NA	N	9	I	Escalation sequence)	procedure	(predefined	numerical	OTD; MTD
17	Nole F, et al. (2006)	3+3 dose-finding	NA	N	44	I	Escalation sequence)	procedure	(predefined	numerical	MTD; OTD
18	Oostendorp RL, et al. (2010)	3+3 dose-finding	NA	N	28	I	Escalation sequence)	procedure	(predefined	numerical	MTD; DLT & PK

	Reference	Trial design characteristics	R	B	Sample Size	Clinical Phase	Dose setting procedure				Trial Endpoints
19	Pasini F, et al. (2005)	3+3 dose-finding	NA	N	47	I	Escalation sequence)	procedure	(predefined	numerical	MTD; toxicity & pathological response rate
20	Ryan DP, et al. (2006)	3+3 dose-finding	NA	N	51	I	Escalation sequence)	procedure	(predefined	numerical	OTDs
21	Pourgholami MH, et al. (2010)	3+3 dose-finding	NA	N	33	I	Escalation sequence)	procedure	(predefined	numerical	DLT; OTD
22	Sykes A, et al. (2004)	3+3 dose-finding	NA	N	24	I	Escalation sequence)	procedure	(predefined	numerical	toxicity & efficacy study
23	Tambaro R, et al. (2003)	3+3 dose-finding	NA	N	30	I	Escalation sequence)	procedure	(predefined	numerical	MTD; OTD
24	Van Kesteren C, et al. (2000)	3+3 dose-finding	NA	N	52	I	Escalation sequence)	procedure	(predefined	numerical	MTD; DLT
25	Venturini M, et al. (2002)	3+3 dose-finding	NA	N	23	I	Escalation sequence)	procedure	(predefined	numerical	OTDs
26	Waters SH, et al. (2009)	6+6 dose-finding	NA	N	12	I	Escalation sequence)	procedure	(predefined	numerical	DLT & MTD
27	Zeuli M, et al. (2001)	3+3 dose-finding	NA	N	25	I	Escalation sequence)	procedure	(predefined	numerical	MTD; DLT
28	Dubinsky R. and C. Gray (2006)	3+3 dose-finding	NA	N	9	I	Escalation sequence)	procedure	(predefined	numerical	MTD; toxicity study
29	Bergmann MA, et al. (2005)	3+3 dose-finding	NA	N	16	I/II	Escalation sequence)	procedure	(predefined	numerical	MTD, DLT & OTD
30	Case Jr DC, et al. (1988)	3+3 dose-finding	NA	N	40	I/II	Escalation sequence)	procedure	(predefined	numerical	response; MTD; toxicity; OTD
31	Janinis J, et al. (2004)	3+3 dose-finding	NA	N	11	I	Escalation sequence)	procedure	(predefined	numerical	MTD; OTD
32	Kocher M, et al. (2005)	3+3 dose-finding	NA	N	14	I/II	Escalation sequence)	procedure	(predefined	numerical	starting dose (I); MTD (II)
33	Lissitchkov T, et al. (2006)	3+3 dose-finding	NA	N	15	I/II	Escalation sequence)	procedure	(predefined	numerical	MTD; DLT
34	Laurent S, et al. (2009)	5+5 dose-finding	NA	N	22	I/II	Escalation sequence)	procedure	(predefined	numerical	efficacy; MTD & DLT
35	Leonardi V, et al. (2009)	3+3 dose-finding	NA	N	9	I/II	Escalation sequence)	procedure	(predefined	numerical	MTD; OTD
36	Matulonis UA, et al. (2006)	3+3 dose-finding	NA	N	27	I/II	Escalation sequence)	procedure	(predefined	numerical	MTD; OTD
37	Okines AFC, et al. (2010)	3+3 dose-finding	NA	N	29	II/III	Escalation sequence)	procedure	(predefined	numerical	DLT; OTD
38	Patnaik A, et al. (2000)	3+3 dose-finding	NA	N	58	I/II	Escalation sequence)	procedure	(predefined	numerical	MTD; DLT

	Reference	Trial design characteristics	R	B	Sample Size	Clinical Phase	Dose setting procedure	Trial Endpoints
39	Jansen EPM, et al. (2007)	3+3 dose-finding	NA	N	32	I/II	Escalation procedure (predefined numerical sequence)	MTD; toxicity study
40	Beldner MA, et al. (2007)	3+3 dose-finding	NA	N	18	I	Escalation procedure (mFS)	OTD; MTD
41	Mukherjee DC, et al., (2003)	1+1 dose-finding	NA	N	7	I	Escalation procedure (mFS)	MTD
42	O'Bryant CL, et al. (2009)	3+3 dose-finding	NA	N	33	I	Escalation procedure (mFS)	MTD; OTD
43	Fizazi K, et al. (2000).	3+3 dose-finding	NA	N	48	I	Escalation procedure (mFS)	MTD; DLT; safety; efficacy; pharmacokinetics
44	Verweij J, et al. (1992)	3+3 dose-finding	NA	N	54	II	Escalation procedure (%)	DLT; OTD
45	Chauncey TR, et al. (2000)	8+8 dose-finding	NA	N	31	I	Escalation procedure (%)	DLT; MTD
46	Chi KN, et al. (2001)	3+3 dose-finding	NA	N	26	I	Escalation procedure (%)	efficacy & toxicity study; MTD; biological effects
47	Blum W, et al. (2007)	3+3 dose-finding	NA	N	11	I	Escalation procedure (%)	MTD
48	Kuenen BC, et al. (2005)	3+3 dose-finding	NA	N	16	I	Escalation procedure (%)	MTD
49	Lesimple T, et al. (2010)	3+3 dose-finding	NA	N	56	I	Escalation procedure (%)	MTD; OTD
50	Mudad R, et al. (2003)	3+3 dose-finding	NA	N	14	I	Escalation procedure (%)	MTD
51	Rubin EH, et al. (2005)	3+3 dose-finding	NA	N	91	I	Escalation procedure (%)	MTD
52	Starling N, et al. (2009)	3+3 dose-finding	NA	N	20	I	Escalation procedure (%)	MTD
53	Steele NL, et al. (2011)	3+3 dose-finding	NA	N	46	I	Escalation procedure (%)	OTDs
54	Glynn-Jones RD, et al. (2006)	6+6 dose-finding	NA	N	18	I	Escalation procedure (predefined numerical sequence)	MTD
55	Dumez H, et al. (2006)	3+3 dose-finding	NA	N	31	I	Escalation procedure (predefined numerical sequence)	MTD; PK & DLT
56	Eatoock MM, et al. (2000)	6+6 dose-finding	NA	N	24	I	Escalation procedure (predefined numerical sequence)	DLT ; OTD
57	Hanuske A-R, et al. (2009)	3+3 dose-finding	NA	N	95	I	Escalation procedure (predefined numerical sequence)	MTD; safety; PK; OTD
58	Huisman C, et al. (2001)	3+3 dose-finding	NA	N	19	I	Escalation procedure (predefined numerical sequence)	OTD & schedule
59	Kobayashi T, et al. (2006)	3+3 dose-finding	NA	N	16	I	Escalation procedure (predefined numerical sequence)	OTD;DLT & MTD
60	Lortholary A, et al. (2000)	3+3 dose-finding	NA	N	32	I	Escalation procedure (predefined numerical sequence)	MTD; DLT; OTD

	Reference	Trial design characteristics	R	B	Sample Size	Clinical Phase	Dose setting procedure			Trial Endpoints
61	Mitchell MF, et al. (1998)	6+6 dose-finding	NA	N	30	I	Escalation sequence)	procedure	(predefined numerical	OTD & MinED
62	Girard NF, et al. (2010)	3+3 dose-finding	NA	N	35	I	Escalation sequence)	procedure	(predefined numerical	MTD; feasibility & efficacy study
63	Prince HM, et al. (1999)	4+4 dose-finding	NA	N	33	I	Escalation sequence)	procedure	(predefined numerical	OTDs
64	Ryan CW, et al. (2004)	3+3 dose-finding	NA	N	35	I	Escalation sequence)	procedure	(predefined numerical	toxicity and PK
65	Botdy JJ, et al. (1999)	3+3 dose-finding	NA	N	30	I	Escalation sequence)	procedure	(predefined numerical	dose escalation procedure; MinED & active dose
66	Yamamoto N, et al. (2008)	3+3 dose-finding	NA	N	15	I	Escalation sequence)	procedure	(predefined numerical	MTD; DLT
67	Souglakos J, et al. (2003)	3+3 dose-finding	NA	N	31	I	Escalation sequence)	procedure	(predefined numerical	OTDs
68	Delord JP, et al. (2000)	3+3 dose-finding	NA	N	36	I	Escalation sequence)	procedure	(predefined numerical	DLT; OTD
69	Stokes Z, et al. (2005)	6+6 dose-finding	NA	N	13	I	Escalation sequence)	procedure	(predefined numerical	MTD
70	Ford J, et al. (1998)	4+4 dose-finding	NA	N	14	I	Escalation sequence)	procedure	(predefined numerical	safety; tolerability; MTD; side-effect study
71	Chi KN, et al. (2005)	3+3 dose-finding	NA	N	25	I	Escalation sequence)	procedure	(predefined numerical	biologically effective dose & toxicity response
72	Tanaka C, et al. (2008)	4+4 dose-finding	NA	N	16	I	Escalation sequence)	procedure	(predefined numerical	OTD & PK
73	Tanaka Y, et al. (2010)	3+3 dose-finding	NA	N	18	I	Escalation sequence)	procedure	(predefined numerical	OTD & MTD
74	Caffo O, et al. (2003)	3+3 dose-finding	NA	N	16	I	Escalation sequence)	procedure	(predefined numerical	MTD; response rate; DLT
75	Blaney SM, et al. (2003)	3+3 dose-finding	NA	N	23	I	Escalation sequence)	procedure	(predefined numerical	OTD; DLT; toxicity profile
76	Oza AM, et al. (1994)	3+3 dose-finding	NA	N	19	I	Escalation sequence)	procedure	(predefined numerical	MTD; OTDs
77	Rebattu P, et al. (2001)	3+3 dose-finding	NA	N	16	I/II	Escalation sequence)	procedure	(predefined numerical	MTD; OTD
78	Yang T-S, et al. (2003)	3+3 dose-finding	NA	N	26	I/II	Escalation sequence)	procedure	(predefined numerical	MTD; DLT
80	Gottlieb AB et al. (2004)	5+5 dose-finding	NA	N	35	I/II	Escalation sequence)	procedure	(predefined numerical	safety; PK
81	Gridelli CL, et al. (2000)	3+3 dose-finding (I)	NA	N	15	I/II	Escalation sequence)	procedure	(predefined numerical	preliminary efficacy

	Reference	Trial design characteristics	R	B	Sample Size	Clinical Phase	Dose setting procedure				Trial Endpoints
82	Kuppens IELM, et al. (2006)	3+3 dose-finding	NA	N	42	I/II	Escalation sequence)	procedure	(predefined	numerical	MTD; DLT
83	Maisano R, et al. (2005)	3+3 dose-finding	NA	N	21	I/II	Escalation sequence)	procedure	(predefined	numerical	MTD
84	Boccardo F, et al. (1996)	3+3 dose-finding	NA	N	12	II	Escalation sequence)	procedure	(predefined	numerical	OTD; toxicity
85	Zarate R et al. (2010)	3+3 dose-finding	NA	N	27	II	Escalation sequence)	procedure	(predefined	numerical	MTD; DLT; OTD
86	Bernstein , et al. (2010)	accelerated titration, dose-ranging	NA	N	17	I	Escalation sequence)	procedure	(predefined	numerical	OD for inhibiting DNA which is be correlated with OTD
87	Galsky MD, et al. (2008)	accelerated titration dose-finding	NA	N	23	I	Escalation procedure				safety profile; PK, immunogenicity;
88	Giaccone GH, et al. (1995)	accelerated titration, controlled dose-finding	NA	N	62	I/II	Escalation procedure				toxicity and PK
89	Hwang JJ, et al. (2010)	accelerated titration dose-ranging; plus 3+3 design	NA	N	27	I	Escalation procedure				DLT; OTD
90	Kearon C, et al. (2000)	accelerated titration, controlled, dose-finding	NA	N	14	I/II	Escalation procedure				efficacy; safety and dose-response
91	Wolchok JD, et al. (2003)	accelerated titration, controlled, dose-finding	NA	N	15	I	Escalation procedure				optimal biological dose; MTD
Model-based design											
92	Kuzuya K, et al. (2001)	dose-finding	NA	N	12	I	mCRM				safety; OTD
93	Levy V, et al. (2006)	dose-finding	NA	N	19	I	CRM				MTD; DLT; PK
94	Monnerat C, et al. (2004)	dose-finding	NA	N	24	I	CRM				MTD; DLT & OTD
95	Saji S, et al. (2007)	dose-finding	NA	N	17	I	CRM				MTD; OTD & PK
96	Elkind MS, et al. (2008)	dose-finding	NA	N	33	I	CRM				MTD
97	Gelmon KA, et al. (2000)	dose-finding	NA	N	29	I	CRM				dose-limit toxicity; MTD; OTD; PK
98	Desfrere L, et al. (2005)	dose-finding	NA	N	20	II/III	CRM				MinED
99	Jimeno A, et al. (2008)	dose-finding	NA	N	21	I/II	mCRM				MTD; PK
100	Morita S, et al. (2007)	dose-finding	NA	N	13	I	CRM				MTD; OTD
Parallel-group design											
101	Gorse GJ, et al. (1996)	dose-ranging	Y	DB	12	I	fixed dose levels				safety and immunogenicity study

	Reference	Trial design characteristics	R	B	Sample Size	Clinical Phase	Dose setting procedure	Trial Endpoints
102	Illei GG, et al. (2010)	dose-ranging	N	N	16	I	fixed dose levels	safety; preliminary data on efficacy
103	Ishigooka J, et al. (2000)	dose-ranging	N	N	156	I	fixed dose levels	efficacy & safety study and OTD
104	Ito K, et al. (1999)	dose-ranging	N	N	9	I	fixed dose levels	OTD
105	Kumar NB, et al. (2010)	dose-ranging	N	N	44	I	fixed dose levels	toxicity; OTD
106	Levin RD, et al. (2010)	dose-ranging	N	N	31	I	fixed dose levels	toxicity; OTD
107	Li J, et al. (2008)	dose-ranging	N	N	10	I	fixed dose levels	toxicity; OTD
108	Overman MJ, et al. (2008)	dose-ranging	N	N	63	I	fixed dose levels	MTD; DLT; OTD
109	Szeimies R, et al. (2008)	dose-ranging	Y	N	132	I	fixed dose levels	toxicity & efficacy study
110	Wirth L J, et al. (2010)	dose-ranging	N	N	17	I	fixed dose levels	MTD
111	Yan Z, et al. (2011)	dose-ranging	N	N	23	I	fixed dose levels	toxicity; PK
112	Young CW., et al. (1988)	dose-ranging	N	N	33	I	fixed dose levels	toxicity and OTD
113	Baumgart DC, et al. (2010)	dose-ranging	Y	N	78	I/II	fixed dose levels	OTD; safety & tolerability
114	Klemm E, et al. (2007)	dose-ranging	Y	DB	210	I/II	fixed dose levels	toxicity & efficacy first dose-response data
115	Ehrlich HJ, et al. (2003)	dose-ranging	Y	N	405	II	fixed dose levels	OTD; DLT
116	Groudine SB, et al. (2007)	dose-ranging	Y	SB	50	II	fixed dose levels	efficacy and safety study
117	Hirsh V, et al. (2001)	dose-ranging	Y	N	34	II	fixed dose levels	dose-effect relationship
118	Iwata H, et al. (2009)	dose-ranging	Y	N	98	II	fixed dose levels	OTD
119	Jacobson MA, et al. (1994)	dose-ranging	Y	N	278	II	fixed dose levels	efficacy & toxicity study
120	Quoix E, et al. (2004)	dose-ranging	Y	N	182	II	fixed dose levels	OTD
121	Wittekindt C, et al. (2006)	dose-ranging	N	N	23	II	fixed dose levels	DLT
122	Cotter,G, et al. (2008)	controlled, dose-ranging	Y	N	301	I	fixed dose levels	DLT; OTD
123	Dzavik V, et al. (2007)	controlled, dose-ranging	Y	N	79	I	fixed dose levels	efficacy; safety study
124	Hamilton JM, et al. (2009).	controlled, dose-ranging	Y	DB	16	I	fixed dose levels	safety; tolerability; pharmacokinetics; pharmacodynamics
125	Hemmerling AW, et al. (2009)	controlled, dose-ranging	Y	DB	12	I	fixed dose levels	safety, tolerability, and OTDs
126	Hunt T L, et al. (1995)	controlled, dose-ranging	Y	DB	80	I	fixed dose levels	first safety and tolerability data
127	McCormack S, et al. (2005)	controlled, dose-ranging	Y	DB	50	I	fixed dose levels	toxicity of OTDs
128	Stephenson I, et al. (2006)	controlled, dose-ranging	Y	SB	100	I	fixed dose levels	efficacy & safety study
Parallel-group design								

	Reference	Trial design characteristics	R	B	Sample Size	Clinical Phase	Dose setting procedure	Trial Endpoints
129	O'Loughlin J, et al. (2010)	controlled, dose-ranging	Y	N	36	I	fixed dose levels	toxicity & safety study; PK
130	Yamaguchi O, et al. (2011)	controlled, dose-ranging	Y	DB	951	II	fixed dose levels	efficacy, safety, and tolerability study
131	Pang PS, et al. (2011)	controlled, dose-ranging	Y	DB	46	II	fixed dose levels	efficacy & safety study
132	Genovese MC, et al. (2008)	controlled, dose-ranging	Y	SB	45	I/II	fixed dose levels	DLT; pharmacodynamics over time
133	Gupta AK, et al. (2005)	controlled, dose-ranging	Y	DB	151	I/II	fixed dose levels	effectiveness & safety study; OTD
134	Abrams P, et al. (1997)	controlled, dose-ranging	Y	SB	126	II	fixed dose levels	OTD
135	Alten R, et al. (2011)	controlled, dose-ranging	Y	DB	277	II	fixed dose levels	Optimal dose regimen; PK; PD
136	Amsterdam JD, et al. (2002)	controlled, dose-ranging	Y	DB	35	II	fixed dose levels	OTD
137	Barker JN, et al. (1999)	controlled, dose-ranging	Y	DB	132	II	fixed dose levels	OTD; efficacy & tolerability
138	Buller H, et al. (2008)	controlled, dose-ranging	Y	DB	392	II	fixed dose levels	OTD; DLT
139	Cunningham ET, et al. (2005)	controlled, dose-ranging	Y	DB	162	II	fixed dose levels	efficacy; safety study
140	Furst DE, et al. (2002)	controlled, dose-ranging	Y	N	268	II	fixed dose levels	efficacy & safety study; OTD
141	Decensi A, et al. (2007)	controlled, dose-ranging	Y	SB	210	II	fixed dose levels	optimal biologic dose and schedule
142	Jilma-Stohlawetz P, et al. (2011)	controlled, dose-ranging	Y	N	58	II	fixed dose levels	efficacy; safety; optimal regimen
143	van Deventer SJH, et al. (2006)	controlled, dose-ranging	Y	DB	112	II	fixed dose levels	minimally effective dose
144	Vohra S, et al. (2008)	controlled, dose-ranging	Y	DB	65	II	fixed dose levels	efficacy & safety study
145	Von Krempelhuber A, et al. (2010)	controlled, dose-ranging	Y	DB	164	II	fixed dose levels	efficacy & safety study
146	Wallace DJ, et al. (2009)	controlled, dose-ranging	Y	DB	30	II	fixed dose levels	safety & tolerability study
147	Turpie AGG, et al. (2005).	controlled, dose-ranging	Y	DB	621	II	fixed dose levels	efficacy & safety study
148	Puhringer FK, et al. (2008)	controlled, dose-ranging	Y	DB	176	II	fixed dose levels	efficacy & safety study
149	Ravn P, et al. (1996)	controlled, dose-ranging	Y	DB	180	II	fixed dose levels	efficacy & safety study

	Reference	Trial design characteristics	R	B	Sample Size	Clinical Phase	Dose setting procedure	Trial Endpoints
150	Runge VM et al. (2000)	controlled, dose-ranging	Y	DB	30	II	fixed dose levels	efficacy & safety study
151	Saini S, et al. (2011)	controlled, dose-ranging	Y	DB	90	II	fixed dose levels	efficacy & safety study
152	Teal P, et al. (2005)	controlled, dose-ranging	Y	DB	240	II	fixed dose levels	safety & tolerability study
153	De Souza JM, et al. (1987)	controlled, dose-ranging	Y	DB	97	II/III	fixed dose levels	efficacy & safety study
154	Matsumoto AK, et al. (2005)	controlled, dose-ranging	Y	DB	491	III	fixed dose levels	efficacy & toxicity study; OTDs
156	Kreisel W, et al. (2011)	multicentre, dose-ranging	N	N	20	I	fixed dose levels	toxicity; OTD
157	Kim SW, et al. (2010)	multicentre, dose-ranging	Y	DB	145	I	fixed dose levels	safety, immunological response; DLT; OTD
158	Okubo K, et al. (2008)	multicentre, controlled, dose-ranging	Y	DB	240	I	fixed dose levels	OTD
Parallel-group design								
159	Cannon CP, et al. (1998)	multicentre, dose-ranging	Y	DB	106	I/II	fixed dose levels	pharmacokinetics; pharmacodynamics; safety; tolerability, OTDs
160	Sacks SL, et al. (1998)	multicentre, controlled, dose-ranging	Y	DB	96	I/II	fixed dose levels	efficacy & safety study
161	Cursiefen CF, et al. (2009)	multicentre, controlled, dose-ranging	Y	DB	40	II	fixed dose levels	tolerability and efficacy; OTD
162	Lewis RJ, et al. (2011)	multicentre, controlled, dose-ranging	Y	N	149	II	fixed dose levels	toxicity; OTD
163	de Francisco ALM, et al. (2006)	multicentre, controlled, dose-ranging	Y	DB	61	II	fixed dose levels	efficacy study; starting dose
164	Lim SG, et al. (2008)	multicentre, dose-ranging	Y	N	31	II	fixed dose levels	OTD
165	Malmstrom, P. U. (2002)	multicentre, controlled, dose-ranging	Y	N	115	II	fixed dose levels	toxicity of OTDs
166	Nota K, et al. (2006)	multicentre, dose-ranging	Y	N	109	II	fixed dose levels	efficacy; OTD
167	Osterborg A, et al. (2007)	multicentre, dose-ranging	Y	Y	93	II	fixed dose levels	efficacy & safety study

	Reference	Trial design characteristics	R	B	Sample Size	Clinical Phase	Dose setting procedure	Trial Endpoints
168	Gallagher JC, et al. (2001)	multicentre, controlled, dose-ranging	Y	N	48	II	fixed dose levels	pharmacokinetics; safety study
169	Paick J-S, et al. (2008)	multicentre, controlled, dose-ranging	Y	DB	119	II	fixed dose levels	efficacy & safety study
170	Povsic TJ, et al. (2011)	multicentre, controlled, dose-ranging	Y	SB	800	II	fixed dose levels	efficacy & safety study
171	Cazzola M, et al. (1995)	multicentre, dose-ranging	Y	N	146	II	fixed dose levels	optimal initial dose
172	Lalezari JP, et al. (2003)	multicentre, controlled, dose-ranging	Y	N	71	II	fixed dose levels	pharmacokinetics; OTD
173	Landewe RBM, et al. (2010)	multicentre, controlled, dose-ranging	Y	DB	39	II	fixed dose levels	efficacy; OTD
174	Saini S, et al. (2000)	multicentre, controlled, dose-ranging	Y	DB	99	II	fixed dose levels	efficacy & safety study
175	Sakai F, et al. (2002)	multicentre, controlled, dose-ranging	Y	N	30	II	fixed dose levels	efficacy & safety study
176	Henry RR, et al. (2009)	multicentre, controlled, dose-ranging	Y	DB	332	II	fixed dose levels	effects, and safety study
177	Thijs VNSs, et al. (2009)	multicentre, controlled, dose-ranging	Y	DB	40	II	fixed dose levels	safety & tolerability study
178	Ste-Marie L-G, et al. (2009)	multicentre, controlled, dose-ranging	Y	N	370	II	fixed dose levels	efficacy & safety study
179	Valecha N, et al. (2010)	multicentre, controlled, dose-ranging	Y	DB	230	II	fixed dose levels	efficacy & safety study
180	Van Cutsem E, et al. (2005)	multicentre, controlled, dose-ranging	Y	DB	164	II	fixed dose levels	toxicity & efficacy study
181	Katz, B. (2005).	multicentre, controlled, dose-ranging	Y	DB	162	II	fixed dose levels	safety & efficacy study

	Reference	Trial design characteristics	R	B	Sample Size	Clinical Phase	Dose setting procedure	Trial Endpoints
182	Khuenl-Brady KS, et al. (2008)	multicentre, dose-ranging	Y	SB	176	II	fixed dose levels	safety & efficacy study
183	Hirsh VJ, et al. (2007)	multicentre, dose-ranging	Y	N	218	II	fixed dose levels	dose-effect relationship
184	Jha TK, et al. (2005)	multicentre, dose-ranging	N	N	120	II	fixed dose levels	dose-response and safety study
185	Wynn D, et al. (2008)	multicentre, dose-ranging	Y	DB	40	II	fixed dose levels	toxicity and OTD
186	Yamamoto A, et al. (2002)	multicentre, dose-ranging	Y	DB	68	II	fixed dose levels	efficacy, safety, and tolerability study
187	Sumpter K, et al. (2005)	multicentre, controlled, dose-ranging	Y	DB	204	III	fixed dose levels	DLT; OTD
188	Haustein J, et al. (1992)	multicentre, dose-ranging	N	N	30	III	fixed dose levels	efficacy and safety study; OTD;
189	Kivitz A, et al. (2006)	multicentre, controlled, dose-ranging	Y	DB	360	III	fixed dose levels	efficacy, dose-response, and tolerability study
190	Johnson CD, et al. (2001)	group-sequential, dose-ranging	N	N	278	III	fixed dose levels	efficacy, toxicity study & survival trials
Cross-over design								
191	Dmoszynska A, et al. (2007)	multicentre, cross-over, dose-ranging	Y	N	64	I/II	fixed dose levels	dose-response; pharmacokinetics study
192	Johnson BA, et al. (2003)	controlled, four-way, cross-over dose-ranging	Y	DB	23	I	fixed dose levels	pharmacological; safety & tolerability study

Notes: R= Random allocation procedure
B= Blinding procedure
SB= Single Blind procedure
DB= Double Blind procedure
MinED= minimal effective dose

DLT= dose limiting toxicity
mFS= modified Fibonacci sequence
NA= Not applicable
PD= Pharmacodynamics
PK= Pharmacokinetic

Table 3-3: Summary of characteristics of included studies of dose optimization in pharmacological clinical literature

Trial designs	Trial design type		Nr of studies
Dose-finding designs			
	Rule-based designs	3+3 dose-finding	73
		4+4 dose-finding	3
		5+5 dose-finding	2
		6+6 dose-finding	5
		1+1 dose-finding	1
		8+8 dose-finding	1
		Accelerated titration	6
	Model-based designs	CRM designs	9
TOTAL			100
Dose-ranging designs			
	Parallel designs		90
	Cross-over designs		2
TOTAL			92

To make in context review results, a brief narrative description of the main features of the trial designs used in dose optimization is reported.

3.4.3 Dose optimization trial designs

As Table 3-4 summarises, in pharmaceutical research there are two main dose optimization approach: dose-ranging or dose-finding.

Table 3-4 Dose optimization approaches and trial designs applied in pharmaceutical research

Dose optimization approaches	Trial designs
Dose-ranging	Parallel group Cross-over
Dose-finding	Rule-based Model-based

As mentioned in chapter 2, in *dose-ranging approaches* each group of patients receives different intervention dose in parallel (parallel group design) or in sequence (cross-over design) [209]. The number of groups and the doses are

defined a-priori to inform on the efficacy and safety of the studied compound at specific dose levels and/or against placebo [205,206]. A random allocation procedure is often used, with or without a control group²⁸. Randomization, control group and blinding procedures²⁹ are applied to increase reliability and generalisability of the results. Estimates of the dose-response and the dose-toxicity relationships can be gained from these studies but they are limited to the pre-selected tested doses. Inferences on other doses are not advisable.

Dose-finding approaches have much to recommend them, given their flexibility [208]. They are commonly defined *adaptive designs*, with adaptive (flexible) conditions seen on randomization procedures [227], sample size [228], test statistics, sequential dose setting [229], outcomes, and target endpoints. Given the focus of this research, the adaptive condition of interest is around the dose setting, also called dose escalation procedure. However, this design flexibility on dose optimization comes with a cost. Generally, no a-priori information is available on the number of groups needed for the study and thus, a random allocation procedure or a balancing group procedure (minimization) are not feasible.

Three assumptions are typically shared by these adaptive designs (or dose-finding designs). First, *the individual's responses (outcomes) to the treatment dose are going to be fairly similar*. In pharmaceutical development this is often achieved by categorizing sub-groups of patients depending on precise biological targets (e.g.: blood cells count, hormone levels, etc.), which identify the disease stage and severity.

²⁸ A control group is a group receiving a placebo intervention. A placebo is any drugs or treatment that actually contains no active ingredients, no actual medication or no therapeutic effect. In research a placebo is used as a control in testing the efficacy of another intervention (<http://www.yourdictionary.com>).

²⁹ Blinding procedures in clinical trials are often refer to single blind when the information about the intervention are kept from the participant until after the test, or double blind if both, assessors and participants are not aware on the allocated intervention.

Second, *the drug effect can be measured in a predictable and often short period of time*. Information on the drug effect over time are often derived from pre-clinical studies. The expected changes typically occurs on a biological level (i.e. changes in the size of the tumor, changes in the blood pressure) and are thought to be intermediate endpoints which are promising for more positive outcomes (i.e.: increase of the surviving rate; reduction of incidence of stroke and heart attack) [230].

Finally, and in particular in cancer research, a key assumption adopted is that *the treatment effect will increase by dose*. As a results, often, in pharmaceutical dose-finding trials the main concern and guidance on the dose escalation procedure is the toxicity response.

Although these assumptions are defensible in pharmaceutical research, the following chapters discussed and tested whether these assumptions held in dose optimization trial design suitable for use in stroke rehabilitation research.

Depending on their operating characteristics, dose-finding designs can be rule-based or model-based.

Table 3-5 illustrates these two groups of dose-finding designs applied in pharmaceutical clinical research highlighting their characteristic dose escalation procedure.

Table 3-5: Main adaptive trial designs and the dose escalation procedures

Trial designs		Dose escalation procedures
Rule-based	3+3 design (and its variants)	<i>Mathematical approaches:</i>
		<ul style="list-style-type: none"> • pre-defines numerical sequence • % dose increments • mathematical sequence (i.e.: modified Fibonacci sequence)
Model-based	Continual reassessment methods (and its variants)	<i>Statistical modelling approaches:</i>
		<ul style="list-style-type: none"> • parametric/non-parametric • Bayesian designs

Rule-based dose-finding designs

The rule-based dose-finding designs typically assign dose levels to subsequent groups of patients (cohorts), according to pre-specified rules based on actual observations of target events from the clinical data. Predefined mathematical sequences are applied to establish dose increments between subsequent cohorts, often without prior assumptions on the dose-toxicity curve [139,209].

Typical example of rule-based designs is the *3+3 design*. This design is considered a conservative design for its limited risk of participants to incur in a DLT compared to other designs (i.e. best to five designs) [231]. The probability of severe toxicity in these designs is of approximately 33%. 3+3 designs are largely applied in pharmaceutical cancer research under the common assumption that efficacy increases with dose and the drug toxicity is often the main concern.

In this design patients are assigned to increasing dose levels in subsequent cohorts of three patients without intra-cohort variation in the dose. The first cohort receives the intervention at the starting dose. The toxicity of the starting dose is evaluated at the end of the intervention for the three patients considered. At this first as well as any following stage (n) three scenarios can occur.

1. No toxicities were observed in the entire cohort. In that case the dose is escalated for the following cohort, which is then assessed at the end of the new intervention period.
2. Two or more patients in a cohort experienced an unacceptable level of toxicity (the dose-limiting toxicity: DLT). In this case the trial is stopped and the trial dose endpoints derived (i.e. the maximal tolerable dose: MTD, and the recommended dose for phase II trial: RPTD).
3. One participant experienced a DLT. An additional three patients receive the same dose with results that could then fall in condition 1 or, the trial stops and the trial dose endpoints are derived.

There are five main variations of a 3+3 design³⁰.

³⁰ For more details on rule-based designs see Storer (2001) and Le Tourneau et al. (2009).

The *2+4 design* has stopping rules similar to a 3+3 design but an additional cohort of four patients is added if a DLT event occurs in a cohort composed by two patients.

The *3+3+3 design* has an additional cohort of three patients used when at least two of the six patients in the first two cohorts experienced a DLT. The trial terminates (and the MTD derived) if at least three of nine patients experience a DLT.

The *best-to-five design* (3+1+1) is commonly considered an aggressive design implemented when preclinical data indicate a wide therapeutic window or when the tested drug is for life-treating illnesses with no other treatments available. The probability of severe toxicity in this design is higher than the 33% threshold often accepted in phase I trial. In this design one additional patients is added if one or two DLTs are observed among three patients. Then, another patients is added if two DLTs are observed among the four treated patients. Dose escalation is allowed if none of the three, one of four, or two of five patients experienced a DLT. The trial will stop and the MTD is derived if three or more DLTs are observed. The *Storer's two-stage designs* [232] has a single patient that enters in the first stage with a starting dose level. If the first patient does not experience a DLT, the dose is escalated until a patient experiences a DLT. If that happen a second stage begins at a lower dose for a subsequent cohort with a fixed number of patients, generally from 3 to 5. The treated cohort is assessed and the next cohort is treated at higher, the same, or lower dose depending on whether none, one or more than one patient experienced a DLT.

The *Accelerated titration designs* combine features from the traditional 3+3 design and the model-based design although the patient assignment to dose is based on pre-specified rules. The size of the cohorts and the rules on toxicity to define the MTD vary among the Accelerated titration designs family (referred to as Accelerated titration design 1, design 2, design 3, and design 4). The first type of designs (design 1) shares the rules of a standard 3+3 design but with a 40% increments between cohorts. Design 2 sees single patient cohorts during the accelerated phase. When a first-course DLT or a second first-course moderate toxicity are observed, cohorts expand and evert to design 1. Design 3 has single

patient cohorts with double dose escalation steps (80%). It reverts to design 1 with same trigger as design 2. Design 4 is equal to design 3 but triggers to revert to design 1 if any course DLT or second instance of any course moderate toxicity is experienced.

Model-based dose-finding designs

Model-based dose-finding designs apply statistical models to data on previous cohort to identify dose levels in subsequent cohorts. The shape of the dose-toxicity curve is estimated (parametrically³¹ or non-parametrically) using collected data from a selected dose. Bayesian models are the most common statistical models applied in model-based designs³². In simplified terms, statistical models start with a prior distribution (estimation) of the toxicity curve which is, generally, derived from available preclinical data. This estimation provides the starting dose. Then, the occurrence, or not, of a DLT in the cohort treated, provides further information on the toxicity curve. New available data are used to estimate a posterior distribution that provides the new dose level for the following cohort. This process continues until pre-specified conditions on toxicity are met. A model-based design can provide good estimation of dose endpoints and data on the dose-response relationship but it might expose patients to high toxic dose, in particular if safety rules are not in place [208,233]. Besides, advanced statistical expertise is required to implement such a design, alongside with the availability of expensive software to fit the model in real time.

The *Continual reassessment method (CRM)* was the first Bayesian model-based method applied in phase I trial design, introduced in 1990 [234]. In this design the estimate of the probability to incur in a DLT is updated for each new patient

³¹ Main characteristics of parametric methods is the assumption that the data has come from a type of probability distribution and makes inferences about the parameters of the distribution.

³²These trial designs can provide good estimation of dose endpoints and data on the dose-response relationship. However, reviews reported a possible risk to espouse patients to high toxic dose if specific safety rules are not in place [208; 232].

who enters the study until a pre-specified condition on toxicity is met. Then the MTD and recommended dose for phase II are derived (RPTD) [235]. Variations of this design are seen since then to increase design efficacy and patients' safety. Few examples are reported.

The *Escalation with overdose control (EWOC)* is a modified CRM with additional safety measures to avoid excessive dosing and thus, excessive toxicity. Using statistical simulations, the probability to deliver a dose which is higher than the MTD is tested before a new cohort starts and the trial stops if this probability exceeds a predefined threshold.

The *Time to event endpoints (TTE) CRM* design uses surrogate endpoints to reduce trial duration in phase I trials. Intermediate endpoints which are relevant to the final outcome (i.e. overall survival rate) are used to minimise trial duration [230].

Review results: dose optimization trial designs and studies features

Among included studies, ninety-two (47.9%) applied a dose-ranging approach. Characteristics of these studies were as follow:

- ninety studies (97.8% of ninety-two studies) applied a parallel group trial design; two studies applied a cross-over design;
- seventy-seven studies (83.7% of ninety-two studies) applied a randomised allocation procedure to balance baseline characteristics among groups or cohorts;
- fifty-five studies (59.8% of ninety-two studies) implemented a control group;
- fifty-three studies (57.6% of ninety-two studies) implemented a blinding procedure towards intervention groups. The majority (46 studies) applied a double-blind procedure with which both, -the patients and research staff- were blind to the allocated intervention;
- thirty-five studies (38% of ninety-two studies) were conducted in more than one site (multicentre studies);

- 25% of ninety-two studies were implemented in phase I; 59% in phase II; 8% in a seamless phase I/II; and 8% in phase III (or seamless phase II/III);
- safety and tolerability of the studies dose levels were investigated in 67% of the studies. The OTD or optimal schedule was explored in 39% of the studies;
- a total of 14,994 patients were included in these studies with a mean of 163 patients per study (minimum of nine participants; maximum of 951 participants).

The remaining one hundred included studies (52.1%) applied an adaptive dose-finding approach to dose optimization. In detail:

- ninety-one studies (91% of the hundred studies) applied a ruled-based design. Among them:
 - seventy-three (80.2% of the ninety-one studies) applied a 3+3 design; six studies applied a 6+6 design; three studies applied a 4+4 design; two studies applied a 5+5 design; one studies applied a 1+1 design; one study applied a 8+8 design; and six studies applied an Accelerated titration design;
 - to set the dose levels in subsequent cohorts -outcome adaptive dose escalation procedure- the majority of these studies (seventy-six studies, 83.5% of the ninety-one studies) used a predefined numerical sequence; ten studies applied a % increments; and four studies applied a predefined mathematical sequence called the modified Fibonacci sequence;
- nine studies applied a model-based design using the CRM or a modification of it. A statistical approach was used in these studies to set the dose levels in subsequent cohorts;
- 78% of these one hundred studies were implemented in phase I of the clinical pathway; 18% in a seamless phase I/II; two studies in phase II; and two studies in a seamless phase II/III;

- the MTDs and DLTs were investigated in more than 68% of these studies; the OTDs were investigated in 52% of studies;
- a total of 2,669 participants were included in dose-finding studies, with a mean of 26.6 participants per study (minimum of seven participants; maximum of 95 participants).

3.5 Interpretation

This review highlighted the standard procedures applied to dose optimization in pharmaceutical clinical research to inform a dose optimization approach suitable in stroke rehabilitation research. Included studies revealed that, both dose-finding and dose-ranging approaches were used to dose optimization in pharmaceutical research, with a slightly preference for dose-finding designs (52.1%). However, dose-finding designs were mainly applied in the early phase of the research pathway. 78% of the dose-finding studies included were applied on phase I. This was due to the scope and ability of dose-finding designs to provide the first indication of the dose-response and dose-toxicity relationships and to gather the first evidence on appropriate dose to take forward in confirmatory studies. These designs were able to maximise efficacy in targeting dose endpoints. They avoided the selection of sub-therapeutic doses thanks to the implementation of interim analyses and were more flexible than dose-ranging design in setting dose levels while minimizing the required number of participants.

The majority of dose-finding studies applied a rule-based design to target dose endpoints whereas, model-based designs were applied in only 9% of the reviewed studies. Model-based designs are advocated as being more efficient in targeting dose but their novelty and complexity could explain their limited implementation in clinical trials.

Rule-based designs applied pre-defined rules on toxicity events which guide the escalation procedure until the target dose endpoint is reached. A pre-defined

numerical sequence was used in the majority of these studies to guide dose escalation procedures. Random allocation procedure or other procedure aiming at balancing patients' baseline characteristics were not applied in these adaptive designs.

Applied in 80.2% of the retrieved rule-based studies, 3+3 trial designs were the most commonly used designs. This is in line with pharmaceutical literature that argued that, despite the recent advances in the designs of innovative dose-finding trial designs and the theoretical consensus on the superiority of model-based designs, the 3+3 dose escalation design remains the most popular method employed in phase I of the research pathway [236,237].

On the other hand, the majority of studies that have applied a dose-ranging approach (about 60%) were implemented in phase II of the research pathway. Dose-ranging studies efficiently seek the confirmation of the optimal therapeutic dose among a range of appropriate doses previously identified in phase I trials [206,208,225]. The implementation of randomization procedures and control groups were common in these designs to increase validity of the results. In line with the purpose of testing dose efficacy, overall, the studies implementing dose-ranging designs have used a considerably bigger sample –on average, 163 participants- than the one used in dose-finding studies -on average, 27 participants-.

3.6 Conclusion

The results of this review could be put in the context of the current debate on dose optimization in pharmaceutical clinical research. In this field of research, dose-ranging and dose-finding approaches were known to be used in different phases of the research pathway to answer different questions on dose [139,211,213,231,238]. While dose-finding designs were known as the most appropriate designs to target accurately dose endpoints [139], dose-ranging designs were often used to subsequently test the efficacy of promising dose levels against placebo or other available treatments [206,239]. In pharmaceutical

research the availability of preclinical data, the relevance of drug adverse events, the severity of the illness, and the availability of other effective treatments were also important determinants of the appropriateness of the selected trial design [209].

Although the traditional 3+3 designs were the most common designs in pharmaceutical phase I dose-finding studies, some aspects of these designs have been challenged. By using sophisticated model-based dose-finding approaches it has been shown that a 3+3 design could possibly deliver sub-therapeutic doses involving more participants. As a result, 3+3 designs can and be less precise (and efficient) in targeting dose endpoints, such as the maximal tolerable dose and the recommended phase II dose [210,236]. However, the challenge in implementing the statistical aspects of model-based designs was perhaps the major limit to a wider use in clinical research [205,215,236,240]. These challenges and issues in implementing model-based approaches could be more relevant when transferring dose-finding approaches in stroke rehabilitation research.

3.7 Review limits

The major limit of this review was the limited number of papers retrieved, considering the number of drugs commercialised. This was an issue beyond my control. It is in fact a common practice in pharmaceutical research to publish in scientific journals only a limited and selected number of research, leaving the majority of research inaccessible to other scholars [241]. This selective trial dissemination is often in favour of studies which show statistically significant results [242,243]. However, it was unlikely that this paucity of studies could have impacted on the generalisability of the results on the “gold” standards used in pharmaceutical dose optimization research.

Only one researcher (myself) was involved in the selection and extraction procedure creating possible bias. Furthermore, the limited knowledge of the researcher involved in the data extraction procedure on pharmacy and chemistry may have precluded the understanding of specific procedures. However, this

should not have impacted on the objectives of this review. The focus of this literature review was on the methodology applied to dose optimization per se, rather than on drugs efficacy and studies evaluation. Furthermore, the high level of standardization of the selection and data extraction procedures should have reduced the likelihood of possible bias.

3.8 Clinical and research implication

Results from this review were useful to inform the debate on dose optimization procedures suitable for motor interventions in general and stroke rehabilitation clinical research in particular. So far, no reviews of this kind has been published with the specific aim of providing key features from the pharmaceutical field to inform dose optimisation methods for stroke rehabilitation.

Summarising, the keys points emerged from pharmaceutical dose optimization research, and possibly relevant to stroke rehabilitation research were: there was a clear and standardised research pathway which saw the implementation of early dose-finding studies as precursor of clinical efficacy dose-ranging studies. These subsequent trials, often, tested efficacy and safety of the selected dose, in larger samples.

Furthermore, dose-finding designs were implemented under the following three key assumptions: 1) individual responses to the dose were relatively homogeneous; 2) the expected outcomes could be measured directly in a known and short time frame; and 3) the response to the treatment increased by dose. Assessing the relevance and validity of such hypotheses (or deviation from them) is of paramount importance, especially in the light of applying pharmaceutical dose optimization approaches to other domains. Finally, although promising in term of efficacy, the model-based designs were still rarely applied (9%) in clinical research. Rule-based designs were the standard procedure in phase I dose optimization trials and appeared the appropriate designs to stroke rehabilitation research.

The devising of a new dose optimization study for stroke rehabilitation research is discussed in the following chapter.

Chapter 4:

Development of an innovative dose-finding design for motor interventions after stroke

4.1 Introduction

Chapter 2 documented the limited availability of dose optimization trials in exercise-based training research (ExBT). Chapter 3 demonstrated that the designs commonly employed in pharmaceutical clinical research can provide useful recommendation to stroke-related research.

The aim of this chapter was to use the information gathered from the two preceding reviews to devise a novel phase I dose optimization trial design for motor intervention (*Overall aim 1; objective 1.c*). A methodological framework and a description of the key elements for a dose optimization trial design in stroke rehabilitation research were reported in this chapter. The protocol and main results of a feasibility phase I dose optimization trial design with stroke survivors were reported in the subsequent chapter 5.

4.2. The dose optimization approach

Chapter 3 documented the two dose optimization approaches used in pharmaceutical clinical research: *dose-ranging* and *dose-finding*. While Table 4-1 summarises the advantages and disadvantages of the two approaches, the following section focuses on how such approaches could potentially inform stroke rehabilitation research.

Table 4-1: Pros and Cons of dose-ranging and dose-finding approaches

Approach	Advantages	Disadvantages
Dose-ranging	Simple approach. Trial key features planned a priori. Use of balanced groups and of randomization procedure. Possible implementation of a control group.	Only pre-specified dose are tested. Results depends on: the accuracy of prior information on selecting and defining tested doses. Low level of efficacy and accuracy in targeting dose levels. Large sample-size are generally required.
Dose-finding	High level of efficacy and ability to deal with limited prior data on the dose-response. Flexibility in setting various aspects of the design (adaptive designs). Control for type I error ³³ . Potentials in informing accurately the dose-response relationship and in identifying target dose while preserving patients' safety. Reduced requirements in terms of sample-size.	Complex approach. In general, it is not possible to plan in advance all the key features of the trial. Random allocation procedure not possible. It assumes that individual responses to the dose are relatively homogeneous. It assumes that expected outcomes can be measured directly in a known and short time frame.

Dose-ranging approaches, with parallel or cross-over designs, were the current standard for dose optimization in stroke rehabilitation research [65,127,244,245]. It has been acknowledged, however, that these approaches were unable to provide strong evidence on appropriate doses for motor interventions [66,83,131] and to improve current understanding of the dose-response relationship for stroke rehabilitation [84]. Specifically, the rigidities imposed by a dose-ranging approach made it unsuitable in identifying dose thresholds for efficacy and safety such as, the minimal effective dose or the

³³ Type I error refers to the incorrect rejection of a true null hypothesis (a "false positive").

maximal dose above which detrimental effects are seen. In a dose-ranging approach only pre-planned dose levels were tested, imposing, by construction, restrictions in identifying the possible optimal dose and endpoints. In a dose-ranging study tested doses should be properly spaced to avoid uncertainty in the definition of the dose-response curve that arises when tested dose levels were too far apart. To avoid non-identification of dose endpoints, a large range of doses should be implemented in these trials at the important costs of requiring large sample sizes for testing all pre-specified doses³⁴. Besides such important inefficiencies, in particular when recruiting participants is costly, time-consuming and difficult, the likelihood to identify the “optimal”³⁵ dose using dose-ranging approach is marginal.

To overcome the inefficiencies of dose-ranging approach in identifying dose endpoints in stroke rehabilitation research, a novel and more complex dose optimization approach based on a *dose-finding (adaptive) design* was implemented. Furthermore, as it happened in pharmaceutical research, dose-finding studies were applied in the early phase (phase I) of the research when the uncertainty on the dose-response relationship is greater. This appeared even more the case in stroke rehabilitation where the dose-response relationships were unknown.

The novelty and complexity of this approach for stroke rehabilitation brought uncertainty on the success of this trial. However, the emerging need to identify appropriate doses to improve stroke rehabilitation outcome and the promising advantages brought by this approach put aside these uncertainties.

This study was planned as a *feasibility study*. Feasibility studies are aiming at testing new designs and approaches to help subsequent confirmatory studies [246,247,248]. They can enhance the likelihood of success of future dose-finding studies informing on possible treatments and challenges [249]. The implementation of

³⁴ It should be noticed that the average number of pre-defined dose in stroke rehabilitation trials was limited to two. See Chapter 4 for details.

³⁵ Optimal is in bracket to underline the still early stage of the research and thus of the result on doses.

feasibility studies on dose optimization in stroke rehabilitation is also endorsed by the research community [73,132,133,216].

4.3. The dose identification procedure

Depending on the dose identification procedure applied, dose-finding trial designs can be grouped in: *rule-based* and *model-based* designs. While fully described in chapter 5, Table 4-2 summarises the main advantages and disadvantages of these designs.

Table 4-2: Dose identification procedures: advantages and disadvantages

Design	Advantages	Disadvantages
Rule-based designs	Simple. Good level of efficacy when certain conditions are verified. Good accuracy on targeting dose endpoints.	Decision to escalate the dose is based solely on data from current dose. Need adequate rules to preserve participants' safety.
Model-based designs	Higher level of efficacy. Decision to escalate the dose is based on continuous estimation of the dose-response/toxicity curve. High accuracy on targeting dose endpoints.	Complexity. Need prior knowledge to infer on the dose-response curve (prior-distribution). Need of costly statistical software. Need of statistical expertise.

A *rule-based design* was chosen for this trial for four reasons. First, it avoided the complexity of implementing statistical modelling (e.g., Bayesian analysis) while preserving the ability to deal with uncertainty on the dose-response relationship. Simplicity was key aspect in setting a successful first attempt to implement a dose-finding study for complex motor interventions such as stroke rehabilitation. Second, the lack of background knowledge on the dose-response curve in stroke rehabilitation precluded any reliable assumption on the shape of the dose-response curve (prior-distribution) that was required for the correct implementation of Bayesian models. This, ultimately, reduced the efficacy of a model-based design in our context.

Third, pharmaceutical research suggested that dose endpoints can be identified with acceptable levels of precision and efficiency by using rule-based designs together with appropriate sequential interim analysis [208,250], rather than by embarking in the implementation of a more complex model-based design [251]. Finally, the possibility to adapt trial rules, the trial algorithm, and the dose escalation procedure embedded in a rule-based design seemed very appealing given our purpose to implement such designs in a new field.

Among the rule-based designs³⁶, a *3+3 design* was chosen for four reasons. First, the 3+3 design is the commonest and more studied design in pharmaceutical phase I dose-finding design [231,237]. The reliability of this design is therefore undeniable. Second, the use of cohorts composed by three participants appeared potentially appropriate to increase trial efficacy but preserving validity of results. Third, when 3+3 designs are used in conjunction with an adequate dose escalation procedure, the sample size is minimised [252] and the efficiency of the whole design increases. This was important in our context given the difficulties and the costs in recruiting participants. Recruitment procedures are often challenging in stroke rehabilitation research and efficient trial designs that are able to provide reliable results using small sample size are welcomed.

Finally, a 3+3 design is often suggested to be a conservative design that is appropriate when limited data are available on the toxicity response. This is because reduces the number of participants that risk to incur in a DLT compared for example to other rule-based designs, such as a best to five design [231].

The complexity of implementing a 3+3 dose-finding design in stroke rehabilitation and the differences with pharmaceutical research were taken into account when selecting all the operating characteristics of this trial which were detailed in the following sections.

³⁶ For more detail on the family of rule-based designs refers to Chapter 3 section 3.4.3. Dose optimization trial design.

4.4. The dose escalation/de-escalation procedure

A *dose escalation procedure* is a plan applied to dose-finding studies which guides the selection of dose levels on subsequent cohorts.

Pharmaceutical dose-finding studies mainly use escalation procedures because of the common assumption that the toxicity is a non-decreasing function of dose. This is particularly true in cancer research where the optimal therapeutic effect is achieved maximizing the dose [139,224]. This assumption might not hold in motor interventions and when dealing with the central nervous system. In our context, to account for a more flexible dose-response function a *dose de-escalation procedure* was embedded in this trial.

Dose escalation procedure

Table 4-3 summarises the main dose escalation procedures applied in rule-based dose-finding designs in pharmaceutical clinical research.

Table 4-3: Dose escalation procedures

Dose escalation procedure	Description
Fixed numerical sequence (i.e.: d_1 ; $2d_1$; $3d_1$; etc.)	Given a starting dose d_1 then, the following dose are increase by an amount equal to the starting dose (e.g. with $d_1=50$ then, $d_2=100$; $d_3=150$; etc.).
% increment	Given a starting dose d_1 then, the following dose are increase by an equal percentage of the first dose (e.g. with a 10% increment then, $d_1=100$; $d_2=110$; $d_3=120$; etc.).
Pre-defined mathematical sequence	Predefined mathematical sequences define the increments of subsequent dose levels. An example of a mathematical sequences commonly used is the modified Fibonacci sequence (see Table 4-4 and text below for more details).

In the context of a dose-finding trial for motor intervention, the *modified Fibonacci sequence (mFBS)* was used as the dose escalation procedure. With respect to a fixed numerical or a % increment sequence, the mFBS had the

advantage of using an incremental ratio which tends to a smaller constant number, as Table 4-4 shows. In other words, the mFBS provided a sequence of dose increments which were initially large, when the adverse reactions (toxicity) were likely to be minimal, and then dose increments became smaller as the dose became higher, and the likelihood for adverse reactions (toxicity) increased. Increments were also relatively large, providing meaningful differences between subsequent doses and reducing the implementation of sub-therapeutic doses [253].

Table 4-4: Classic modified Fibonacci dose escalation procedure in phase I trials

Dose (n)	mFBS	Dose increments
1		Starting dose D_1
2	1	$2D_1$
3	0.67	$1.67D_2$
4	0.5	$1.5D_3$
5	0.4	$1.4D_4$
6	0.33	$1.33D_5$
Etc.	0.33	$1.33D_{n-1}$

Notes: this table reports the dose spacing derived from the modified Fibonacci sequence (mFBS) at each dose level, column 2 shows the corresponding modified Fibonacci spacing (ratio) whereas column 3 reports the applied increase with respect to previous dose.

In this trial the mFB sequence was used as commonly applied in pharmaceutical a dose-finding clinical trial. In detail: if the results from the first cohort of participants, at the initial dose D_1 , were positive (suitable to escalate the dose depending on the trial rules) then, the first increment for the second cohort was set at 100% of the starting dose ($2D_1$). Thereafter, and as long as a new cohort was needed, the increments for subsequent cohorts were set respectively at 67% ($1.67D_2$), 50% ($1.5D_3$), 40% ($1.4D_4$), and 33% ($1.33D_{5,...n}$) of the preceding dose.

Dose de-escalation procedure

When a dose decrement was needed, a dose was decreased, for the subsequent cohort, by 50% of the previous increment. If this occurs immediately after the starting dose, the following dose was decreased by 50% of the starting dose.

4.5. The predefined rules

This dose-finding trial followed predefined rules commonly applied in 3+3 dose-finding pharmaceutical trials, but adjusted to fit motor interventions. Trial rules were based on actual observations of target events from each cohort at the end of their training period and were implemented to guide the dose escalation, the dose de-escalation procedures and the stop of the trial.

In pharmaceutical trial the main target event is dose efficacy/toxicity. In this trial, due to the required participants' effort needed to comply with the training dose (physical effort, mental effort and time-required in performing the task), the feasibility of the dose was also checked and used to guide the trial development. Alongside with efficacy and feasibility rules checking rules were introduced. These rules should limit the issue of implanting small cohort size avoiding that a dose was not deemed feasible or efficacious because of the individuals in that particular cohort, rather than the dose itself. They may reduce, in some respect, the issues of heterogeneity on patients' presentation and therapy response common in stroke population and neglected in these kind of designs. The trial rules were reported as follow.

Feasibility rules. The dose feasibility was defined as participants' adherence to the target training dose. Adapting pharmaceutical standard rules, the target training dose was considered feasible for this trial if at least two of the three participants in a cohort were able to complete the exercise at the assigned target dose and no more than one participant experienced an adverse reaction (toxicity).

Efficacy rules. The training dose was defined efficacious if at least two of the three participants in a cohort experienced a positive effect on the selected measure.

Checking rules. The first checking rule was that if the dose was found not feasible for two of the three participants, a new cohort was allowed at the same dose. If this dose was found again not feasible for at least two participants of this subsequent cohort then, the subsequent cohort was decreased following the dose de-escalation procedure.

The second checking rule was the following. If a dose was feasible but not efficacious for at least two participants in a cohort, then the mFBS was adhered to and the dose for the subsequent cohort was increased. If that cohort also did not experience any improvement on the selected outcome measure, then the stopping rules were considered.

Stopping rules. The trial was stopped if the dose of two subsequent cohorts (which have been increased following checking rule 2) were found feasible but no gains in the observed outcome occurred in at least two participants on each of the two cohorts. This first stopping rule was made to stop the trial if the trial intervention was found not efficacious or in the event of a plateau stage.

The second stopping rule operated when the dose difference between two cohorts was equal or less than a certain pre-determined amount which was thought to be not meaningful in terms of amount of exercise undertaken. This amount was strictly related to the trial intervention. For the intervention applied in the following feasibility phase I dose-finding study this limit was set to 10% difference between doses.

4.6. The trial algorithm

The general deriving structural process (the trial algorithm) of this 3+3 dose-finding design adjusted to fit motor interventions is reported in Figure 4-1. In detail:

- participants were enrolled into cohorts of three people;
- a cohort must have completed the training programme and the data had to be assessed before another cohort can be assigned to a subsequent dose;

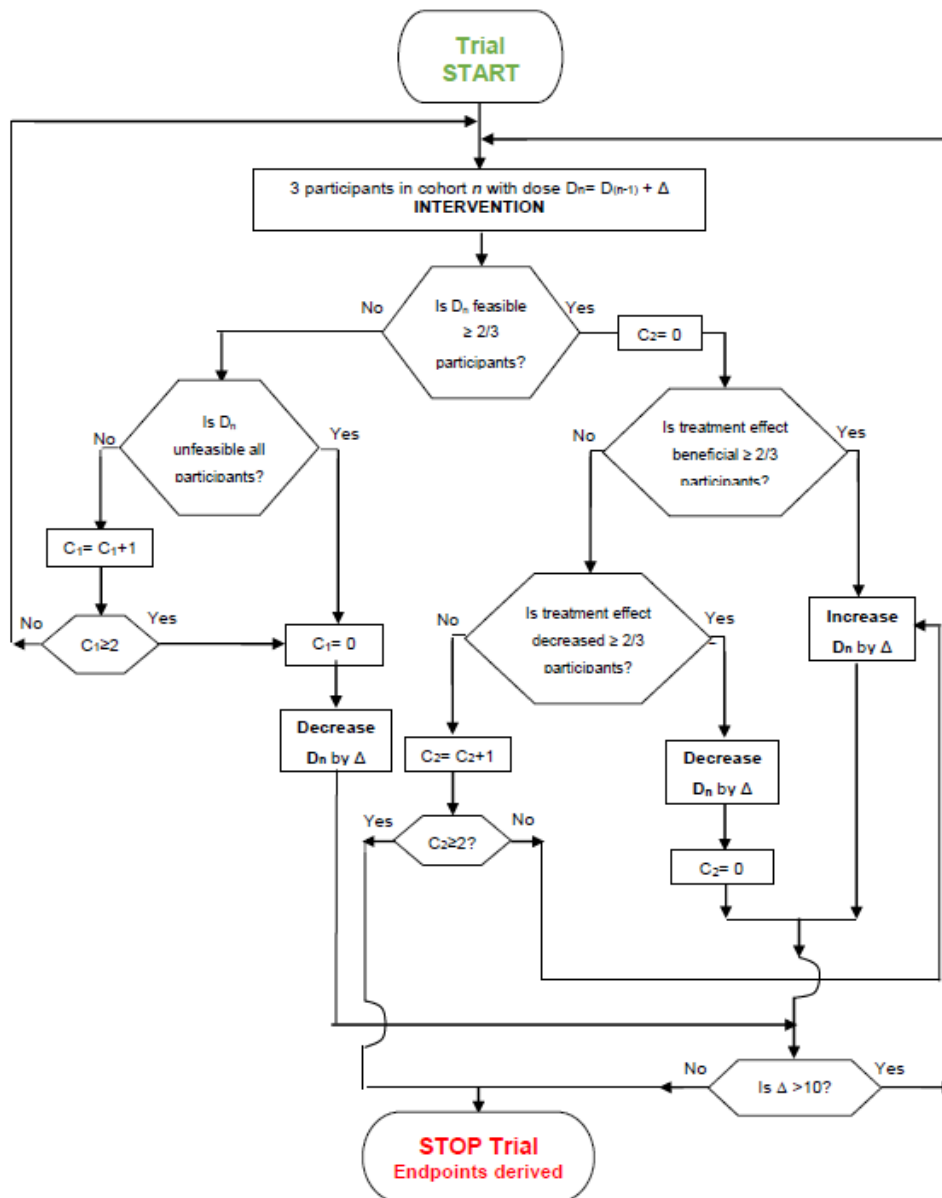
- the first cohort ($n=1$) started at the starting dose (d_1);
- data coming from cohort n , where $n=1, \dots, N$, were evaluated at dose level d_n at the end of the intervention period for each cohort. At this point four scenarios were possible:
 1. d_n was found feasible and efficacious for all three participants. The subsequent dose was escalated to d_{n+1} according to the mFBS;
 2. the target dose level d_n was found not feasible for all three participants. The subsequent dose was decreased following the dose de-escalation procedure $[(d_n - d_{n-1})/2]$. Thereafter, if the new dose level became feasible and efficacious, the dose for the subsequent cohort was increased by 67% of the previous increment and so on following again the mFBS;
 3. the target dose d_n was found not feasible for two participants then, checking rule 1 was applied;
 4. the target dose level d_n was found feasible for at least two of three participants but no gains in treatment efficacy were seen. Two possibilities were considered.
 - a. No change in the selected measure between pre and post intervention points for at least two of three participants and maximum one participant experienced a detrimental effect. Checking rule 2 was implemented.
 - b. Observed decrease in the selected measure between pre and post intervention points for at least two of three participants. The dose for the subsequent cohort was decreased following the dose de-escalation procedure as in point 2.

This process was repeated until the study stopping rules were met.

Two counters (C_1 and C_2) were used in the algorithm to control the correct implementation of the two checking rules. These counters were increased by 1 every time a checking rule was verified and were used to monitor that the

checking rules were not applied more than once consecutively. Counters were set equal to 0 at the beginning of the trial.

Figure 4-1: Flowchart of the algorithm of the dose-finding trial for exercise-based intervention



Notes: Δ = variation of dose level according to modified Fibonacci sequence (mFBS). C_1 and C_2 are the counters to control checking rules. They are set equal to 0 at the beginning of the trial.

4.7. The trial dose endpoints

The conventional main dose endpoint of pharmaceutical phase I dose escalation trials is the Maximum Tolerable Dose (MTD). In pharmaceutical research, the MTD is defined as the dose above which the drug toxicity is not tolerated by the group studied. In this trial, the MTD was defined as the highest dose above which the dose was not more feasible or efficacious for the selected sub-group of stroke survivors.

In this trial a second dose endpoints for efficacy was set: the identification of the optimal dose to bring forward for following efficacy phase II studies. This dose is also known as recommended phase II dose (RPTD).

In pharmaceutical trials, the optimal therapeutic dose (OTD) is generally derived by investigating the dose-response curve and defined as the dose at which the physical intervention is likely to be feasible, with the observed highest patients' benefit defined by the selected outcome measure. Similarly, in this trial, the RPTD was defined as the appropriate dose to bring forward in the research pathway which had demonstrate to be feasible with the observed highest patients' benefit defined by the selected measure.

The approach to investigate the intervention efficacy seemed appropriate to motor intervention for the following two reasons. First, the aim of rehabilitative interventions is enhancing motor recovery. Therefore, our focus was to investigate the dose-response relationship to identify the OTD that maximises therapy effect, rather than, to identify the highest possible prescribed dose (the MTD). Second, in stroke rehabilitation the "toxicity" of the intervention may not be the main concern. Therefore, the MTD and the optimal dose may not be the same as it happen, for instance, in cancer drug research. In stroke rehabilitation the assumption that efficacy increases monotonically with dose has not been verified yet.

This approach also addressed one of the major critique of phase I 3+3 designs, which focuses only on the MTD while neglecting the treatment efficacy [139,238]. To derive the RPTD, the statistical approach applied in pharmaceutical phase I dose optimization research to estimate –parametrically- the dose-response

relationship was used [139,209,231,254]. Specifically, the appropriateness of two parametric models – with a linear and a quadratic specification- were judged by means of goodness-of-fit statistics. The parametric model which potentially fitted better the data defined the dose-response curve. The RPTD was then the local maxima³⁷ of this curve. In addition to the current pharmacological practice, a locally weighted regression of the outcome variable(s) on dose was run³⁸. The graphical comparison of the estimated curves under this nonparametric model with the curves obtained from the parametric ones served to guide on which parametric model was more appropriate.³⁹

³⁷ Also called *relative maximum* of the function studied.

³⁸ A locally weighted regression is a non-parametric regression method. Despite being computationally intensive, non-parametric methods have the advantage of being free of assumptions about the distribution from which the data were drawn. On the other hand, parametric statistical procedures rely on assumptions about the shape of the distribution of the data. When such assumptions are correct, parametric methods will produce more accurate and precise estimates than non-parametric methods. Moreover, the simplicity of parametric formulas (line and parabola, in our case) enables us to use estimated parameters in deriving dose endpoints, such as the local maxima.

³⁹ All analyses were undertaken using Stata 13 statistical software.

Chapter 5:

Feasibility of a phase I dose-finding design for stroke rehabilitation research

5.1 Introduction

In this chapter the term feasibility was used with two specific and different meanings. Firstly, it was used to identify the dose-finding trial as a feasibility study. The focus of the dose-finding trial was to investigate the methodological feasibility of the applied trial design towards dose optimization to help subsequent confirmatory studies. Feasibility trials have the characteristics to test new designs and approaches to help subsequent bigger confirmatory trials [246,247]. Secondly, the term feasibility was used in relation to the dose of training participants were able to sustain and tolerate which was defined as a feasible dose (or not).

The main aim of this chapter was to test the feasibility of the operating characteristics of the dose-finding trial design devised in the previous chapter (*Overall aim 2 and specific objectives*). Furthermore, the relevance of the results in informing current and future stroke rehabilitation research was explored.

The first part of this chapter presents the protocol of the feasibility phase I dose-finding study for motor interventions assessed among participants with moderate upper limb paresis following stroke. The motor intervention applied was a repetitive model-task intervention for the upper limb. The second part of this chapter details trial results.

5.2 Method

5.2.1 Design

A single arm, 3+3 rule-based, outcome-adaptive dose escalation design was applied (more details were available on chapter 4).

5.2.2 Recruitment procedure

A multi-stage recruitment procedure was planned, given the sequential feature of a 3+3 design. This avoided over-recruiting and subsequent possible ethical issues of contacting people who were not going to be involved in the research. Figure 5-1 provides the flowchart of the multi-stage recruitment and participation procedures applied. The interim analysis which guided the multi-stage procedure is highlighted.

Interim analysis was planned for each cohort, at the end of the two weeks intervention period. Retrieved data was used to guide the progression or the end of the trial. If the trial continued (the stopping rules were not verified and the dose endpoint not already reached⁴⁰), then a new cohort was needed and the recruitment procedure (re-)started until three new participants entered the trial. A gap of about six to eight weeks was anticipated between two following cohorts. This gap allowed sufficient time to: deliver the trial intervention, undertake the outcome measures, perform the data analysis, initiate the recruitment process for a new cohort, and organize the start of a new cohort.

⁴⁰ For more details see trial algorithm on Chapter 4

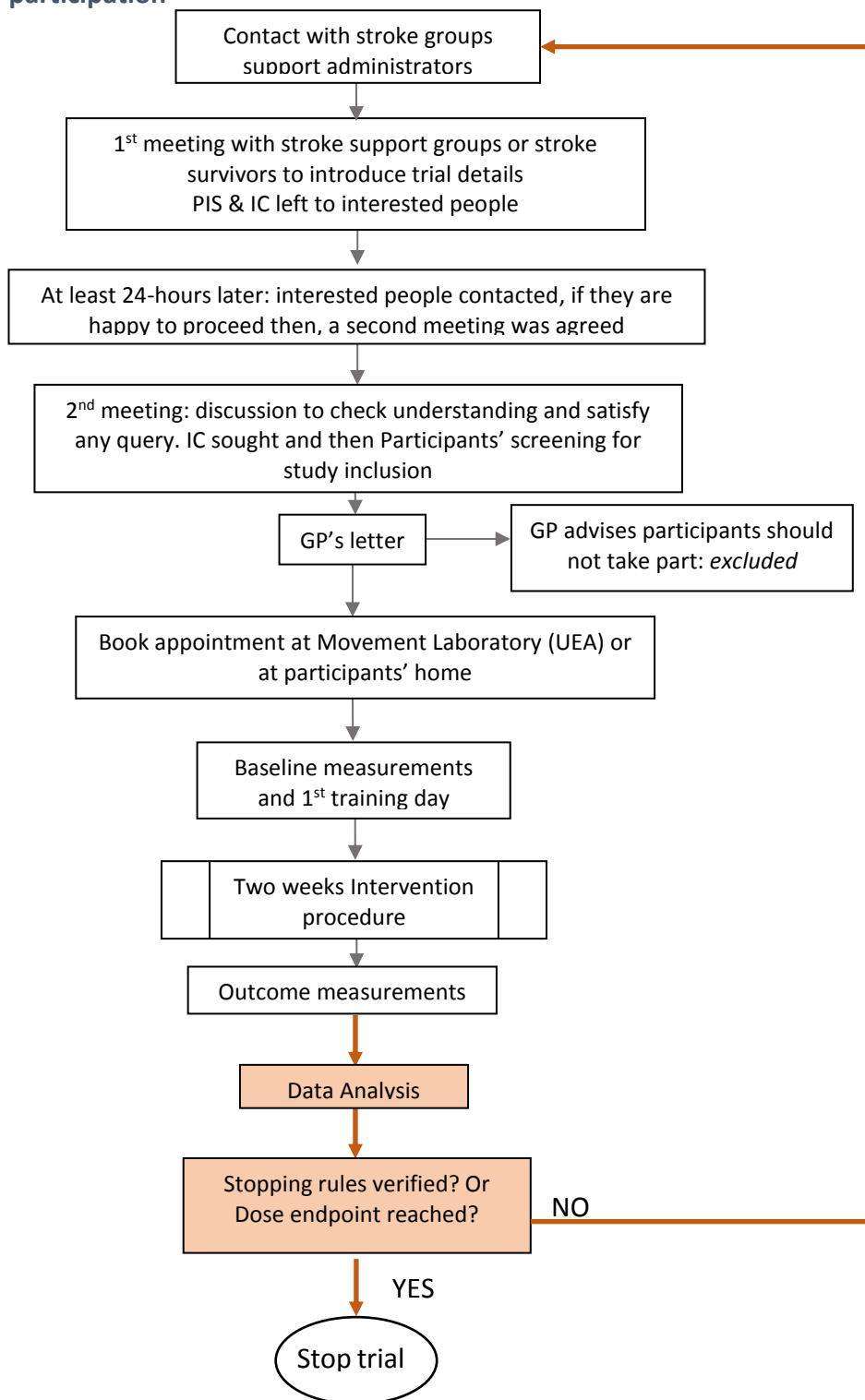
Potential participants were recruited from the local community through stroke survivors support groups that were active in the East Anglia at the time. When a new cohort was needed, the administrator of a new stroke group was contacted to agree a meeting and present the trial to possible participants. This process progressed until the cohort was formed.

When possible, the researcher requested to present the trial during a support group meeting. However, a face-to-face meeting was possible if potential participants expressed the preference to do so. The participant information sheets (PIS) and the informed consent (IC) were left with interested stroke survivors during those meetings. Their interest in taking part in the trial was then recorded. No less than 24-hours later, the researcher contacted (by phone) interested people to seek confirmation of their willingness to participate in the trial. A second appointment was then made with those interested to further discuss trial details, to clarify any queries, to seek written IC and, ultimately, to test subjects for inclusion. Following written IC and satisfactory inclusion criteria, the subject was enrolled in the trial.

If enrolled, a letter providing information about the trial was sent to the participant's GP, requesting whether he/she had any medical concerns on patients' participation in the study. If no concerns were expressed within seven working days, the participant was formally enrolled, seeking an agreement on dates to start the study intervention.

The PIS, IC, GP letter and participant screening form are confined in Appendix E .

Figure 5-1: Flowchart of the multi-stage recruitment procedure and participation



Notes: In orange the interim analysis which guide the multi-stage recruitment procedure.

5.2.3 Target population and inclusion criteria

Adults (18+ years) discharged from stroke rehabilitation care by the Health Service at any time after stroke, and able to participate independently in the training, were potentially eligible for this trial if they were able to meet the following criteria:

1. presence of moderate upper limb impairment following stroke. Moderate upper limb impairment was defined as the ability to open and close the most affected (paretic) hand for six times in one minute, but inability to do this for 26 times in one minute⁴¹ when an extra, extra-light elastic rubber band⁴² was placed around their fingers and thumb.

These upper and lower thresholds on participants' motor ability were set considering a balance between limiting the variations in participants' baseline presentation and preserving the feasibility to enrol participants. A restriction in inclusion criteria was needed due to the features of this design which did not imply randomisation procedure and used cohort of three participants. At the same time, implementing to restrict criteria on upper limb limitation could bring difficulties on the recruitment procedure due to the broad spectrum of stroke survivors' presentations;

2. ability to imitate actions with the less impaired (non-paretic) upper limb. This ability was assessed by the researcher that, by sitting alongside the potential participant performed the intervention task for five times while the potential participant observed. Participants were then required to perform the same task five times with the less impaired arm. The accuracy of the task imitation was assessed and scored using the following point scale: 2 points= task correctly reproduced; 1 point= task reproduced but incorrectly (i.e. participant was not able to place the elastic band correctly on the tripod; see

⁴¹ An effort was made to select these inclusion criteria as directly relevant to the trial task. Ninety repetitions of the tested task in one minute was considered an achievable target for the normal population as tested among twenty-five health adults.

⁴² Rubber band manufactured by: *DIGI-EXTEND*[®] and identified as xx-light; colour beige. See Figure 5.4 for detail.

Figure 5.2); 0 point= task not reproduced. Subjects scoring 8/10 or above were considered able to imitate;

3. not being involved in any rehabilitative training to improve motor–function for their paretic upper limb. This criteria was introduced to avoid potential confounding effects that arise from participation in other rehabilitative interventions. However, participants were asked to continue with their usual activities and trainings.

Trial participant’s screening form is available in Appendix E.

5.2.4 Research setting

Participants self-trained in their own homes for two weeks with no supervision for the majority of the training period. Participants gathered three times at the Movement and Exercise Laboratory (MoveExLab) at UEA with no financial costs. In these occasions participants were supervised by the primary research. Specifically:

1. in the first trial day (training day 1, week 1). All participants of a cohort gathered to undertake pre intervention (baseline) measures, set the physical task intensity identifying their appropriate elastic band, receive instructions and conduct the first supervised training session;
2. in the first training day of the second week (training day 1, week 2). All participants in a cohort gathered to reinforce training dose adherence, control the accuracy of the physical task, and discuss any possible concern or problem;
3. between one to seven days from the end of the training period. Participants came to the MoveExLab to undertake post intervention (outcome) measures.

To increase participants’ adherence to the intervention and follow-up it was aimed that all three participants of a cohort attended the MoveExLab on the same day and time. If needed the researcher could visit participants in their home instead.

5.2.5 Ethics

The ethical approval for the feasibility phase I dose-finding trial was granted on the 7th of February 2014 by the Norfolk NRES Committee East of England (Reference ID: 14 EE 0005). See Appendix F which provides the NRES ethical approval documentations.

The University Research and Enterprise service (REN) approval was received beforehand with a site specific approval and insurance cover for the duration of the entire trial. No amendments to the original protocol were needed.

5.2.6 Sample size

Sample size is not usually pre-defined for this type of open-ended dose-finding study [139,209]. Typically, the final sample size is based on each cohort's data which informs the decisions on subsequent dose following the trial algorithm.

In pharmaceutical research, the number of patients enrolled in phase I dose-finding trials range between 12 and 40 [255]. In line with this evidence, our review on pharmaceutical literature (chapter 5) found that the average number of people engaged in dose-finding was around 26 participants per study.

Although there was no pre-imposed limit on the number of cohorts, for this study, it was estimated that between 4 to 7 cohorts (twelve to twenty-one participants) were required to estimate the predefined dose endpoints and to gain early data on the dose-response relationship. This expectation arose from the following trial features:

- the initial high increment rate of dose brought by the mFBS which should avoid sub-therapeutic doses reducing sample size;
- the implementation of checking rules in the trial algorithm;
- the results from mathematical simulations ran before the trial begins which considered trial feasibility and efficacy rules (see section 7.2.11).

5.2.7 Trial motor intervention

The delivery, control and adherence to the target dose can be challenging for any intervention. As discussed in chapter 1, this is surely true for motor interventions

given also the multifactorial aspects of the training dose. Indeed, the risk of bias can dramatically increase if all the key aspects of the training dose were not taken into account. This becomes particularly relevant in a dose optimisation study where the true effect of dose could be then mistaken.

In a dose-finding study the applied intervention should be identical among participants and sessions, apart from the dose. Moreover, to avoid bias, all parameters of the dose (studied and not) should be controlled and any variation, away from the target dose, should be reported for evaluation.

In considering the key features of a dose-finding study and the training-induced principles of neuroplasticity (see chapter 1), the trial intervention was set as following:

1. a repetitive physical task;
2. challenging but achievable;
3. meaningful for stroke survivors;
4. novel for the majority of participants;
5. enabling control of the training dose and schedule;
6. allowing minimal variation between tasks to guarantee that tasks are similar across sessions and among all participants in the trial;
7. allowing equalization of all parameters of the dose among participants minimizing differences on participants' initial level of upper limb impairment;
8. all parameters of the training dose are recordable;
9. the intervention can be undertaken in participants' home without supervision.

To some extent, for this phase I trial, the intervention was created similar to the one used in animal model studies investigating motor recovery after brain injury.

5.2.8 Intervention task model and training device

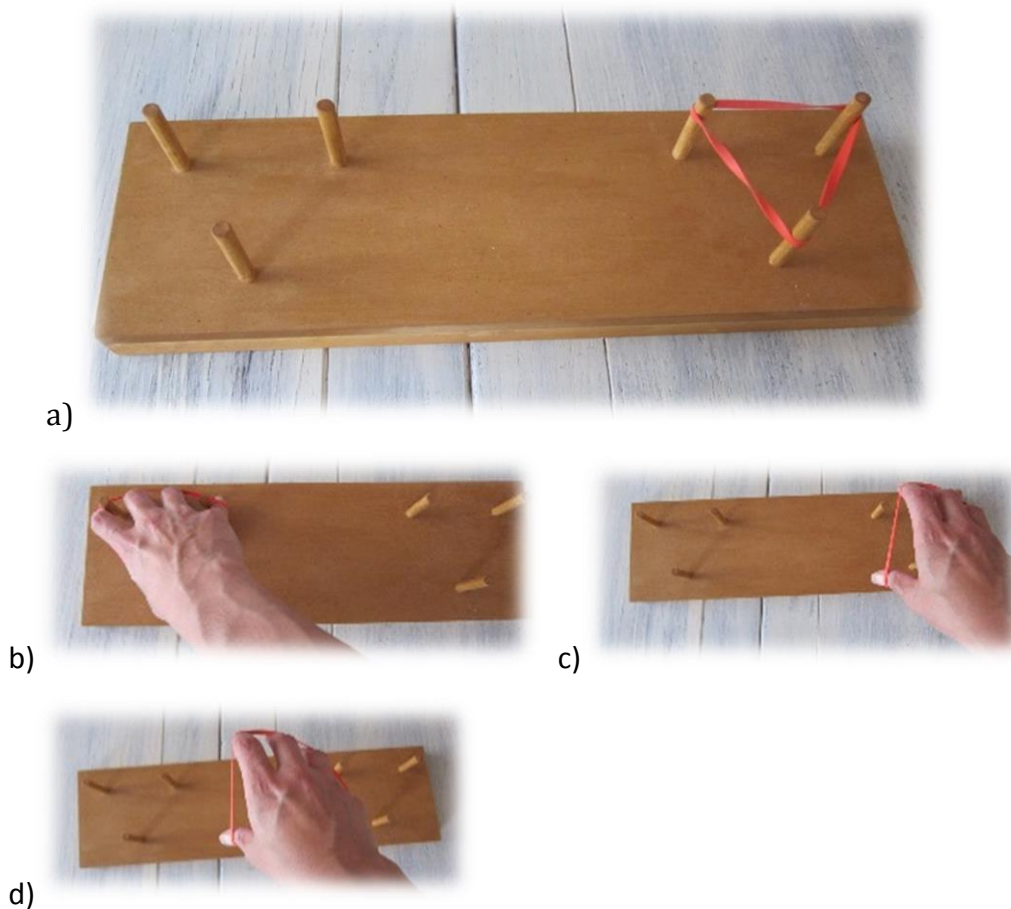
The training task devised for this trial was a model of a motor intervention. A simplified training task, rather than a “real word” rehabilitative intervention, was applied to allow high level of control in the dose and to limit further complications

in evaluating the feasibility of this study design. However, the features of a rehabilitative task remained by the implementation of a meaningful, repetitive and challenging task alongside with strengthening components. The trial intervention was designed to increase participants' ability to produce and modulate voluntary force in the antagonistic muscle groups of the paretic hand and forearm. Very often stroke survivors experience difficulty in releasing their grip on objects with their paretic hand. This difficulty can limit their ability to perform fundamental everyday tasks such as drinking, washing, and cooking.

The trial task involved a synergistic extension and abduction movements of the fingers and thumb of the paretic hand against a tailored resistance applied by a resistance-graded rubber band. This task was thought to contrast the decline of muscle strength, which may also contributing to the loss of movement and performance often experienced after stroke [256].

The training task consisted of inserting fingers and thumb into a tripods frame (see Figure 5-2 a) and then, opening the hand (extend and abduction fingers and thumb) to take off the rubber band and place it on a second but identical frame (see Figure 5-2 sequences b-d). Each removal and placing of a band counted as one repetition.

Figure 5-2: Tripods frame exercise device



Notes: figure a) shows the tripods wooden frame exercise device with red rubber band; sequence b) to c) shows a repetition task.

Participants were asked to move the elastic band from one tripod frame to the other, and back again, for the assigned (target) daily number of task repetitions. Participants were asked to train five days per week for two consecutive weeks at the assigned training dose.

An electronic counter with display was supplied to help participants in tracking and recording the achieved number of daily task repetitions (Figure 5-3). The counter was controlled by a switch and two buttons. The switch turned on and off the counter. The red button on the right side initialised the SD card integrated in the counter whereas, the black left button was the actual count recorder. Every time the black button was pressed the number on the display increases by one.

The tripods frame and counter were originally designed with the contribution of the Mechanical Laboratory at UEA.

Figure 5-3: Electronic counter provided with the tripods exercise device



Notes: participants initialized the session pushing the red button; by pushing the black button participants recorded the number of repetitions achieved in a SD card.

5.2.9 Training protocol and dose

As discussed in chapter 2, the complexity and multi-factorial aspects of the training dose and protocol brought two main challenges when studying a dose-response relationship. Firstly, if the parameters of the training protocol, or the characteristics of the dose, were not controlled the risk of bias could arise. Secondly, manipulating more than one characteristic of the dose at the same time complicated the understanding of trial results. Which characteristic of the training dose could have influenced outcomes remained unclear.

The first issue of controlling and limiting any variations on the training protocol (apart from the studied dose characteristic) was taken into account by creating a simplified trial intervention task (model intervention) and device.

To avoid the second issue only one characteristic of the training dose was manipulated in this trial, and all other parameters of the training protocol and dose remained fixed among sessions and participants during the entire study.

In line with the recommendation endorsing to use specific terminologies and definitions regarding the training protocol and its components in stroke rehabilitation [37], in this dose-finding trial the training protocol comprised of three parameters defined as follow.

- The **dose of training**, which, in turn, was composed by:
 - *amount of training* (A) defined by the number of task repetitions participants achieved daily (the total number of rubber band removed and replaced each day by participants). Amount of training was the studied characteristic of the dose, which was manipulated (varied) across cohorts to study the dose-response relationship and to identify dose endpoints of the applied training task. The amount of repetitive practice was investigated due to its key role on driving positive functional neurological reorganization (see chapter 1). The number of task repetitions achieved daily by participants was recorded by the electronic counter and self-reported by participants in the dose-monitoring form;
 - *intensity of training* (I) defined by the level of resistance applied to the repetitive task. The level of resistance was graded using resistance-graded rubber bands which identified participants' effort to complete the task. Five different colour-code resistance-graded rubber bands were available by manufacturer (Figure 5-4).

Intensity was equalized among all trial participants. For each participant, the training intensity was set during the first training session and it was kept constant throughout all the training period. At each participant was assigned the strongest resistance band which enable them to perform six task repetitions in one minutes. To identify participants' trial band, and thus, training intensity, they were tested starting with a yellow band which corresponds to an extra-light intensity. Participants then progressed up or down in the resistance depending on their personal ability until the participants' trial resistance band was found.

Figure 5-4: Colour-coded resistance-graded rubber bands



Notes: colour-coded rubber bands manufactured by: DIGI-EXTEND®. From the first row left side: xx-light (beige); x-light (yellow); light (red). From the second row right side: medium (green); hard (blue).

- The **frequency of the training** was defined as the number of days participants exercise per week. In this trial the frequency was set at five training days a week. Participants reported the dates of the training in the dose-monitoring form.
- The **training total length** was defined as the total length in weeks of the training protocol. In pharmaceutical research the time needed to evaluate drug effect is often short as well as predictable from early preclinical studies. Whereas, in stroke rehabilitation evidence on the appropriate length of the training protocol to see optimal therapeutic effect are lacking. Investigation on the time-course effect of rehabilitative interventions are still limited. Previous literature suggested improvement in motor function in response to a two weeks period of training [257,258,259]. Thus, to minimise the possibility of attrition and increase adherence to the target training dose while preserving the possibility to induce motor-changes, the trial length was set at two weeks.

Data on the **duration of the training session** were also collected. This was defined by the total time (in minutes) participants spent daily on the repetitive tasks. The duration of the training was self-reported by participants as well as recorded by an internal clock in the electronic counter. Participants reported the duration of the daily sessions on a dose-monitoring form reported in Appendix G.

Participants were allowed to split the daily session as needed to achieve the target training dose.

Participants were instructed to strictly follow the given training protocol to increase the rigour of this research.

5.2.10 Starting dose

One of the crucial aspects to minimize the number of patients required in the trial and increase trial efficacy was to identify an appropriate starting dose.

In phase I dose-finding pharmaceutical studies the starting dose is typically based on pre-clinical data and it represents a safe dose which should avoid any toxicity but higher than the minimal effective dose (MinED).

A conservative starting dose (d_1), which was thought to show motor improvements, was selected for this trial equals to:

$$d_1 = 50 \text{ daily task repetitions} \times I \quad (1)$$

where I was the intensity of the repetitive task assigned by the trial and equalised for each participant.

The starting dose was justified by:

- the choice of using a conservative starting dose to avoid onset of adverse reactions such as, fatigue and tiredness;
- the background knowledge on animal models [92], clinical research [69,88,260,261] and quantitative analyses [7,26,35,42,66,72,118,122,123,262,263,264,265] which indicated that

relatively high dose of training were feasible and can be required to induce motor learning after stroke (chapter 1);

- the use of a dose escalation procedure (mFBS) which allowed for initial rapid increments of the training dose, as described with the mathematical simulation in Figure 5-5;
- the recommended 45 minutes of therapy a day issued by the Royal College of Physician⁴³;
- participants' motor ability thresholds set as trial inclusion criteria. If participants were able to open and close their paretic hand six time in one minute against the lighted bans (lower threshold), it was estimated that they should be able to undertake 50 task-repetitions in about 30 minutes of training.

5.2.11 Mathematical simulation of the trial dose escalation

Before the trial began, a mathematical simulation with four possible dose escalation scenarios was run with the main aims to: anticipate a possible trial sample size, estimate the trial starting dose and early assess the feasibility and acceptability of some numerical scenarios on trial doses.

These hypothetical simulations were based on background knowledge on animal models with induced brain injury and stroke survivoirs which suggested the need and the feasibility of a large amount of task-specific daily repetitions to facilitate motor learning.

Figure 5-5 shows the four possible scenarios of trial dose escalations analysed. In detail:

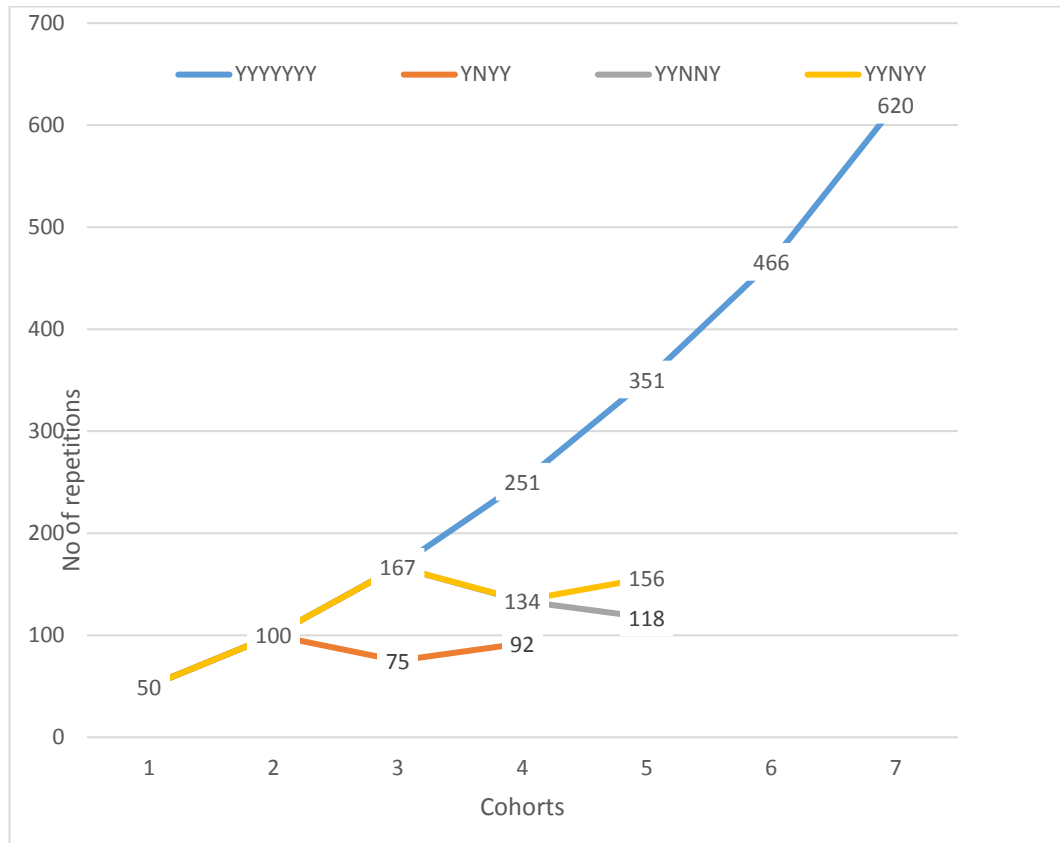
Case 1 (condition: YYYYYYY, blue line in Figure 5-5)

In this case all dose were considered feasible, efficacious until cohort 7. Table 5-1 reports the numerical results of the dose escalation applied using the mFBS.

⁴³ <http://www.rcplondon.ac.uk/sites/default/files/national-clinical-guidelines-for-stroke-fourth-edition.pdf> (last visit 11/04/13).

The simulation was stopped at cohort 7 because the following dose of 827 daily repetitions (highlighted in grey) was considered not feasible because too high.

Figure 5-5: Mathematical simulation of trial dose escalation



Notes: blue line= case 1; orange line=case 2 grey line= case 3; yellow line= case 4

Table 5-1: Mathematical simulation on dose escalation: case 1 following the mFBS

CASE 1:			
Cohort (n)	mFBS	Dose Increment	Cohort Dose D(n)
1		0	50
2	1	50	100
3	0.67	67	167
4	0.5	83.5	251
5	0.4	100.2	351
6	0.33	115.7	466
7	0.33	153.9	620
8	0.33	206.7	827

Note: case 1 all dose were considered feasible, efficacious until cohort 7 (monotonic increments, condition: YYYYYY). The first column reports the cohort number, the second column the mFBS, the third column the dose increments derived by the mFBS and the last column the assigned dose starting with an initial dose of 50 daily repetitions. Dose is expressed in daily number of task repetitions.

Case 2 (condition: YNY, orange line in Figure 5-5)

Table 5.2 refers to the numerical results on the dose escalation for case 2. The feasible doses were highlighted in bold, the first not feasible dose was highlighted in red, when the stopping rule was verified the following dose was highlighted in grey.

In detail, the first dose was considered feasible and efficacious thus, following the mFBS, the second dose was increased by 100%. The second dose was considered not feasible (or efficacious) and therefore, the third dose was decreased by 50% of the previous increment following the trial dose de-escalation procedure. This new dose (third) was considered feasible and efficacious and thus, the fourth dose was increased by 67% of the previous increment reaching 92 daily repetitions. The following dose (fifth) should have been increased by 50% of the previous increments (by 8 repetitions) but a stopping rule was considered because the difference between the two doses was less than 10% (see chapter 4 for trial algorithm and rules).

Table 5-2: Mathematical simulation on dose escalation: case 2 following the mFBS

CASE 2:							
Cohort (n)	mFBS	Dose Increment	Cohort Dose D(n)	Dose Decrement	Cohort Dose D(n)	Dose Increment	Cohort Dose D(n)
1		0	50				
2	1	50	100	25			
3	0.67	67	167		75	16.8	
4	0.5	83.5	251			8.4	92
5	0.4	100.2	351				100

Note: Case 2 condition: YNY. The feasible and efficacious dose were highlighted in bold whereas, the dose which were not feasible or efficacious were highlighted in red. In grey was highlighted the first not included dose. The first left column reports the cohort number, the second column the mFBS, the third, fifth, and seventh columns report the dose increments or decrements derived by the mFBS and the fourth, sixth, and eighth columns the assigned dose. Dose is expressed in daily number of task repetitions.

Case 3 (condition: YNNY, grey line in Figure 5-5)

Table 5.3 refers to the numerical results on the dose escalation for case 3. In detail, the first and second doses were considered feasible and efficacious seeing an increment of 100% and 50% respectively for the second and third cohorts. The third dose was considered not feasible (167 daily repetitions, highlighted in red). Thus, the following (fourth) dose was decreased by 50% of the previous increment (134 daily repetitions). This new dose was considered again not feasible (or efficacious) (highlighted in red) and the following (fifth) dose was decreased by 50% of the previous increment. The fifth dose was considered feasible and efficacious but the trial was stopped because the following (sixth) cohort would have set at 141 daily repetitions with an increment by 67% of the previous increment, but this new dose was above a dose already found unfeasible (134 daily repetitions).

Table 5-3: Mathematical simulation on dose escalation: case 3 following the mFBS

CASE 3:							
Cohort (n)	mFBS	Dose Increment	Cohort Dose D(n)	Dose Decrement	Cohort Dose D(n)	Dose Increment	Cohort Dose D(n)
1		0	50				
2	1	50	100				
3	0.67	67	167	33.5			
4	0.5	83.5	251	16	134		
5	0.4	100.2	351		118	23	
6	0.33	115.7	466				141

Note: case 3 condition: YNNYY. The feasible and efficacious dose were highlighted in bold whereas, the dose which were not feasible or efficacious were highlighted in red. In grey was highlighted the first not included dose. Cohort number is reported in the left column followed by the modified Fibonacci sequence, dose increments (or decrements) derived by the mFBS and the assigned dose. Dose is expressed in daily number of task repetitions.

Case 4 (condition: YNYY yellow line in Figure 5-5)

Table 5-4 refers to the numerical results on the dose escalation for case 4. As the previous case the first and second dose were considered feasible and efficacious but the third dose was not (highlighted in red). Thus, the following (fourth) dose was decreased by 50% of the previous increment (134 daily repetitions) which in

this case, was considered feasible and efficacious. Thus, the fifth cohort saw an increase of 67% of the previous increment (156 daily repetitions). This new (fifth) dose was considered again feasible and efficacious but the trial was stopped because the following dose, increased by 50% of the previous increment at 169 daily repetition was above a dose already considered unfeasible (167 daily repetitions).

Table 5-4: Mathematical simulation on dose escalation: case 4 following the mFBS

CASE 4:							
Cohort (n)	mFBS	Dose Increment	Cohort Dose D(n)	Dose Decrement	Cohort Dose D(n)	Dose Increment	Cohort Dose D(n)
1		0	50				
2	1	50	100				
3	0.67	67	167	33.5			
4	0.5	83.5	251	16	134	23	
5	0.4	100.2	351			11.5	156
6	0.33	115.7	466				169

Note: case 4 condition: YNYY. The feasible and efficacious dose were highlighted in bold whereas, the dose which were not feasible or efficacious were highlighted in red. In grey was highlighted the first not included dose. Cohorts are reported in the left column followed by the modified Fibonacci sequence, dose increments (or decrements) derived by the mFBS and the assigned dose. Dose is expressed in daily number of task repetitions.

As a result of this analysis, the gaps between doses and the trials rules seemed appropriate for this trial and intervention.

Furthermore, from these analyses, it was estimated that between 4 to 7 cohorts were required for this trial which was likely to suggest a dose between 134 and 620 repetitions.

5.2.12 Trial endpoints

Coherently with the discussions in chapter 3 and chapter 4, the dose endpoints for this trial were derived at the end of the trial as:

1. **the maximal tolerable dose (MTD)** defined as the highest dose that was adhered to by at least two of the three participants in a cohort and for which no more than one of the three participants experienced an adverse

consequence. The MTD was derived from the analysis on participants' adherence to the assigned daily dose;

2. **the recommended phase II dose (RPTD) and the dose-response relationship.** The RPTD was derived from the intervention dose-response relationship analysis. The RPTD represented the dose at which the motor intervention was likely to be feasible with the observed highest patients' benefit (local maxima).

5.3 Outcome measures

In phase I pharmaceutical trials treatment effect is often estimated by assessing changes on a biological level (i.e. changes in the size of the tumor, changes in the blood pressure, and changes in the cells count). These changes, commonly used as surrogate endpoints for the definitive outcomes (i.e.: increase of the surviving rate; reduction of incidence of stroke and heart attack), are measurable in a known and often short period of time.

Similar specific outcomes and background knowledge are not yet available in stroke rehabilitation. As a consequence, the selection of the outcome measures is often a challenging step in planning a clinical trial [266]. To overcome these issues:

- a) the primary outcome focussed on the impairment level as the most sensitive to change brought by the intervention [267] and as predictive of neurological and functional recovery after stroke [268,269,270].
- b) a battery of secondary measure was used to investigate changes from pre to post intervention on an impairment and functional level. Ideally, the selected measure battery should: be appropriate to measure a change brought by the intervention; be sensitive enough to depict changes; have good psychometrics properties; be validate among the studied group of people; and assess more than one level as state by the ICF classification (impairment, activity and participation) [271,272,273].

- c) an objective assessment of the changes in the corticospinal pathway was included. Neurophysiology changes after the two weeks of intervention were explored using a non-invasive neuroimaging tool. This measure was thought to be a more sensitive assessment than clinical examination to detect brain reorganization and thus recovery [274]. The appropriateness and feasibility of this non-invasive tool was explored in dose-finding trial.

Participants' characteristics were collected to allow descriptive analyses and explore potential relationships with outcomes. Patients' characteristics obtained were: age and gender; time since stroke; side of stroke; and dominant side affected.

The trial baseline (pre intervention) and outcome (post-intervention) measures sheets are available in Appendix H and Appendix I.

In the following sub-sections details are provided on all trial measures.

5.3.1 Dose feasibility measures

The feasibility of the training dose was defined as participants' adherence to the assigned training daily dose. In detail, the daily dose was defined feasible if adherence to the assigned dose was 100% for at least two of the three participants in a cohort ($\geq 66\%$ of the cohort) and no more than one participant experiences an adverse reaction ($\leq 33\%$ of the cohort) (toxicity).

To this definition some flexibility was allowed to accommodate the trial intervention to participants' daily life. If participants did not fully adhere to the assigned dose for reasons not related to the trial or the training dose (e.g. hospital appointment; health issues unrelated with the trial; all day personal engagements; etc.) for a maximum of three days on the entire training period, they were still considered adherent to the dose. Participants' adherence was recorded in two ways.

1. Self-reported (SRM) by participants on a daily dose-monitoring form (Appendix G). For each training day participants were asked to record the following information: the training day date, the number of repetitions achieved in that session, and the total time spent on the daily training session

specifying whether they split the session or not. If the daily assigned dose was not achieved, participants were asked to motivate⁴⁴.

2. Electronically by the counter. The counter recorded the number of repetitions achieved for each of the daily training session. Data on number of repetitions, time and duration of the daily training sessions were stored in a SD card enclosed in the counter and are considered as objective measure (OBM).

The participation in this trial training was considered with a low risk of serious adverse events. However, any physical training could be related to an “over-use” syndrome. To control for this possibility participants were asked to note on the dose-monitoring form any adverse occurrences such as: discomfort, pain or fatigue. These data, alongside with participants’ feedbacks and comments on the training dose, were used to support the dose feasibility assessment. Participants were contacted by phone at least in two occasion during the trial intervention to check on possible complains, needs and to improve dose adherence. If necessary, more phone calls were agreed and planned with participants.

5.3.2 Efficacy measures

Independent assessors, blinded to allocation of the training dose, undertook all pre (baseline) and post intervention (outcome) measures to avoid possible bias. Pre intervention measures were administered on the first training day, before the intervention. Post intervention measures were taken within one week after the last training day for all participants to equalize retention of training effect.

5.3.3 Primary efficacy measures

Considering the generalizability of participants’ acquired motor skills, it was desirable to assess a task which is similar to the one treated in the rehabilitative

⁴⁴ Eight pre-formulated possible reasons to not adhere to the assigned daily training dose were provided in the form to facilitate participants. Namely: 1) No time/too busy including; 2) I was bored; 3) I was tired; 4) I was sick or not feeling well; 5) Pain or discomfort on my affected hand or arm; 6) The numbers of repetitions assigned were too much; 7) I cannot do it/I am not able to do it; 8) other, please specify. These added information are used on data analysis and conclusions.

sessions [63]. It was difficult to find a known, economically accessible, and reliable measure tool able to assess the strength in the extensors muscle of the hand and arm which were the muscles trained by the trial intervention task. Thus, a clinical therapy device, was used to explore the efficacy of the intervention from pre to post intervention as a primary efficacy outcome measure. The *Cando Digit-Extend* (Figure 5-6)⁴⁵ finger exerciser⁴⁶. The Cando Digit-Extend is a professional but easy device. It is clinically used to build strength in the intrinsic and extrinsic muscle groups in the hand and forearm. This device is equipped with five coded resistance bands (see Figure 5-4).

In this study, the therapy device was used to assess the effect of the intervention on participants' strength and motor learning focussing on the extensor mechanism of all fingers and thumb of the paretic hand.

The measure took place as follow. Participants inserted the fingers and thumb of their paretic hand in the plastic frame and opened their hand against a coded resistance band. This measure consists of two parts. First, participants were asked to extend their fingers and thumb (open and close their paretic hand) against the lightest resistance band available (xx-light, colour: beige) as many time as possible in one minute (test part A). The achieved number of repetitions was then recorded.

⁴⁵ <http://prohealthcareproducts.com/exercise-stations-c-6/cando-digi-extend-finger-exerciser-package-p-1084> (last visited on 12/13).

⁴⁶ No relationship were present between the researcher or the University of East Anglia and the DIGI-EXTEND® manufacturer.

Figure 5-6: Cando Digit-Extend finger exerciser therapy device



Note: device manufactured by: DIGI-EXTEND®.

The second part of the test assessed the highest level of resistance (colour band) against which participants were able to extend their fingers and thumb of their paretic hand twice in one minute (test part B). The test started with the beige band (lightest band). Zero was assigned if participant was unable to perform the movement. One if participant was able to perform one movement; two if participant was able to extend twice the fingers and thumb with the band. This test was run with all bands using the same point increments. Therefore, the maximum score of 10 points was obtained by a participant that was able to perform the movements with the blue (strongest) resistance band.

The training dose was defined efficacious if at least two of the three participants in a cohort ($\geq 66\%$ of the cohort) experienced significant positive change in at least one of the two parts of the primary measure. A significant positive change in the primary measure was arbitrary chosen as equal or above 10%.

The changes in these measures, as primary efficacy measure, were used to guide the dose escalation and de-escalation in subsequent cohorts following the trial algorithm as well as used to identify the dose-response curve and derive trial endpoints.

5.3.4 Secondary efficacy measures

The *Hand grip test* assessed changes from pre to post intervention in participants' upper limb strength using the JAMAR Hand Dynamometer (Figure 5-7, left side). Measuring power grip strength changes due to motor interventions was considered a sensitive method of charting intrinsic neurological recovery and functional recovery after stroke [268,269,270]. Participants were asked to grip the handle of the dynamometer and squeeze as hard as possible. The Minimally Clinically Importance Change (MCIC) for grip strength was evaluated at around 6 kg in the healthy population [275] and at around 5 kg for stroke survivors [276].

The *Pinch grip test* (thumb and first finger) assessed changes in participants' upper limb strength using a JAMAR Hydraulic Pinch gauge (Figure 5-7, right side). The Hydraulic dynamometer was considered a reliable, valid and sensitive test to establish changes in the upper limb muscles strength and impairment recover over time. Participants were asked to pinch, between the thumb and the first finger, and squeeze as hard as possible.

In both strength tests participants were seated on a table with their elbow supported at about 40° angle with wrist unsupported [277]. The tests were undertaken three times⁴⁷ and the mean value is used for the analyses.

⁴⁷ The devices were set to "zero" before each trial.

Figure 5-7: Hand grip and hand pinch test



Note: this picture shows the hand grip dynamometer on the left side and the hydraulic pinch gauge on the right side. Manufacturer: Sammons Preston Rolyam, distributed by: Homecraft, Ltd., Nottinghamshire UK.

The modified *Box and Block Test* (mBBT). The Box and Block Test is a performance-based measurement of unilateral gross manual dexterity. The BBT, originally developed in 1957 by Hyres and Buhler [278,279], exhibited an excellent test-retest reliability (Interclass correlation coefficient ICC= 0.97 for the right; and ICC= 0.96 for the left hand) and inter-rater reliability (ICC= 0.99 and Spearman rho correlation rho= 0.99) in elderly people with stroke upper limb sensorimotor impairments [280,281,282]. The original test was modified for this trial to assess manual dexterity but in three different hand positions. The mBBT was chosen due to some similarity with the applied repetition task. The control of the extensor muscles of the hand is a key element to perform functional releasing movements. Thus, it was thought that increasing their strength and control in extensor muscle of the hand and arm participants could release objects better and quicker.

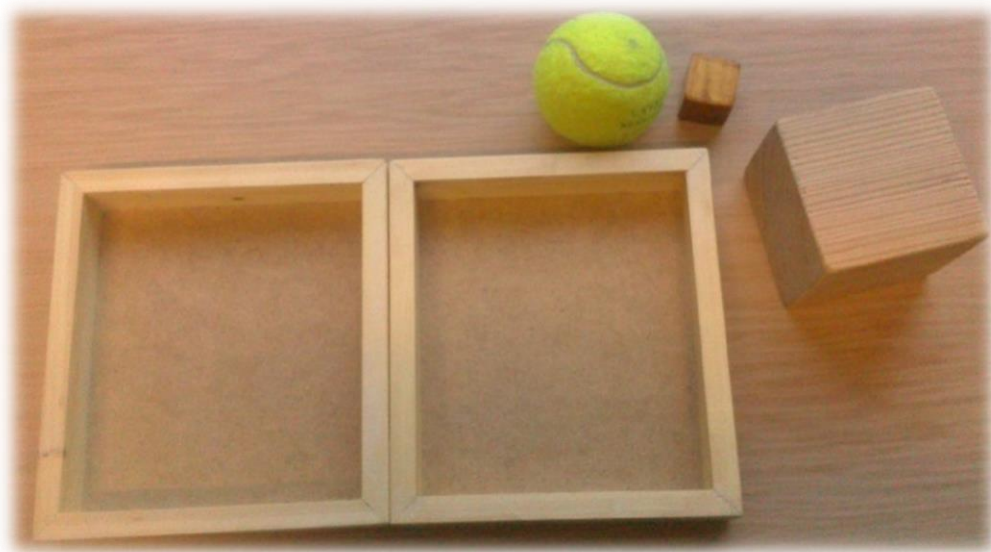
Participants undertook three trials using a different object each time: a tennis ball referred to as modified Box and Block test 1 (mBBT1); a 2 cm cube referred to as modified Box and Block test 2 (mBBT2); and a 5 cm cube referred to as modified

Box and Block test 3 (mBBT3) (Figure 5-8). Five minutes rest were allowed between each trial to avoid over-tiredness. The number of reaching and releasing achieved by all participants in one minute were assessed using the three objects at baseline (pre) and post intervention. Participants' changes were evaluated as the difference between these two measure points.

To undertake the test participants sit on a dining-type chair at a table in front of a divided box. They were asked to pick up an object, between the tip of the index finger and tip of the thumb of the paretic hand and release the object into the other side of the box. This task was repeated as many times as possible in one minute.

A MCIC, for stroke survivors, corresponds with an increment of five blocks [282,283,284].

Figure 5-8: The modified Box and Blocs tests



Note: the figure shows the modified Box and Block test with the used three objects: a tennis ball, a 2 cm cube and a 5 cm cube.

Results from secondary measures were used to test consistency on the dose-response curve and the RPTD obtained using the primary efficacy measure⁴⁸.

⁴⁸The secondary measures did not guide the trial algorithm for efficacy and thus, the MTD could not be derived from these analyses.

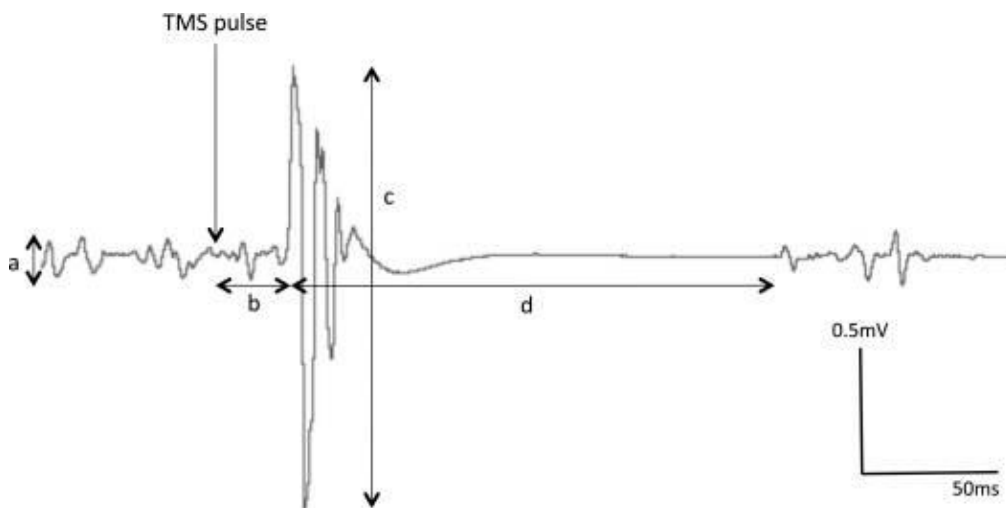
5.3.5 Non-invasive neuroimaging tool: Transcranial magnetic stimulation (TMS)

The TMS is a non-invasive brain stimulator tool able to enhance understanding of the nervous system. It can be used for mapping cortical motor representation in the brain [285].

Recently, it has been used to investigate the neural mechanisms that underline spontaneous and therapy-induced motor recovery after stroke [32,60,62,286,287].

TMS works by passing a transient current through a wire coil placed on the subject's head. The current produces a changing magnetic field in the beneath brain area inducing a depolarization of nerves cells. Single-pulse, low intensity TMS can stimulate the corticospinal tract directly if applied over the primary motor cortex (M1) (trans-synaptically). The response to this stimulus depends on the size, shape, orientation, frequency, and intensity of the TMS stimulus [285] and it can be recorded using motor evoked potential (MEP) by bipolar surface electromyography positioned on target muscles. When TMS is used following standard procedures and guidelines it is considered a safe and painless procedure [58,288]. Figure 5-9 shows the MEP characteristics when a single TMS pulse is recorded from a muscle. The TMS of the M1 can be used to measure several parameters of the integrity and responsiveness of the corticospinal pathway. The more common studied parameters include: the cortical motor threshold; MEP amplitudes and latency; and the central motor conduction time.

Figure 5-9: TMS-derived measures of cortical excitability



Notes: a) background EMG, b) latency, c) peak-to-peak amplitude, d) silent period. Extracted from [58].

The rationale to introduce TMS in this trial was to explore if changes in biological level could be more indicative than changes in motor function to guide dose optimization studies. In other words, if it could be possible to use change in corticospinal excitability as biomarkers for the brain functional reorganization. In detail, the objective of this measure were to:

1. explore if it was feasible to apply TMS to a dose-finding study in stroke rehabilitation;
2. explore if there was a change in the corticospinal excitability pre to post intervention;
3. explore if these changes appeared before any behavioural changes could be found. In other words, if this measure was more sensitive to change than any other measure applied in the trial;
4. explore if the dose of training was correlated with changes in excitability of the corticospinal pathway;
5. assess if changes in corticospinal excitability related to any other measure applied (clinical scores).

Participants' changes pre to post intervention were explored on:

- MEP amplitude. The size of the peak-to-peak MEP amplitude provided information on the integrity of the corticospinal tract. MEP were measured in response to increasing stimulus intensity (supra-threshold TMS at 100% 110%, 120% and 130% of the motor threshold). This enabled exploration on the stimulus response curve (sigmoid curve) or recruitment curve (RC) which can demonstrate the relationship between corticospinal excitability and level of intensity of stimulation [289]. Both hemisphere were investigated because people with motor deficits post-stroke usually presented variability in the excitability of both hemisphere with, often, a reduced MEPs amplitude on the affected motor area compared with the unaffected side [290].
- the resting motor threshold (RMT). The RMT is the basic measure of excitability of the corticospinal tract and it could provide indication of brain plasticity being predominantly influenced by neural excitability and white matter changes [286].

Single pulses of TMS were given over the participants' brain areas of M1 of the stroke and non-stroke hemisphere of three upper limb muscles: the *abductor pollicis brevis muscle* (ABP); the *extensor carpi radialis muscle* (ECR); and the *biceps brachii* (BB). These muscles were considered the principal muscles involved in the trial repetitive task practice. The measures were taken before the start of the trial intervention and between a week post interventions.

Changes in RMT and MEPs amplitudes from pre to post intervention for each assessed muscle were analysed to each individual participants and by cohorts, if possible.

In this study a MAGSTIM appliance with a standard figure-of-eight coil was used (see Figure 5-10) to assess the changes in excitability of the corticospinal pathways pre and post intervention.

Figure 5-10: Transcranial magnetic stimulation machine and figure-of-eight coil



Prior to performing TMS, a screening questionnaire, available in Appendix J, based on guidelines for safety precautions [58,288] was used to assess participants' ability to take part in the measure by the assessors specialised in the tool. Participants were excluded if any metal implants, heart pacemaker was reported or participants suffer from epilepsy.

To undertake the test participants were comfortably seated on an armchair with both arms in resting position. The RMT was located in the hot spot⁴⁹. The hot spot was defined as the brain area where the minimum TMS intensity required to elicit 5 MEPs ($\geq 50\mu\text{V}$) in 10 consecutive stimulus at rest [289]. To identify the hot-spots, the assessor measured the participants' head to find the vertex and then moved laterally the TMS coil in very small increments [289]. When located on the scalp the hot-spot was marked with an indelible ink. This spot was the one used to collect all data. Subsequently, five trials were performed at the intensity of 110%, 120% and 130% to explore muscle recruitment curve. For each studied

⁴⁹ The "hot spot" was defined as the most active scalp position for the target muscle where the minimal intensity is needed to produce an evoked motor response (motor threshold).

muscle the coil was placed on the hot-spot tangentially to the participant's scalp and at 45-degrees to the midline, so that the induced current flowed in a lateral-posterior to medial-anterior direction.

Surface electrodes in a belly-tendon montage were used for electromyography recordings. Disposable CLEARTRACE ECG adult electrodes⁵⁰ were used for the extensor carpi radialis and the biceps brachii muscles. Reusable cup electrodes⁵¹ were used for the abductor pollicis brevis muscles due to their smaller size.

The participant's muscle areas were cleaned before positioning electrodes with an abrasive skin preparing gel and then, an alcoholic wipe.

MEPs data were recorded using Windows compatible Signal software.

5.4 Analysis

The main aims of this dose-finding study were to assess the feasibility of a dose-finding trial design in stroke rehabilitation research and, to explore the relevance of data on dose provided by this study.

The numerical results on dose were not the focus of this study. Instead, the results were only used to suggest the appropriateness of this study to provide relevant results on dose endpoints and on the dose-response relationship.

All participants' data were included in the analysis following an intention to treat procedure to consider attrition and non-compliance. This procedure was found to increase validity of the trial results [291].

5.4.1 Primary analysis: design feasibility

Trial design feasibility was assessed considering:

- the feasibility of the multi-stage recruitment procedure, the time required to recruit participants, and to complete the study;
- the acceptability to participate and complete the trial (retention rate);

⁵⁰ ECG electrodes manufactured by: ConMed Corporation.

⁵¹ Cup electrodes manufactured by: Nicolet Biomedical.

- the feasibility, appropriateness and face validity⁵² of the dose-adherence monitoring procedures [292];
- the appropriateness of the outcome-adaptive dose escalation and de-escalation procedures;
- ease of use of the trial pre-defined rules;
- feasibility in identifying the selected dose endpoints: the MTD and the RPTD by plotting dose-response curves.

5.4.2 Relevance of the dose optimisation information provided

The relevance to stroke rehabilitation of the dose optimisation information provided by this trial were explored through:

- the ability to identify the MTD;
- the ability to derive a dose-response curve and thus, to estimate the RPTD

Changes from pre to post intervention on the primary measure data were used. In accordance with the standard analysis plans applied in pharmaceutical phase I dose optimization research [205,209,231], the appropriateness of two parametric models – with a linear and a quadratic specification- were used to study the association between dose and effect (dose-response curve). The model which showed a better fit with the data using a goodness of fit statistics was used to identify the RPTD. The RPTD was then the local maxima of this curve. A non-parametric⁵³ regression was also run [205] to estimate on which parametric model was more appropriate. The purpose of this analysis was explorative only. The relevance of the trial to inform stroke rehabilitation research and the appropriateness of undertaking the planned analyses were the main focus. The numerical value of the dose endpoints were not intended to use per se or in further studies.

⁵² Face validity is a content validity. It implied that the applied test appeared to users practical, pertinent and related to the aim of the test (Baruch N., 1958).

⁵³ See chapter 4, section 7 for details.

The feasibility of collecting data on training session duration (time) in a dose-finding design was explored. The duration of the training session is often used in stroke rehabilitation as dose of training [31]. Exploring the feasibility to collect this data seemed therefore relevant in a dose-finding study as well as helping in compare results with other trials.

The appropriateness of the obtained trial sample size was evaluated in light of the literature.

5.5 Results

Table 5-5 reports participants' baseline characteristics and pre (baseline) and post (outcome) scores by cohorts and overall.

The mean age of the 15 participants (5 cohorts) was 68.4 years (range 48-81), and 46.7% were women. On average, participants reported a mean of 70 months after stroke (range 9-289), with 33.3% having a right-sided paresis. Overall, mean pre intervention (baseline) motor function scores were: 23.3 (SD= 18.9) repetitions per minute of fingers and thumb flexion/extension; 12.3 (SD= 8.2) Kg for hand grip; 4.6 (SD= 1.8) Kg for pinch grip; 31.7 (SD= 15.4) transfers per minute on mBBT1 (with a tennis ball); 32.2 (SD= 16.7) transfers per minute on mBBT2 (with a 2cm cube); and 33.7 (SD= 17.6) transfers per minute on mBBT3 (with a 5cm cube).

Table 5-5: Participants' baseline characteristics and pre (baseline) and post intervention (outcome) scores by cohorts

	Overall	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
Baseline characteristics						
Age (years): mean (range)	68.4 (48-81)	68.7 (66-71)	71.7 (68-77)	63.3 (54-71)	60.0 (48-75)	74.3 (69-81)
Months post-stroke: mean (range)	70 (9-289)	37 (9-67)	124 (18-289)	78 (12-120)	65 (11-156)	44 (30-54)
Female: %	46.7	67	0	33	100	33
Right side affected: %	33.3	0	33	67	0	67
Dominant Side affected: %	46.7	0	0	67	100	67
Baseline scores: mean (SD)						
Maximum no. repetition	23.3 (18.9)	17.0 (16.5)	25.0 (11.8)	24.7 (38.5)	17.0 (18.7)	32.7 (3.1)
Hand grip (Kg)	12.3 (8.2)	7.3 (7.0)	12.0 (8.3)	19.0 (11.9)	11.0 (8.6)	12 (5.6)
Pinch grip (Kg)	4.6 (1.8)	4.5 (1.8)	5.4 (1.9)	6.1 (2.0)	3.4 (1.1)	3.8 (1.9)
mBB test1 (transfers/minute)	31.7 (15.4)	24.3 (12.9)	21.0 (8.5)	36.7 (17.2)	33.7 (20)	42.7 (15.8)
mBB test2 (transfers/minute)	32.2 (16.7)	22.0 (15.1)	28.0 (13.0)	35.0 (13.5)	40.0 (21.6)	36 (24.3)
mBB test3 (transfers/minute)	33.7 (17.6)	19.7 (15.5)	36.0 (24.3)	34.0 (17.6)	41.3 (19.9)	37.3 (14.6)
Outcome scores: mean (SD)						
Maximun no. repetition	34.3 (28.7)	22.7 (21.2)	38.0 (26.9)	48.7 (55.2)	23.0 (24.2)	14.6 (39.3)
Hand grip (Kg)	14.5 (10.1)	8.1 (6.2)	18.5 (17.9)	21.1 (9.7)	12.1 (5.3)	12.7 (10.1)
Pinch grip (Kg)	5.1 (2.5)	4.2 (1.3)	6.2 (3.9)	7.7 (2.8)	3.4 (1.1)	4.2 (0.9)
mBBT1 (transfers/minute)	38.0 (23.7)	27.7 (22.0)	32.0 (22.7)	40.3 (16.5)	40.7 (39.4)	48.0 (26.9)
mBBT2 (transfers/minute)	39.9 (23.4)	32.3 (22.2)	34.3 (21.5)	38.7(11.8)	49.7 (37.8)	44.3 (31.9)
mBBT3 (transfers/minute)	38.9 (19.8)	32.3 (22.9)	32.7 (20.6)	40.0 (16.4)	47.0 (26.0)	42.7 (24.6)

SD = standard deviation; mBBT1= modified Box and Block test with tennis ball, mBBT2= modified Box and Block test with 2 cm cube, mBBT3= modified Box and Block test with 5 cm cube.

5.5.1 Primary analysis: design feasibility

Feasibility of the multi-stage recruitment procedure & retention rate

The trial recruitment procedure started after receiving the ethical committee consent in March 2014. The trial and recruitment procedure were stopped due to suspended activity by the stroke survivors support groups during the months of August and December and participants' holiday.

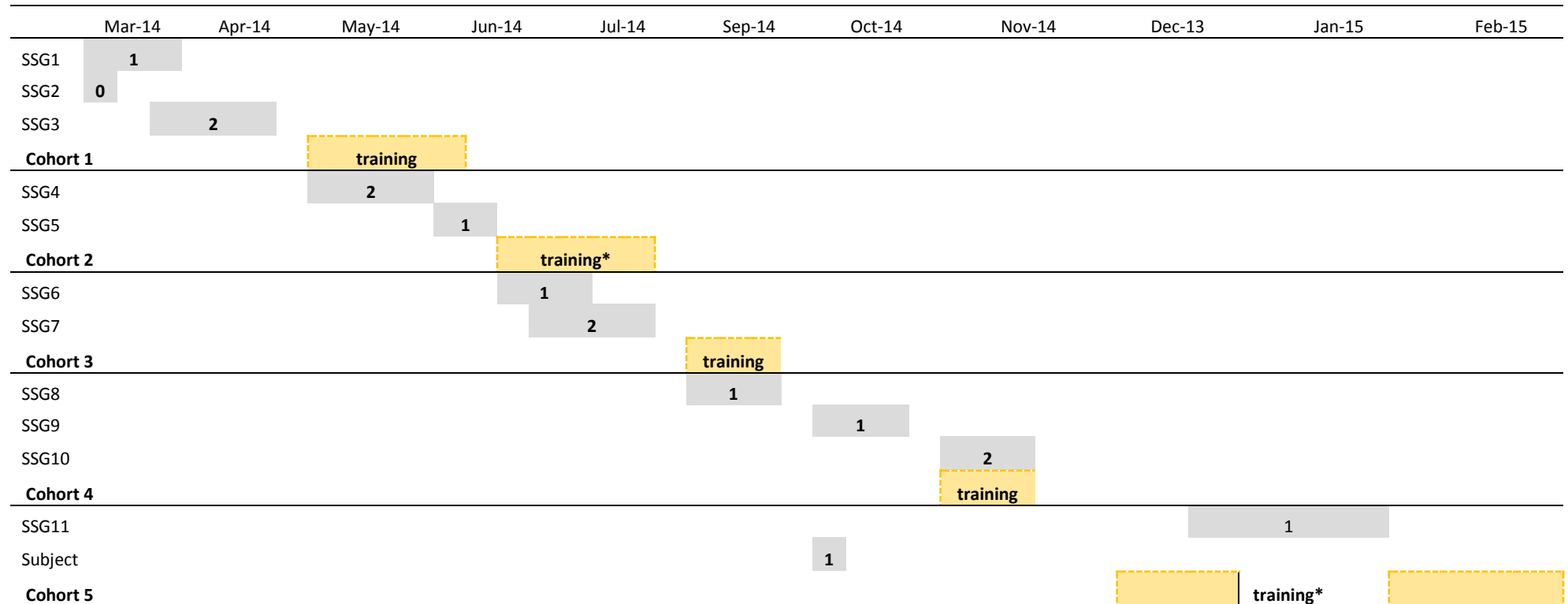
The trial data collection ended on January 2015. A following communication to the Norfolk NRES Committee East of England declared the end of study on the 28th of February 2015. Table 5-6 reports the details on the trial time frame and on the recruitment procedure.

Participants were recruited by contacting thirteen stroke survivors' support groups in the East of England region (eleven groups were located in Norfolk, one in Suffolk and one in Cambridgeshire area). Two of the thirteen stroke survivor groups refused to host a study information presentation. The administrators of these two groups reported an unpleasant experience on previous research trials.

Table 5-6 shows the flowchart of the recruitment and consent rate by stroke survivors' support groups. Approximately 185 people attended the trial presentations made by the researcher. Of these, 24 people expressed an interest and were provided with the ethically-approved information pack. Of the 24 potential participants, ten (41.7%) were excluded because they did not meet all of the study criteria. One eligible subject contacted directly the researcher expressing interest in taking part to the study and was included in the trial because they met the trial inclusion criteria. All the 15 participants provided written informed consent.

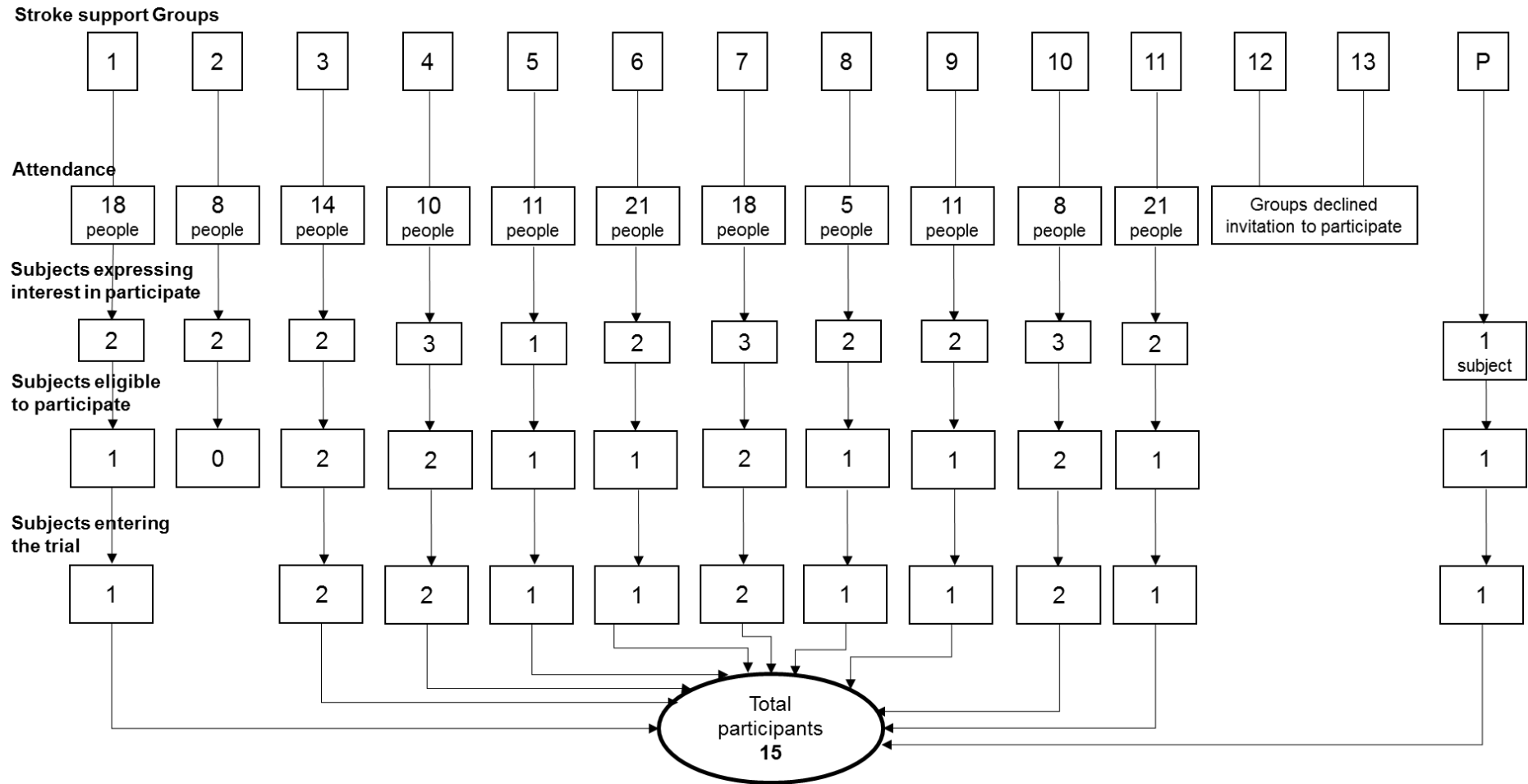
All participants were able to undertake the two weeks of intervention and the post intervention measures. Therefore, retention rate was 100%. This was perhaps due to the length of the study of two weeks and the effort made on engaging participants to the training and overall trial. The importance to adhere to the training dose was highlighted to participants in several occasions.

Table 5-6: Time frame of the recruitment and trial procedures



Notes: figure shows the time of recruitment from the first contact to the second visit for each of the SSG included in the study. The number of participants recruited by SSG is highlighted. For each study cohort the training period is highlighted in yellow. Participants of the same cohort started the trial at different days; SSG= Stroke survivor support group

Figure 5-11: Flowchart of the recruitment and consent rate by Stroke Survivors' Support Groups



Feasibility, appropriateness, and face validity of the dose-monitoring procedure

All participants provided self-reported information (SRM) on the daily number of repetitions achieved completing the dose-monitoring form. Participants also reported that the form was easy and practical to follow. The majority of participants reported no problems in using the electronic counter and therefore, in the collection of the objective measures (OBM). The electronic counter was considered by participants a useful method on tracking the high number of task repetitions undertaken.

Overall, the dose-monitoring procedures applied were considered feasible, appropriate, and valid.

However, some issues were raised by few participants on the electronic counter. Two participants raised initial concerns on the complexity of the sequential procedure needed to store data on the SD card. These issues were resolved after few days of practice. One more participant⁵⁴, reported having difficulties in using the counter for the entire duration of the trial period with the comments: *“not being able to remember”* and *“getting confused on the correct procedure to switch ON and OFF the counter”*. Counter data for this participant were sparse and often incomplete. Another participant claimed that the display was too small causing difficulties and possible errors in recording the daily number of repetitions.

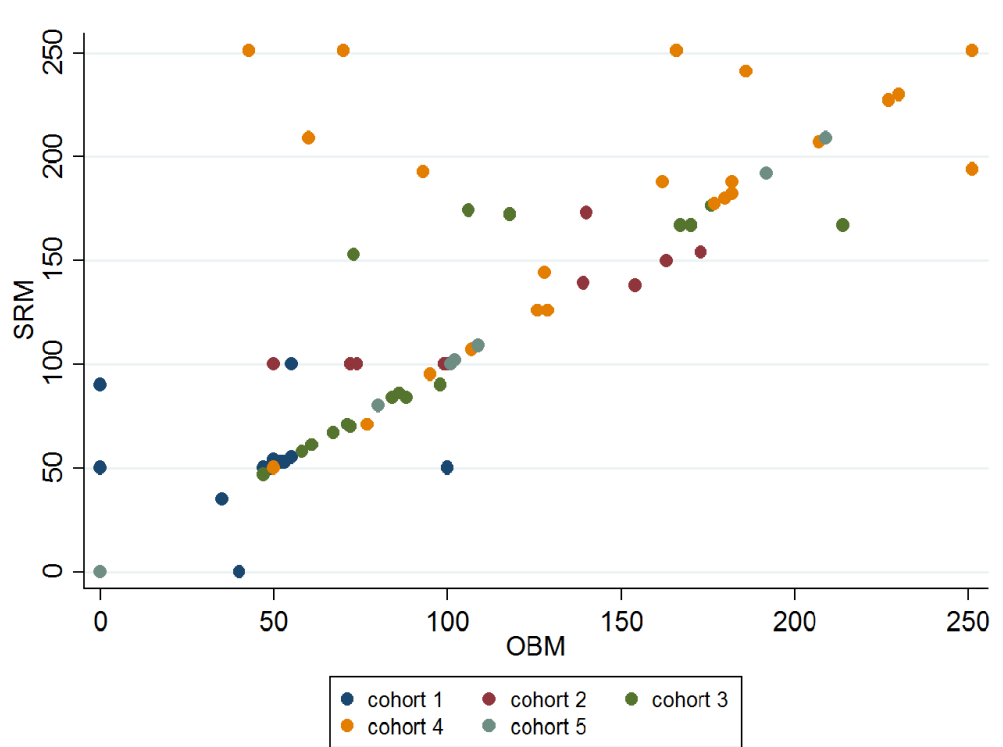
Following the rate of agreements between SRM and OBM was assessed by plotting the two measures for each observations (participant x daily observation) on a graph (SRM are on the y-axis and OBM are on the x-axis) to check how close the observation were to the line of equality. The line of equality (or identity line) was represented by the 45° line (OBM=SRM). Figure 5-12 shows an acceptable agreement between the SRM and OBM as most observations were close to the identity line. The Pearson’s correlation coefficient r was derived to estimate the

⁵⁴ DF-14.

linear correlation between the two measures. The correlation between SRM and OBM was $r= 0.86$, $p<0.001$.

Overall, participants tend to slightly self-report more exercise than those actually recorded by the counter. Table 5-7 reports the number of repetitions by cohort reported by OBM and SRM and the mean difference between these measures⁵⁵. Cohort 4 reported the greatest difference of about -31 repetitions between OBM and SRM.

Figure 5-12: Rate of agreement between Self-reported (SRM) and objective measure (OBM) measures by cohort for all participants' daily training



Notes: dots correspond to all training days for each participant enrolled in the trial. Each cohort is highlighted with a different colour. Correlation found between measure was $r=0.86$ ($p<0.001$). SRM= self-reported measure; OBM= objective measure

⁵⁵ Data on OBM for participant DF-14 (in cohort 5) were available only for five days.

Table 5-7: Mean number of repetitions by cohort reported by OBM and SRM and the mean difference between these measures.

Cohort	OBM (mean)	SRM (mean)	Mean diff. (OBM-SR)
1	44.53	48.00	-3.47
2	105.57	108.53	-2.97
3	128.32	128.66	-4.93
4	154.50	185.87	-31.37
5	128.70	128.65	0.05

Note: table shows the average number of OBM (objective measure) and SRM (self-reported measure) repetitions reported by cohorts. The differences between the two means are reported on the right column, the greater difference is highlighted in red.

Appropriateness of the outcome-adaptive dose escalation and dose de-escalation procedure

The outcome-adaptive procedure and algorithm were implemented in this trial and setting with no emerging issues.

The starting dose of 50 daily repetitions was found feasible for all three participants (cohort 1).

Application of the mFBS and the dose de-escalation procedure determined discernibly different dose for subsequent cohorts (i.e. differences above 10% between subsequent cohorts). In detail, the training dose was escalated in the three subsequent cohorts, with an increment of 100% (2d₁, 100 daily repetitions), 67% (1.67d₂, 167 daily repetitions) and 50% (1.5d₃, 251 daily repetitions), respectively. The fourth dose (251 daily repetitions) become not feasible for all three participants. Consequently, the dose de-escalation procedure was used to define the dose for the following (fifth) cohort (decreased by 50% of the previous increment, 209 daily repetitions). This new dose level was feasible but then, the trial met a stopping rule as the dose for the sixth cohort would have been less than 10% difference between the dose above (see chapter 4, section 4.5 for detail on stopping rules).

Feasibility of the trial predefined rules on dose feasibility and dose efficacy, dose checking and trial stopping rules

The predefined trial rules were all clear, unambiguous and implemented without any issue. Checking rules were not required during this study. (See details on trial rules in chapter 4)

Adherence to the target dose was important for the application of the trial rules for feasibility and efficacy. Table 5-8 provides details of individuals' adherence to the target dose and change in primary and secondary measures from pre to post intervention.

In summary, all participants in cohorts 1 and 2 adhered to the assigned dose and only one participant in cohort 1 did not show at least 10% improvement from pre intervention on the selected primary measure (treatment efficacy). Therefore, the dose was increased after both cohorts.

Cohort 3 had a target dose of 167 daily repetitions. One participant of cohort 3 did not adhere (mean number of repetitions=73) but all three experienced improvements well above 10% level on the selected primary measure (range 60.9% to 600%). The dose was therefore increased to 251 repetitions for cohort 4 in accordance with the trial predefined rules.

In cohort 4 all three participants were not adherent to the assigned dose. Although they showed improvement well above the 10% level, the dose was decreased by 50% of the previous increment for cohort 5 (dose de-escalation procedure).

In cohort 5 only one participant was not adherent to the assigned dose of 209 daily repetitions and two participants had improvement above the 10% level. One participant experienced a negative change above 10% level (-25.0%).

Following the trial rules, the dose for the subsequent cohort 6 should increase by 67% of the previous increment equal to 237 daily repetitions. But this difference in dose between two subsequent doses ($251-237=14$ repetitions) is lower than 10%. Thus, the trial was stopped at cohort 5 because a stopping rule was verified.

Table 5-8: Individuals' adherence to target dose and change in primary and secondary measures from pre to post intervention

Cohort	Participant	Target dose (repetitions)	Repetitions performed (mean by OBM)	Dose feasible	Primary outcome Max number repetitions Cando-Digit Extend % change from baseline	Dose efficacious	Hand grip ^a % change from baseline	Pinch grip ^a % change from baseline	mBBT1 ^b % change from baseline	mBBT2 ^b % change from baseline	mBBT3 ^b % change from baseline
1	DF-01		51		27.3		45.0	5.9	35.9	46.2	56.8
	DF-02	50	54	Yes	0	Yes	75.0	-7.7	-6.7	40.0	100.0
	DF-03		56		44.4		-9.1	-13.2	-15.8	52.9	66.7
2	DF-04		127		17.9		2.3	0.0	10.0	14.3	19.0
	DF-05	100	100	Yes	91.4	Yes	103.6	47.6	93.3	37.2	-12.5
	DF-06		100		16.7		0.0	-25.0	23.1	0.0	-26.1
3	DF-07		170		480		39.1	2.4	29.0	48.4	63.0
	DF-08	167	172	Yes	60.9	Yes	-5	42.2	1.8	-10.0	0.0
	DF-09		73		600		21.4	34.8	4.3	4.2	4.8
4	DF-10		217		32.4		0	-7.3	59.3	55.2	28.1
	DF-11	251	163	No	100	NA	89.8	-18.7	-36.4	-4.3	-2.1
	DF-12		140		35.7		13.1	29.7	7.1	-6.3	10.5
5	DF-13		209		13.9		-5.0	24.7	31.7	26.6	31.5
	DF-14	209	207	Yes	-25.0	Yes	30.4	-13.8	-12.8	15.0	0.0
	DF-15		72		76.7		2.7	49.8	6.9	20.8	-3.2

Notes: OBM= objective measure (electronic counter); mBBT1= modified Box and Block test with tennis ball; mBBT2= modified Box and Block test with 2 cm cube; mBBT3= modified Box and Block test with 5 cm cube. (a) = (kg); (b)= transfer per minute

Feasibility to identify the selected dose endpoints

The feasibility to identify the MTD and the RPTD by plotting dose-response curves is explored in detail in the following section.

5.5.2 Rehabilitation relevance of the dose optimisation information provided

The MTD was derived from the analysis on dose feasibility. Counter measures (OBM) were used to assess participants' adherence to the assigned daily training dose (*dose feasibility*) because thought to be more objective.

The OBM was not available for participant DF-14. For this participant SRM were used instead as it was showed in section 7.5.1 that these were very close.

Participants' adherence rate (R) to the assigned daily dose was derived as the absolute value (ABS) of the ratio between the daily achieved dose ($D_{achieved}$) by participant and the daily assigned dose ($D_{assigned}$):

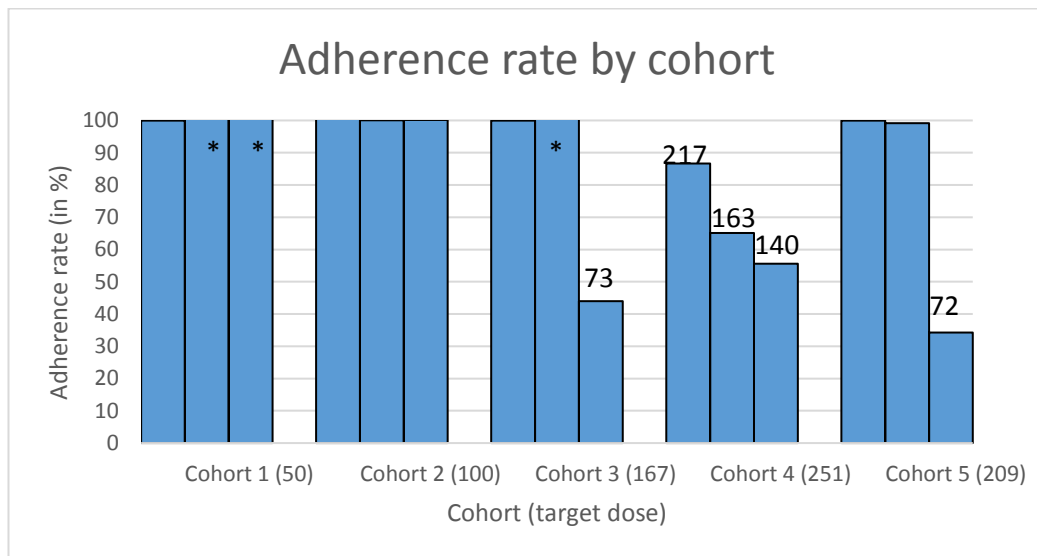
$$R = \left[ABS \left(\frac{D_{assigned} - D_{achieved}}{D_{assigned}} - 1 \right) \right] \times 100 = ABS \left(- \frac{D_{achieved}}{D_{assigned}} \right) \times 100$$

Using this formula, adherence rate was equal to 0 when $D_{achieved}=0$ and 100 when $D_{achieved}= D_{assigned}$. It should be notices that R could also be greater than 100 if the participant exercised more than required ($D_{achieved}>D_{assigned}$).

Figure 5-13 reports R for each participants in all 5 cohorts, flattened at 100% to ease reading of the results⁵⁶. The mean number of daily repetitions achieved in the training period is shown in the graph for those who did not adhere to the assigned daily dose.

⁵⁶ Figure 7-1 in the Appendix K reports participants' adherence rates with no adjustment at 100%. The figure also includes the mean number of daily repetitions achieved in the training period of two weeks for each participants.

Figure 5-13: Participants' adherence rates (in %) by cohort flattened at 100%



Notes: the vertical bars reports adherence rate to the assigned dose; the x bar reports cohort of study and numbers of assigned repetitions (in parenthesis). Figures above the bars shown average number of daily repetitions achieved in the training period for participants who did not adhere. (*) highlights participants who were considered adherent but did not fully compliant with the target dose for reasons not related to the trial or the dose.

The adherence rates (R) for the first two cohorts was 100%. In cohort 3 two participants adhered to the assigned dose whereas one participant achieved only 44% of the assigned dose (assigned dose= 167 repetitions, mean achieved repetitions= 73). None of the participants of cohort 4 adhered to the assigned dose of 251 daily repetitions, achieving on average 217; 163 and 140 daily repetitions, respectively. One participant of this cohort (ID=10) was not adherent to the target dose on the first four days of training. Two participants of cohort 5 adhered to the assigned lowered dose of 209 repetitions. One participant achieved only 34% of the assigned daily dose (on average 72 daily repetitions achieved).

In this feasibility study for the model task applied, the *maximal tolerable dose* was found to be about 209 daily repetitions.

Changes from pre to post intervention on primary and secondary outcome measures were used to derive the *dose-response relationships* and the resultant *recommended phase II dose* of the model task applied. Two parametric models (linear and quadratic) and a non-parametric one (see chapter 4 for justification)

were fitted on these data. The mathematical models were used to study the trial dose-response curve and to graphically show the associations between dose and intervention effect.

Primary efficacy measure: the RPTD

Figure 5-14 shows the dose-response relationships derived using the Cando Digit-Extensor measure test part A⁵⁷, using the three statistical models. In the x-axis it is reported the overall daily number of repetitions obtained from the OBM (panel a), the SRM (panel b) and the trial target repetitions (assigned dose) ($D_{assigned}$) (panel c).

Figure 5-14 shows that the three analyses on participants' changes on the primary measure (test part A) provide similar results, no matter the way in which repetitions are included in the analysis.

The mathematical model that fitted the data best was the *quadratic one*, according to the goodness-of-fit statistic (R^2). The highest training effect observed from this analyses, which represented the vertex of the curve, lied at 162 daily repetitions. In this feasibility study this dose level would represent the potential recommended phase II dose for the model-task applied (RPTD).

Table 5-9 reports participants' maximum number of repetitions achieved with the Cando Digit-Extensor test part A at pre (baseline) and post intervention (outcome). The changes on the measure from baseline for all participants and by cohort are reported in the table.

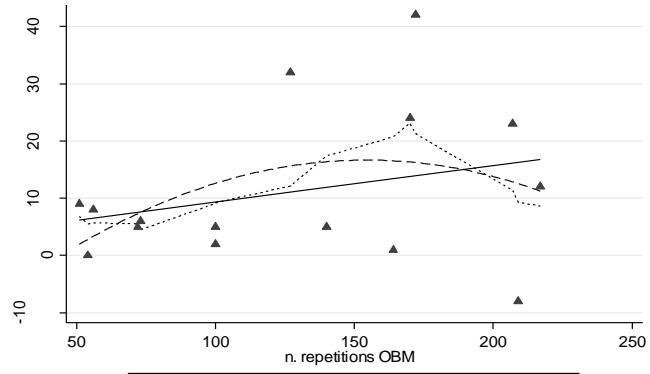
Participants' changes on part B⁵⁸ of the primary measure are reported in Table 5-10.

⁵⁷ Changes assessed in the maximal number of repetitions achieved by each participant from pre intervention.

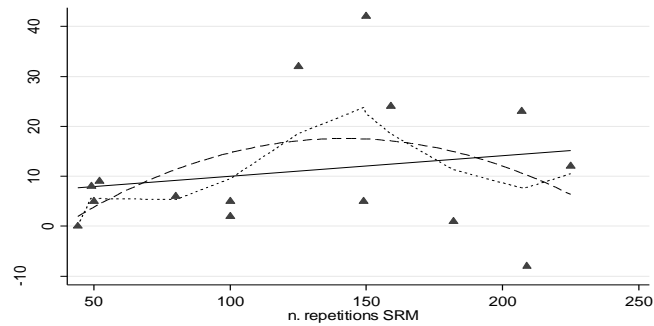
⁵⁸ Test B on the primary outcome assessed the highest level of resistance against which participants were able to extend their fingers and thumb of their paretic hand twice in one minute.

Figure 5-14: Trial dose-response relationships of primary measure change from baseline and mean number of daily repetitions for all participants in the trial.

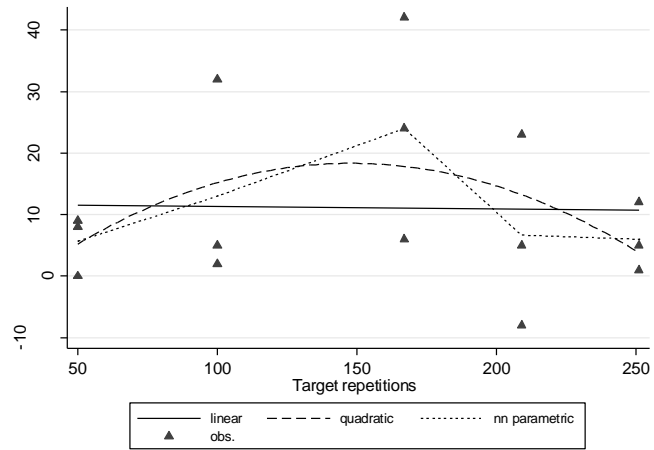
a)



b)



c)



Notes: triangles (Obs.) represent the participants' mean daily repetitions. The solid, dashed and dotted lines refer respectively to the linear, quadratic and non-parametric mathematical models fitted to the data. (a) shows the dose-response relationships derived using the OBM (linear $r^2 = 0.08$ and quadratic $r^2 = 0.15$); (b) shows the dose-response relationships derived using SRM (linear $r^2 = 0.04$ and quadratic $r^2 = 0.18$); and (c) shows the dose-response relationships using the trial assigned dose (linear $r^2 = 0.00$ and quadratic $r^2 = 0.18$).

Table 5-9: Changes on part A of the primary outcome from baseline for all participants on the trial

Cohort	Participant	Baseline ^a	Outcome ^a	Difference ^a from baseline	Mean difference by cohort	% change from baseline
1	DF-01	33	42	9	5.67	27.3
	DF-02	0	0	0		0.0
	DF-03	18	26	8		44.4
2	DF-04	28	33	5	13.00	17.9
	DF-05	35	67	32		91.4
	DF-06	12	14	2		16.7
3	DF-07	5	29	24	24.00	480.0
	DF-08	69	111	42		60.9
	DF-09	0	6	6		600.0
4	DF-10	37	49	12	6.00	32.4
	DF-11	0	1	1		100.0
	DF-12	14	19	5		35.7
5	DF-13	36	41	5	6.67	13.90
	DF-14	32	24	-8		-25.00
	DF-15	30	53	23		76.70

Note: a= maximum number of repetitions

Table 5-10: Changes on part B of the primary measure from pre (baseline) to post intervention (outcome) for all participants in the trial

Cohort	Participant	Baseline ^a	Outcome ^a	Difference from baseline ^a
1	DF-01	10	10	0
	DF-02	0	0	0
	DF-03	10	10	0
2	DF-04	10	10	0
	DF-05	10	10	0
	DF-06	2	2	0
3	DF-07	10	10	0
	DF-08	10	10	0
	DF-09	10	4	-6
4	DF-10	10	10	0
	DF-11	0	1	1
	DF-12	5	7	2
5	DF-13	10	10	0
	DF-14	6	8	2
	DF-15	10	10	0

Notes: a= number of repetitions; negative changes are highlighted in red. Participants who scored 10/10 points at pre (baseline) and post intervention (outcome) are highlighted in bolt.

Nine participants out of fifteen scored ten points, the highest possible value, at both assessment points (highlighted in bolt). Eleven participants did not see any change between pre and post intervention. One participant (DF-09) saw a decrease in the level of resistance achieved after the intervention period (highlighted in red). Unfortunately, the low sensitivity to changes and low ceiling effect showed by this measure precluded any further analysis on these data.

Secondary efficacy outcomes

Aim of this analysis was to explore whether secondary outcomes provided different results in the dose-response relationship and, consequently, in the RPTD.

The analysis was made using OBM⁵⁹ data. SRM data (not reported but available on request) confirmed OBM results, in line with what shown for the primary measure.

Upper limb Strength tests

Participants undertook each strength tests (hand grip and pinch tests) for three times. The average of these three trials was used for the analysis.

Table 5-11 and Table 5-12 show the pre (baseline) and post intervention (outcome) scores for the hand grip test and the pinch grip test by all participants respectively. Changes from pre intervention are reported as numerical differences as well as percentage (%) changes.

⁵⁹ For all participants OBM were used apart from participant DF-14 where SRM data were used instead.

Table 5-11: Hand grip strength test by all participants in the trial

Cohort	Participant	Baseline ^a (mean)	Outcome ^a (mean)	Difference ^a from baseline	% change from baseline
1	DF-01	6.7	9.7	3.0	45.0
	DF-02	0.7	1.2	0.5	75.0
	DF-03	14.7	13.3	-1.3	-9.1
2	DF-04	14.7	15	0.3	2.3
	DF-05	18.7	38	19.3	103.6
	DF-06	2.7	2.7	0.0	0.0
3	DF-07	15.3	21.3	6.0	39.1
	DF-08	32.3	30.7	-1.7	-5
	DF-09	9.3	11.3	2.0	21.4
4	DF-10	18.7	18.7	0.0	0
	DF-11	1.7	3.2	1.5	89.8
	DF-12	12.7	14.3	1.7	13.1
5	DF-13	9.8	9.3	-0.5	-5.0
	DF-14	7.7	10	2.3	30.4
	DF-15	18.3	18.8	0.5	2.7

Note: a= Kg

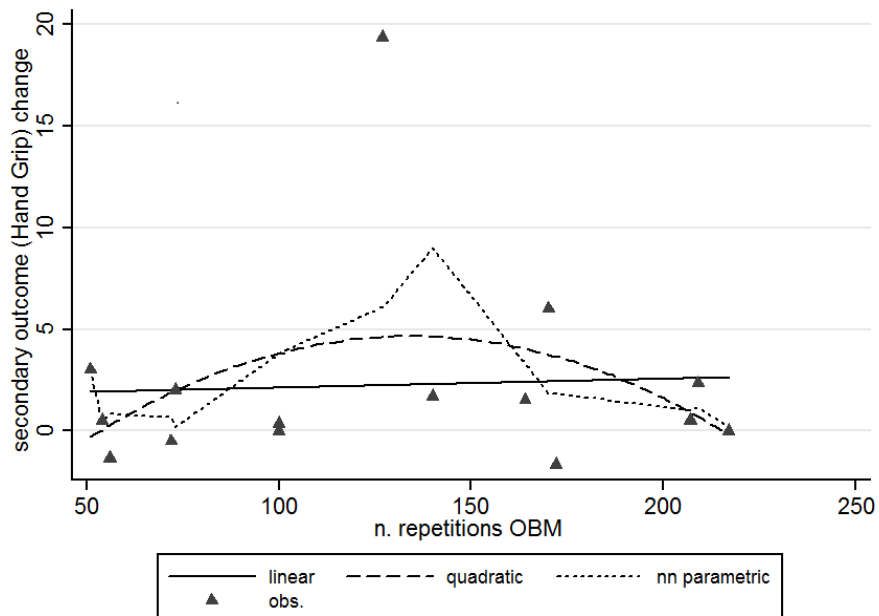
Table 5-12: Pinch grip strength test by all participants in the trial

Cohort	Participant	Baseline ^a	Outcome ^a	Difference ^a from baseline	% change from baseline
1	DF-01	2.8	3.0	0.2	5.9
	DF-02	4.3	4.0	-0.3	-7.7
	DF-03	6.3	5.5	-0.8	-13.2
2	DF-04	5.8	5.8	0.0	0.0
	DF-05	7.0	10.3	3.3	47.6
	DF-06	3.3	2.5	-0.8	-25.0
3	DF-07	7.0	7.2	0.2	2.4
	DF-08	7.5	10.7	3.2	42.2
	DF-09	3.8	5.2	1.3	34.8
4	DF-10	4.7	4.3	-0.3	-7.3
	DF-11	2.7	2.2	-0.5	-18.7
	DF-12	2.8	3.7	0.8	29.7
5	DF-13	2.7	3.3	0.7	24.7
	DF-14	6.0	5.2	-0.8	-13.8
	DF-15	2.7	4.0	1.3	49.8

Note: a= Kg

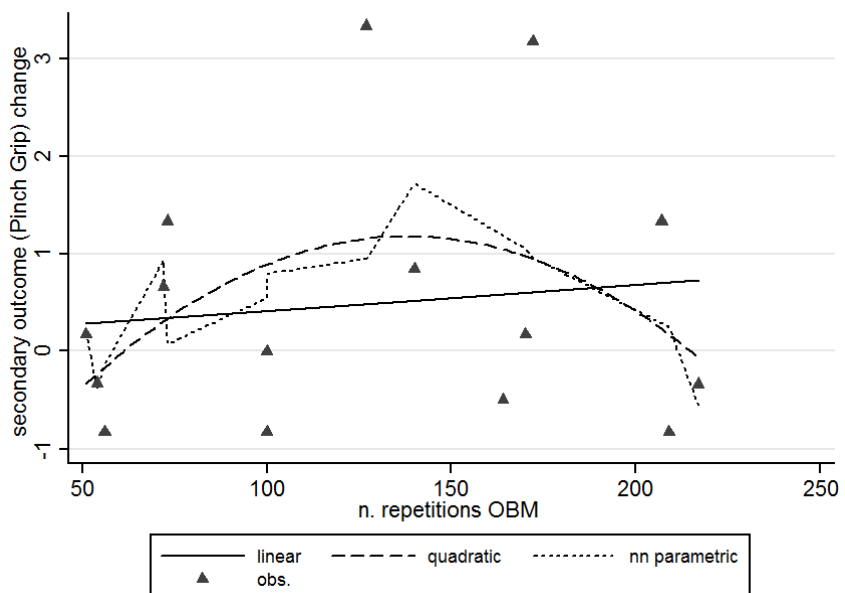
Figure 5-15 and Figure 5-16 show the dose-response relationships derived using changes from pre to post intervention and OBM on the hand grip strength and pinch grip tests respectively.

Figure 5-15: Trial dose-response relationships of changes from baseline on the hand grip strength test and mean number of daily repetitions for all participants.



Notes: triangles (Obs.) represent the participants' mean daily repetitions observed by OBM. The solid, dashed and dotted lines refer respectively to the linear, quadratic and non-parametric mathematical models fitted to the data.

Figure 5-16: Trial dose-response relationships of changes from baseline on the pinch grip strength test and mean number of daily repetitions for all participants.



Notes: triangles (Obs.) represent the participants' mean daily repetitions observed by OBM. The solid, dashed and dotted lines refer respectively to the linear, quadratic and non-parametric mathematical models fitted to the data.

The analysis on participants' upper limb strength changes from pre to post intervention from hand grip and pinch grip tests confirmed that a *quadratic interpolation* fitted the dose-response relationship best. The higher outcome, curve vertex, was observed as 134 daily repetitions for the Hand Grip test and 138 daily repetitions for the Pinch Grip test. This would represent the potential RPTD for the applied model-task.

Modified Box and Block tests

Table 5-13 shows the changes from pre (baseline) and post intervention (outcome) on the three mBB tests⁶⁰ for all participants and the mean tests changes by cohort.

Figure 5-17 shows the dose-response relationships derived using participants' changes from baseline on the mBBT1 (panel a), mBBT2 (panel b), and mBBT3 (panel c), by the mean daily number of repetition from OBM. From this analysis it could be observed that the three tests provided seemingly different dose response relationships.

A *quadratic form* seemed to fit better the dose-response relationship for the mBBT1 (panel a), with a higher outcome observed around 130 daily repetitions. This would represent the potential RPTD. However, the reduced curvature of the quadratic form pointed out the relatively small estimated variation of mBBT1 by number of repetitions. This was also confirmed by an almost flat line depicted from the linear interpolation⁶¹.

Results from mBBT2 (panel b) showed a non-statistically significant relationship of this outcome according the number of repetitions, determining a flat dose-response relationship. In this case, a linear interpolation fitted better the data, but the coefficient associated to the number of repetitions (and then the slope of the line) was not significantly different from zero at conventional significance

⁶⁰ mBBT1=tennis ball test; mBBT2=2 cm cube test; and mBBT3=5 cm cube test.

⁶¹ The coefficient associated to number of repetition of the linear model was not significant at conventional levels.

level. Since the RPTD would be the minimum dose associated with the highest outcome, results would suggest inefficacy of the therapy.

For the mBBT3 (panel c) a *quadratic form* obtained the best fit in a statistical point of view. The estimated parameter associated with the quadratic term of dose was negative, implying a concave down parabola. Since the RPTD would be the minimum dose associated with the highest outcome, results would suggest inefficacy of the therapy. In support of this result, the estimated slope from the linear model was negative, meaning that more therapy was associated with lower outcomes.

A summary of the trial dose endpoints found by primary and secondary outcomes is reported in Table 5-14.

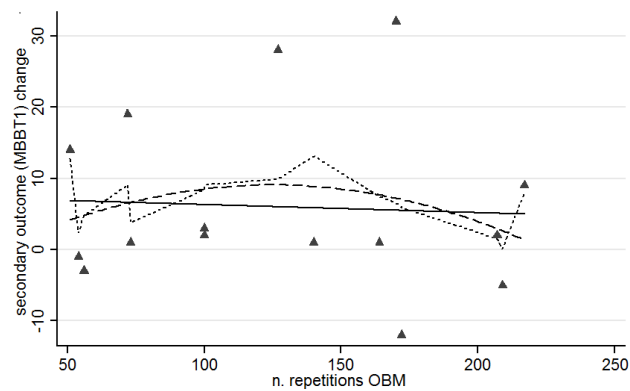
Table 5-13: Modified Box and Block tests (mBBT1- mBBT2- mBBT3) changes from baseline by all participants and by cohort

mBBT1 ^a					mBBT2 ^a					mBBT3 ^a				
Baseline	Outcome	Diff. from baseline	% change from baseline	mean diff. by cohort	Baseline	Outcome	Diff. from baseline	% change from baseline	mean diff. by cohort	Baseline	Outcome	Diff. from baseline	% change from baseline	mean diff. by cohort
39	53	14.0	35.9		39	57	18.0	46.2		37	58	21.0	56.8	
15	14	-1.0	-6.7	3.3	10	14	4.0	40.0	10.3	7	14	7.0	100.0	12.7
19	16	-3.0	-15.8		17	26	9.0	52.9		15	25	10.0	66.7	
20	22	2.0	10.0		21	24	3.0	14.3		21	25	4.0	19.0	
30	58	28.0	93.3	11.0	43	59	16.0	37.2	6.3	64	56	-8.0	-12.5	-3.3
13	16	3.0	23.1		20	20	0.0	0.0		23	17	-6.0	-26.1	
31	40	9.0	29.0		31	46	15.0	48.4		27	44	17.0	63.0	
56	57	1.0	1.8	3.7	50	45	-5.0	-10.0	3.7	54	54	0.0	0.0	6.0
23	24	1.0	4.3		24	25	1.0	4.2		21	22	1.0	4.8	
54	86	32.0	59.3		58	90	32.0	55.2		57	73	16.0	28.1	
33	21	-12.0	-36.4	7.0	46	44	-2.0	-4.3	9.7	48	47	-1.0	-2.1	5.7
14	15	1.0	7.1		16	15	-1.0	-6.3		19	21	2.0	10.5	
60	79	19.0	31.7		64	81	17.0	26.6		54	71	17.0	31.5	
39	34	-5.0	-12.8	5.3	20	23	3.0	15.0	8.3	27	27	0.0	0.0	5.3
29	31	2.0	6.9		24	29	5.0	20.8		31	30	-1.0	-3.2	

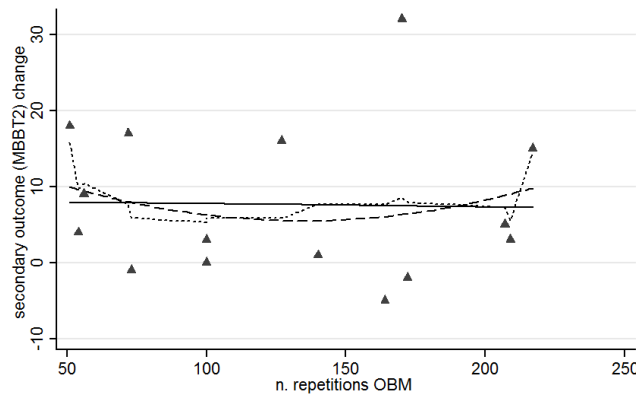
Notes: participants' changes from baseline are reported as numerical differences as well as % changes. A = transfer per minute; mBBT1= modified Box and Block test 1 with tennis ball; mBBT2= modified Box and Block test 2 with 2 cm cube; mBBT3= modified Box and Block test 3 with 5 cm cube.

Figure 5-17: Trial dose-response relationships derived from the three mBB tests

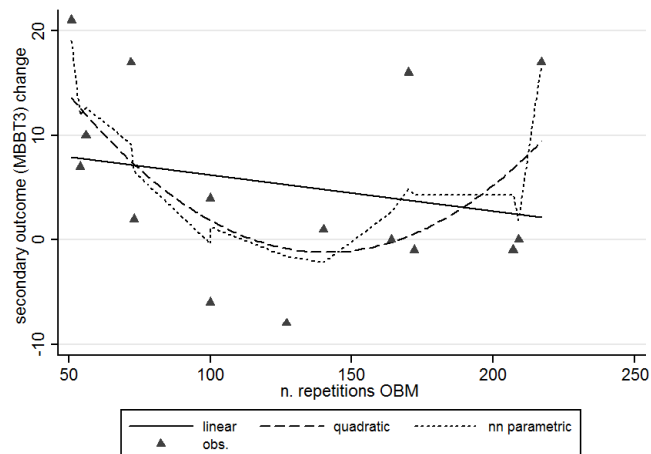
a)



b)



c)



Notes: triangles (Obs.) represent the participants' mean daily repetitions by OBM. The solid, dashed and dotted lines refer respectively to the linear, quadratic and non-parametric mathematical models fitted to the data on mBBTs changes from baseline. (a) shows the dose-response relationships derived from mBB test 1; (b) shows the dose-response relationships derived from mBB test 2; (c) shows the dose-response relationships derived from mBB test 3.

Table 5-14: Trial dose endpoints by primary and secondary outcomes

Outcome	MTD	RPTD
Primary outcome		
CandoDigit-Extensor ^a	209	162
Secondary outcome		
Hand grip test ^b	n.a.	134
Pinch grip test ^b	n.a.	138
mBBT1 ^c	n.a.	130
mBBT2 ^c	n.a.	NN
mBBT3 ^c	n.a.	NN

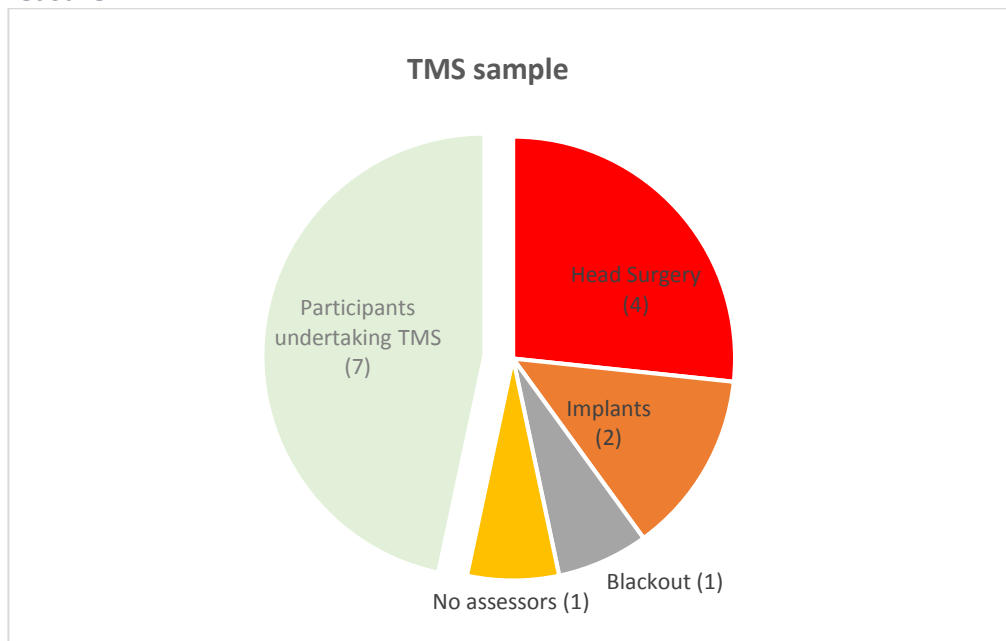
Notes: MTD= maximal tolerable dose; RPTD= recommended dose for further studies; mBBT1= modified Box and Block test 1 with tennis ball; mBBT2= modified Box and Block test 2 with 2cm cube; mBBT3= modified Box and Block test 3 with 5cm cube; a= Maximum number of repetitions; b= Kg; c= transfer per minute; n.a. not applicable.

Non-invasive neuroimaging tool: Transcranial Magnetic Stimulation

It was possible to retrieve TMS data only for seven participants out of fifteen (46.7%). Participants undertaking TMS were spread among cohorts as follow: two in cohort 1; two in cohort 2, and one participant in each of the remaining cohorts (cohort 3, 4 and 5). Among participants receiving TMS measure, it was well tolerated with no reported complains.

TMS was contraindicate for seven participants and one participant did not undertake the measure due to assessor annual leave. Figure 5-18 highlights the reasons for not undertaking the measure among the entire trial sample.

Figure 5-18: Trial sample undertaking TMS and reasons for not undertake the measure

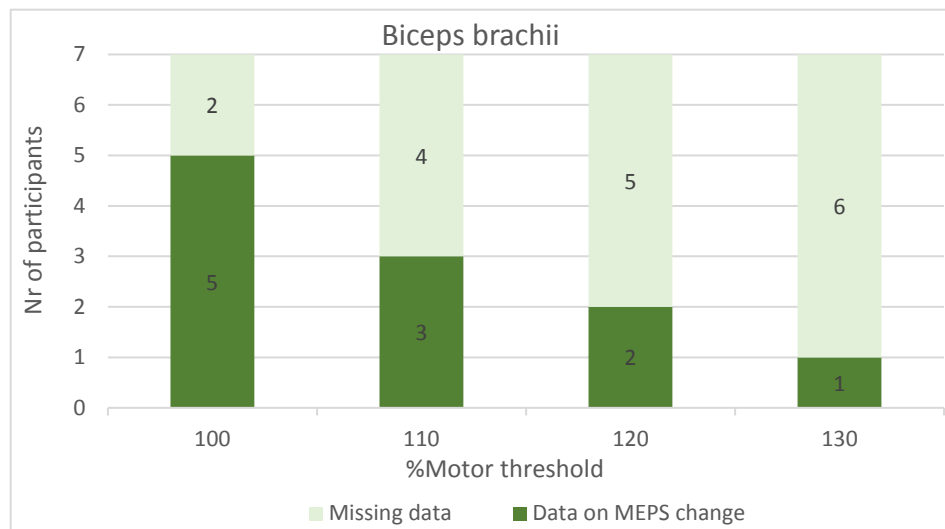


Note: the pie chart highlights the reasons for not undertaking the TMS measure and the number of participants for each reasons is in brackets.

As reported from Figure 5-19 to Figure 5-21, data on MEPS amplitude were further limited as the TMS stimulus gets bigger (MEP amplitude in response to supra-threshold stimulus). This because the resting motor threshold for stroke survivors had to be higher because the size of the TMS response is smaller than in healthy people [58]. This was observed for all the three examined muscles in general, and for the biceps brachii in particular (see Figure 5-19).

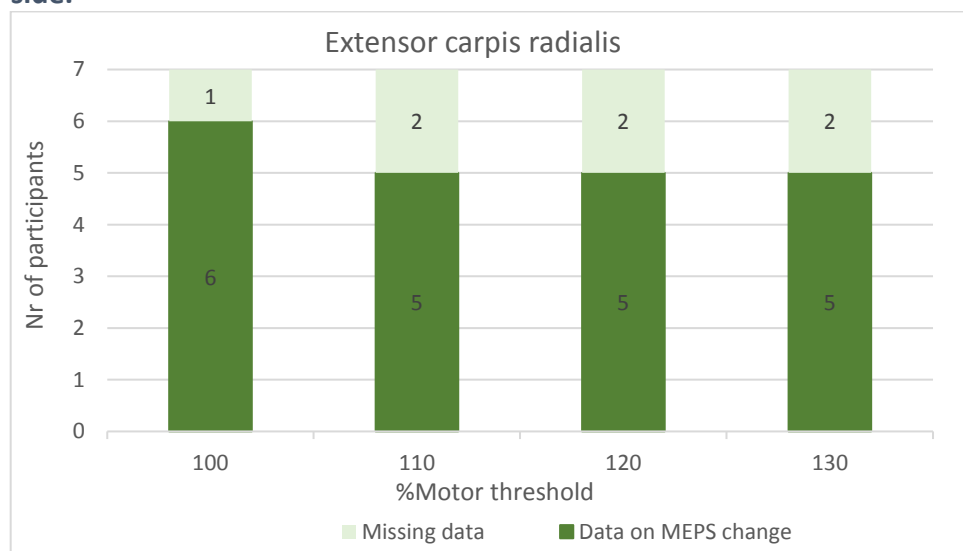
It was therefore, not possible to use TMS data in this dose-finding study. All data and analyses on TMS are confined in Appendix L.

Figure 5-19: Data availability on biceps brachii muscle MEPS amplitude changes from pre intervention by % of the motor threshold stimulus on affected side.



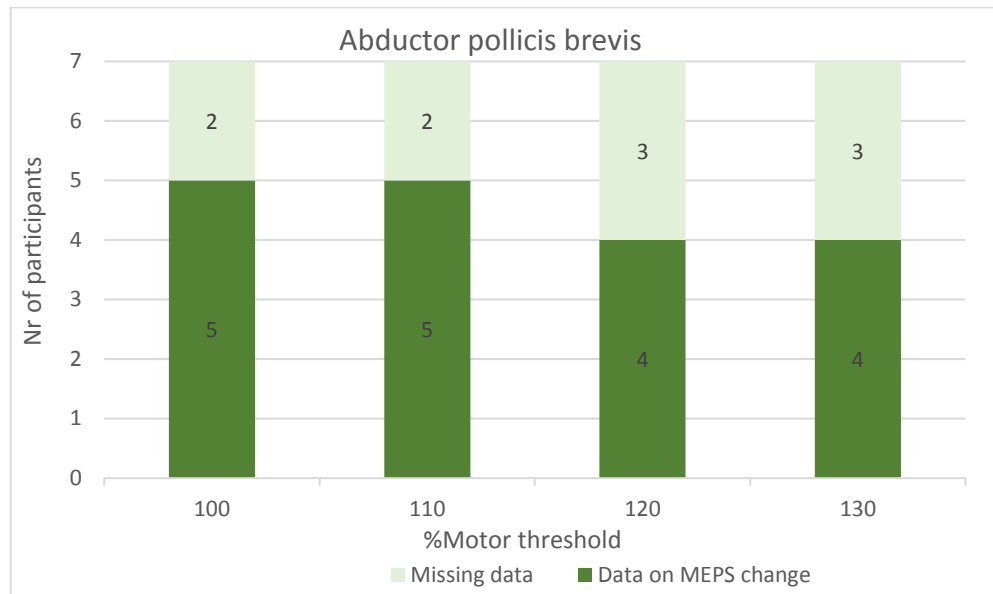
Notes: bars represents availability of TMS data by % of the motor threshold (dark bar sections) on the sample of participants undertaking TMS (7 total participants).

Figure 5-20: Data availability on extensor carpi radialis muscle MEPS amplitude changes from pre intervention by % of the motor threshold stimulus on affected side.



Notes: bars represents availability of TMS data by % of the motor threshold (dark bar sections) on the sample of participants undertaking TMS (7 total participants).

Figure 5-21: Data availability on abductor pollicis brevis muscle MEPS amplitude changes from pre intervention by % of the motor threshold stimulus on affected side.



Notes: bars represents availability of TMS data by % of the motor threshold (dark bar sections) on the sample of participants undertaking TMS (7 total participants).

Training session duration (time)

Table 5-15 shows the mean duration of the daily sessions in minutes (self-reported) for all participants and by cohorts. Ten participants (66.7%) exercised for less than an hour per day. All three participants of cohort 4, who did not adhere to the 251 daily repetitions, spent a lot more than an hour exercising with on overall average of 164.5 minutes a day of training.

Table 5-15: Mean duration (in minutes) of daily training session by all participants and cohorts.

Cohort (dose)	Participant	Mean time (mins)	Mean time by cohort (mins)
Chort 1 (50)	DF-001	96.5	56.6
	DF-002	45.0	
	DF-003	28.3	
Chort 2 (100)	DF-004	53.9	43.8
	DF-005	28.8	
	DF-006	48.6	
Chort 3 (167)	DF-007	56.0	37.0
	DF-008	24.0	
	DF-009	30.9	
Chort 4 (251)	DF-010	77.3	164.5
	DF-011	328.0	
	DF-012	88.1	
Chort 5 (209)	DF-013	59.0	60.1
	DF-014	82.2	
	DF-015	39.0	

Notes: participants who exercised for less than an hour were highlighted in bold. In red is highlighted the cohort which exercise in average more than an hour.

Sample size

The trial involved five cohorts with a final sample size of 15 participants. These numbers are in line with existing literature on dose optimization in pharmaceutical research (see chapter 3). The cohorts' size appeared appropriate to guide the trial algorithm through the dose escalation and de-escalation procedures.

5.6 Discussion

All the operating characteristics of this feasibility phase I dose-finding trial were found feasible using the applied model-task intervention among moderately impaired stroke survivors.

The multi-stage recruitment was feasible and allow the recruitments of the needed sample. However, for the sequential feature of this process, the time required for the recruitment should be carefully considered and optimized in order to minimize *idle times* between cohorts.

The time commitment needed for the trial interim analyses (decision making processes between subsequent cohorts) was feasible in a clinical setting and doable in the foreseen time frame.

The dose-monitoring procedures were feasible and able to provide data on participants' achieved training dose. We found a high level of consistency between self-reported and objective measures of training dose and therefore both were appropriate to monitor it. However, participants welcomed the use of an electronic counter to keep track on the number of repetitions undertaken during daily training sessions. We do not exclude the possibility that measures from the electronic counter were used by participants' in their self-reported activity.

Although the trial task was a model-intervention task, it was meaningful to participants because they could see the relationship to letting go of objects, an issue often experienced by stroke survivors and difficult to exercise in the everyday activities. This promoted motivation to self-practice, with potential beneficial effects in enhancing dose adherence.

The definition of the training dose (number of daily repetitions x intensity) was appropriate and unambiguous. It was feasible to set, manipulate and control all the characteristics of the training dose (amount and intensity) and protocol (frequency and total length of the training) for all participants. This has limited the ambiguity in the dose-response relationship and has enhanced the reliability of the dose optimization process.

The applied predefined trial rules were appropriate to guide the trial algorithm to target dose endpoints. The implementation of feasibility rules, alongside with efficacy rules appeared meaningful to motor interventions because investigating two key aspects of the training dose. The proportions used to define feasible and efficacious doses -the dose had to be feasible/effective for at least two of the

three participants in a cohort ($\geq 66\%$ of the cohort) with no more than one participant experiencing an adverse reaction ($\leq 33\%$ of the cohort)- appeared balanced to guarantee meaningful results for motor interventions, and preserve participants' safety.

The outcome-adaptive dose escalation and de-escalation procedure provided discernibly different target doses for subsequent cohorts. Dose increments and decrements were adequately spaced to the purposes of this trial. Dose increments were larger at the beginning to avoid sub-therapeutic dose and then, smaller to target the dose endpoints with more precision. The use of a de-escalation procedure, not commonly contemplated in pharmaceutical studies given the assumption that the outcome is a monotonic increasing function of dose, allowed to closely target the dose endpoints.

Two weeks of training were considered enough to test the feasibility of the phase I trial providing indication of the changes brought by the training dose. Other evidence reported changes in motor functions from two weeks of therapy [257,258,259]. It is possible that two weeks of training could be not enough to depict the efficacy of a rehabilitative intervention. However, the changes measured in this dose-finding study has to be considered as intermediate endpoints promising for further significant changes as it happen in other medical fields and pharmaceutical research [230].

In this respect it is also important to note that all the outcomes (primary and secondary) which assessed changes at the impairment level (strength) showed similar dose-response relationship curves. On the other hand, results from the modified Box and Blocs tests, which assessed changes in the functional level, were less clear. This could imply the limited transferability of the model-task intervention on a functional level, or suggesting that a longer training period may be required to observe relevant changes on a functional level.

This trial involved 5 cohorts, with a final sample size of 15 participants. This sample size could appear small comparing to trials evaluating the efficacy of rehabilitative intervention. Although more confirmatory data are needed, in particular on how to obtain homogeneous and balanced cohorts in small sample

studies, cohorts of three participants seemed adequate to guide the trial algorithm through the dose escalation and de-escalation procedure. This is promising for efficient studies in stroke rehabilitation where recruiting large samples is challenging. However, the underlying assumption – also common in pharmaceutical research - that individual’s responses to the treatment dose are fairly similar might deserve further consideration.

This trial was able to provide information on doses. Acknowledging that the purpose of this trial was to test the feasibility and informative nature of the design and not to evaluate the model-task intervention as a potential intervention or to use the numerical data further, sufficient data were provided from this trial to derive the targeted dose endpoints (the maximal tolerable dose and the recommended phase II dose) and to explore the intervention dose-response relationship through statistical modelling. Holding the needs for more research, due to the piloting nature of this trial, this result seemed promising for stroke rehabilitation research to enhance the methodology of the current practice that seeks at identify dose-response relationships of motor interventions.

It was also feasible to retrieve data on the mean duration of participants’ daily therapy sessions. This would enable comparison with other research and the current national clinical guideline for stroke rehabilitation [31].

LIMITATIONS

Trial limitations

The complexity and novelty of dose optimization processes on motor intervention have led to the implementation, in this dose-finding study, of a model-task intervention enabling high level of control on the applied dose. This model could have reduced the transferability of the results when applying “real-world” rehabilitative interventions and might explain the inconclusiveness of results from the secondary outcomes at the functional level (box and blocks

tests). Therefore, further research with complex rehabilitative interventions are needed.

Considering the high numbers of daily task repetitions assigned to participants, they could have benefit from some days of training preparation to gradually reach the assigned dose. This was not planned in this trial and it may have influenced participants' adherence to the dose.

Cohorts were found not balanced. Heterogeneity was found on participants' limitations, time since stroke and other characteristics. Although the focus of the study was to test the feasibility of implementing a dose-finding design to stroke rehabilitation research, rather than providing results on relevant doses of the model-task intervention, some considerations are needed for further research. In fact, this variability on participants' characteristics is thought to affect results on dose and it is difficult to control in 3+3 designs. In dose-finding designs in general there is the common assumption that participants respond fairly homogenous to treatment. Thus, restriction of trial inclusion criteria seems the vehicle to reduce variability on participants' characteristics, and then to increase the reliability of the dose optimization results. The categorization of patients in sub-groups could improve the dose-response estimation by taking into account differences due to, for example, their presentation, age, time since stroke. The categorization, however, is likely to introduce challenges on the recruitment process, increasing study recruitment time due to the restriction of inclusion criteria on stroke presentation. In this study, 41.7% of the potential participants were excluded because they did not meet the inclusion criteria which are now considered as over inclusive.

It could be argued that larger cohorts can improve the confidence in dose-optimization studies considering the complexity of motor intervention research and the heterogeneity on treatment outcomes. However, two aspects should be considered. First, a larger cohort size would increase the cost and time required for the study. Second, whatever the cohort size, it is advisable to follow a dose escalation study with a phase II dose-ranging study. As in pharmaceutical research, a dose-ranging study seeks in a larger sample the identification of an

optimal dose among a range of doses close to the recommended dose provided by the phase I trial [224,225,238]. Further assessment and adjustment on the proposed recommended dose can be done at this second stage. Dose-ranging studies also entail randomisation procedure and are already implemented for dose-optimization in rehabilitation trials [245].

Although the trial stopping rules were useful in avoiding the delivery of similar doses between subsequent cohorts, it could be argued that a maximal tolerable dose which lies between 209 and 250⁶² was imprecise. The limit of 10% difference between subsequent cohorts was therefore over estimated considering the rapid increments in the numbers of repetitions assigned by the escalation procedure. However, the numerical values provided by the mathematical simulations appeared appropriate in relation to the applied intervention, a difference between doses which was less than the starting dose seemed not meaningful. The implementation of different interventions could benefit from a different stopping rule limit. For example, a 10% difference from the last beneficial dose could be more appropriate than 10% difference between subsequent cohorts as in this study

Although the trial algorithm considered the use of checking rules to avoid biased information by sample characteristics, they were not verified in this trial. More research is needed to evaluate whether these trial rules were appropriate or needed some revisions.

Pharmaceutical dose optimization studies assumed that the expected outcome are directly measured in a known time frame. This information, often derived from preclinical studies, guides the decision on the appropriate length of treatment. In stroke rehabilitation this information is not available and investigations on the time-course effect are still limited. The following chapter

⁶² In our trial the fourth dose of 251 daily repetitions was found not feasible. The fifth cohort was de-escalated at exercised at 209 daily repetitions which was found again feasible. The following cohort should have exercised at 237 daily repetitions but the difference between the 251 and 237 is less than 10% and the trial ended.

(chapter 6) addressed this lack of data on the appropriate length of rehabilitative interventions after stroke implementing a longitudinal⁶³ studies. However, two weeks of intervention seemed appropriate to check the feasibility of this study providing indication of changes in participants' motor function. This result was in line with previous literature suggesting improvement in motor function in response to a two weeks period of training for stroke survivors [257,258,259]. Furthermore, two weeks of training could have maximised the adherence to the training and the training dose.

Although, the electronic counter was considered by participants a good support to track high number of task repetitions, few issues were acknowledged causing some missing or incorrect data recording. These issues were foreseen at the point when the counter was constructed and discussed with the technician involved. No structural changes were made because considered unfeasible for the mechanical laboratory team.

The trial traveling commitment could have precluded the participation of more impaired stroke survivors or those less motivated. This is a limitation common in rehabilitation trials. However, the home-based nature of the intervention, the availability of the therapist to travel to subjects' homes to undertake visits and assessments and the trial arrangements should have limited this issue.

Measures limitations

The use of a clinical therapy device, the Cando Digit-Extend, as a primary measure, instead of a more reliable and validated measure among stroke population, could be a matter of concern. However, it was not possible to identify a known and affordable measure tool able to assess the strength in the extensors muscle of the hand and arm. The focus of the study on the methodology, rather than on assessing the intervention efficacy guided this decision.

⁶³ A longitudinal study is a study that apply repeated measures of the same variables over a period of time.

The primary outcome test part B⁶⁴ showed low sensitivity to changes and low ceiling effect which, unfortunately, precluded the use of this data.

It was feasible to undertake TMS measures for less than half of the sample (46.7%). This was due to the technique contraindications, which made the TMS a challenging tool to be applied in the stroke population, rather than an issue deriving from the dose-finding design itself.

Due to the feature of dose-finding studies, the availability of measures able to early assess treatment outcomes is paramount. Other assessment tools able to identify early changes at the biological level brought by the intervention should be therefore tested in these designs.

5.7 New circumstances

At the time this chapter was revised a new study was published by Dite and colleagues implementing a 3+3 dose escalation design in stroke rehabilitation research [293]. This study used a different design compared to our study. In the Dite and colleagues' study each cohort of three participants were involved for a 12-week period split into a preparation phase (weeks 1-4), an adaptation phase (weeks 5-8) and a dose maximisation phase (weeks 9-12). The dose escalation 3+3 design was only applied during the second two weeks of the dose maximisation phase. Dose escalations were planned a priori for two cohorts and the increments were applied among the same cohort at the end of each maximisation training week, if participants were able to exercise at the target dose and no dose-limiting toxicity were experienced. The dose of exercise per week, for all cohorts, was 360 minutes for the preparation phase and 420 minutes for the adaptation phase. High-velocity progressive resistance training was added in the second week. The starting dose for the maximisation phase was increased

⁶⁴ Primary outcome test part B assessed the highest level of resistance against which participants were able to extend their fingers and thumb of their paretic hand twice in one minute.

by 30 minutes for weeks one and two (cohort one exercised for 450 minutes). At the beginning of week three of the maximisation phase an increase of 120 minutes was planned followed by an increase of 60 minutes in week four (total of 630 minutes for cohort one). The design was for subsequent cohorts to start their dose maximisation phase at the final dose achieved by the preceding cohort and then, increase 60 minutes in week two, and 120 minutes in week three and four.

Summarising the major differences between ours and Dite and colleagues' study were that in the cited study:

- the starting dose was relatively high. As a consequence, only two cohorts were undertaken before the maximal tolerable dose was found. A dose-limiting toxicity was experienced on the first cohort and thus, no increment was allowed on the second cohort;
- at the end of each maximisation week the dose was increased (dose escalation between the single cohorts);
- training protocol comprises of more than one intervention which differs among participants and between training weeks;
- a de-escalation procedure was not considered;
- checking rules were not applied;
- the dose escalation plan was not based on clinical efficacy. Therefore, unlike our design, this study was only able to indicate the maximal tolerable dose. No dose-response information was generated and therefore the recommended phase II dose cannot be determined. This approach is consistent with pharmaceutical studies where the main concern is toxicity and there is the assumption that the drug efficacy increases monotonically with the dose. This cannot be true for the central nervous system and has to be verified for motor interventions. In motor interventions, using the maximal tolerable dose for evaluation in subsequent clinical efficacy trials could mean that people participate in more exercise than they need for production of optimal clinical efficacy.

Interestingly, in our study the RPTD was found about 78% of the maximal tolerable dose. In health service terms this represents a considerable resource saving compared with provision of the maximal tolerable dose. Furthermore, some safety issues can arise implementing the maximal tolerable dose in subsequent testing.

Our design therefore may have advantages over the study by Dite and colleagues [293].

Chapter 6:

Feasibility of a repetitive assessment procedure for stroke survivors engaged in a rehabilitative trial

6.1 Introduction

Chapter 1 highlighted the need of reliable information on the optimal therapeutic dose (OTD) and on the appropriate length of motor intervention to enhance stroke rehabilitation outcome in a cost effective manner. Chapter 5 drawn attention to the need of data on the time-course effect and on the appropriate length of rehabilitative interventions to set dose optimization studies for stroke survivors.

This chapter addressed the feasibility and acceptability of undertaking a longitudinal study to investigate how the therapy effect evolves over time and therefore, how to derive the appropriate length of training (protocol) (*Overall*

aim 3 and specific objectives). To do so, the observation of within-patients' variations of a given outcome at different time points are required using a *repetitive assessment procedure*.

In stroke rehabilitation research, repetitive assessment procedures are not commonly undertaken [127,130]. The common practice in this field is to assess participants' change on two time points, generally at the beginning (pre intervention) and end of the trial (post intervention). The resultant difference in outcomes identifies the therapy effect. This rather simplistic approach, however, does not enable to discern the appropriate length of the training protocol because the trend on therapy effect cannot be explored.

The implementation of repetitive assessments in a rehabilitation trials is not straightforward and needs further study. These procedures can be costly -in terms of effort- for both, the stroke survivors and the researcher, and they generally require extra financial resources to be devoted to the research.

The implantation of longitudinal studies is in line with the suggested framework for complex interventions which endorsed the use of feasibility studies early in the research pathway [138] and with the step-by-step approach required for robust scientific evaluation of complex rehabilitation interventions which promoted the identification of key information before moving forward in the research pathway [74,138,214].

6.2 Methods

6.2.1 Research Design

The reported study was designed as a longitudinal feasibility study embedded in a phase II clinical efficacy trial (FeSTivALS). This trial was planned as an embedded study for the following three reasons.

First, the main aim of this study was to test the feasibility of a repetitive assessment procedure in stroke rehabilitation and not to test the efficacy of any intervention. Thus, it appeared more convenient, in terms of time and financial costs, to exploit an already running trial.

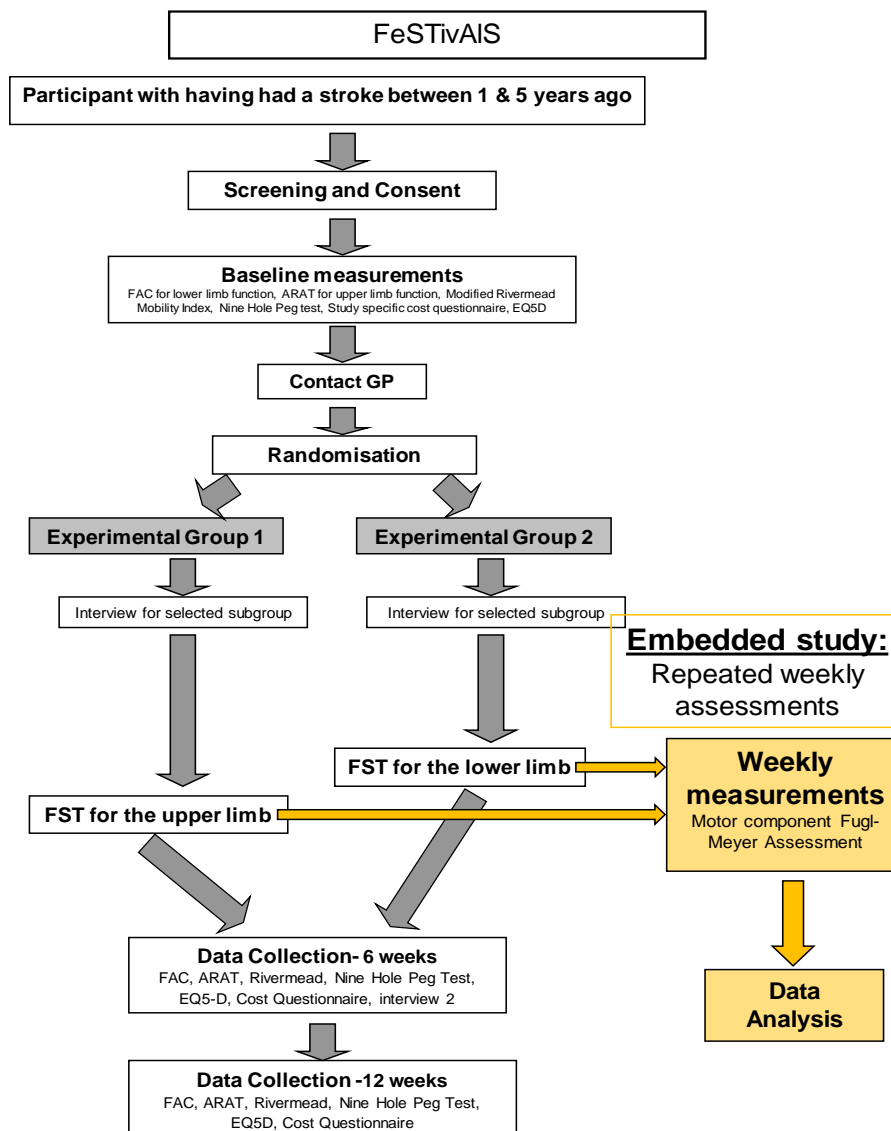
Second, early efficacy trials seemed to be the most appropriate stage of research at which to introduce such a procedure, to maximise research efficacy and increase the informative value of the trial.

Third, the features of FeSTivALS as a randomized, observer-blind trial increased the validity of the embedded trial results. FeSTivALS trial was a randomized, observer-blind, phase II clinical trial evaluating the efficacy of the Functional Strength Training (FST) for upper and lower limbs motor function [294]. The flowchart of FeSTivALS trial design and the embedded repetitive assessment study (highlighted in blue) is reported in Figure 6-1.

The embedded longitudinal feasibility study consisted of delivering an additional motor assessment (Fugl-Meyer motor functioning assessment) to FeSTivALS trial to investigate the intervention response over time.

The protocol features of FeSTivALS trial (randomization and recruitment procedures, participants' inclusion criteria, trial intervention and research setting) were briefly reported to contextualise the embedded study. These were already in place when this trial started. For more information on FeSTivALS trial refers to Mares et al., 2013 [294]

Figure 6-1: Flowchart of FeSTivALS trial and the longitudinal embedded study



Note: the embedded longitudinal study is highlighted in orange

6.2.2 Recruitment procedure

Potential participants were identified from three sources: the discharge database of one acute stroke service from the local acute hospital, the six-month post-stroke clinic of the same stroke service, and therapists' referral.

A recruitment letter was sent to each potential participant with an expression of interest form attached. They were asked to send the expression of interest in taking part in the study back, in a stamped addressed envelope or by phone. On receipt of an expression of interest form, the researcher from FeSTivALS contacted the potential participants to initially screen whether they met the trial inclusion criteria. If this was likely then, the same researcher arranged a home visit to discuss the practicalities of taking part in the study, to assess inclusion criteria and to go through the Participant Information sheet (PIS). After not less than 7 days from this visit the potential participants were contacted to check their willingness to participate in the study. If they confirm their intention an appointment was made with the blind research assessor. During this visit, after providing informed consent (IC), participants undertook the measurement battery (baseline). A letter was sent to participants' GP to inform on the patient's participation in the study asking to report back if GP disagreed with patient's participation. A summary of the study was attached to the letter so that GP could make an informed decision about the medical suitability of their patient. If no reply was received within ten working days, the participant was contacted again to agree on date to start the study. The trial recruitment letter, the expression of interest form, the PIS, the IC, and the GP letters are confined in Appendix M to R. Following baseline measures participants were randomly allocated to either FST for their upper limb (FST-UL) or FST for their lower limb (FST-LL).

6.2.3 Randomization procedure

Random group allocation was determined by a telephone call to an independent randomization service within the Norwich Clinical Trials Unit. The baseline scores for the Functional Ambulation Category (FAC) and Action Research Arm Test (ARAT) were used to minimize any imbalance in allocation of participants to

either FST-UL or FST-LL [294,295]. Minimisation of baseline imbalance between treatment groups was based on the Pocock and Simon's range method [296].

6.2.4 Participants

Inclusion criteria:

- adults aged 18+ years;
- six months to five years after either an infarct or haemorrhagic stroke in the anterior circulation;
- able to walk four steps with the continuous support from one person and/or assistive device, but unable to step on and off a step 7.5cm high more than fourteen times in fifteen seconds with either their affected or unaffected leg (the step test) [297];
- have sufficient voluntary activity in the paretic upper limb to move the paretic hand from a position on their lap to the table top in front of them, but unable to pick up four £1 coins individually from a table top and stack them evenly in a pile;
- able to follow a 1-stage command with the non-paretic upper limb i.e. sufficient communication/orientation to undertake the trial interventions.

Exclusion criteria:

- diagnosed with a known pathology contraindicating participation in FST;
- receiving formal upper or lower limb physical therapy.

6.2.5 Sample size estimates

Given the feasibility nature of FeSTivALS trial a power calculation was not possible. However, it was estimate a target of 58 stroke survivors⁶⁵.

⁶⁵ 26 participants per group would have 90% power at 5% significance to detect: a change of 1 point on the FAC, assuming a standard deviation of 1, and a change of 5.7 points on the ARAT, assuming a standard deviation of 5.7. By allowing for an estimate 10% attrition rate the final recruitment targeted of FeSTivALS was set at 58 stroke survivors. For more detail refers to Mares et al., 2013.

On the same line, a power calculation was not feasible for the embedded longitudinal study given its feasibility nature and the use of an additional measure to FeSTivALS trial (not the primary outcome measure). However, to provide an idea of the needed sample size for future studies implementing the Fugl-Meyer motor functioning assessments as a primary outcome, a power analysis was derived from the literature. Assuming a clinical relevance of 10% difference on the Fugl-Meyer motor functioning assessments score [298], a standard deviation of 3.2 [299], and a loss of patients at follow-up of 10%, 20 patients would be sufficient in each group to have an 80% chance of detecting a statistically significant difference in improvements between the two groups.

6.2.6 Ethics

Ethical approval for FeSTivALS trial was granted by the Norfolk Ethics Committee (reference number 09 H0308 147). FeSTivALS trial was also registered on the Current Controlled Trials database (ref: ISRCTN71632550).

Ethical approval for the repetitive assessment procedure was provided as a substantial amendment (amendment number 7) by the Cambridgeshire 2 Research Ethics Committee (ref: 09 H0308 147).

All relevant documents are included in Appendix S.

6.2.7 Intervention

Functional Strength Training (FST) was an exercise-based therapy implemented to enhance cortical reorganization to recover functional skills lost after stroke. It was a hands-off progressive resistive exercise involving repetitive daily functional activities directed by the therapist.

FST for the lower limb (FST-LL) focussed on functional activities involving the lower limb such as:

- standing up and sitting down;
- ascending and descending stairs and/or using a block for step up/step down exercise;
- practice of balance activity including one-leg standing;
- walking whilst avoiding and/or stepping over obstacles.

FST for the upper limb (FST-UL) focussed on improving the production of appropriate force in the shoulder, arm and hand to improve functional movements. Example of FST-UL were:

- reaching, picking up a jug containing water and pouring contents into a container;
- picking up a container and removing the screw lid;
- reaching down to a foot and then using both hands to lace up a shoe;
- picking up and then moving everyday objects of various weights and sizes to position them in a different locations of diverse heights.

In FeSTivALS trial training progression was informed by the Oxford program [300] through increasing the amount of resistance (external resistance bands and/or weights), increasing task difficulty and increasing the number of repetitions. Participants were randomised to either FST-UL or FST-LL for one hour a day, on four days a week, for six weeks.

6.2.8 Research setting

FeSTivALS trial intervention, trial measurement battery, as well as the additional weekly assessments of this embedded trial took place in participants' homes with the supervision of a research therapist.

6.2.9 Outcome measures

FeSTivALS trial outcome measures

FeSTivALS primary efficacy outcome measures were the Functional Ambulation Category (FAC) [301] for the lower limb, and the Action Research Arm Test (ARAT) [302] for the upper limb collected at baseline (pre intervention), after the six weeks of intervention (post intervention) and a six weeks after the end of the intervention (follow-up).

The FAC is a functional walking test that evaluates ambulation ability using a six point scale [303], largely used with patients with stroke in research and clinical practice. Mehrholz et al. (2007) examined the FAC psychometric properties in

hemiparetic patients after stroke. They found that it has an excellent reliability, good concurrent and predictive validity, and good responsiveness [304].

The ARAT is an arm-specific measure of functional ability which has been found appropriate and largely used with stroke survivors [305]. The ARAT showed high inter-rater and test-retest reliability as well as content validity and construct validity [306].

Secondary outcome measures were also collected (see Mares et al. (2013) for details [294]).

Embedded trial: repeated measures

A fundamental and challenging step in implementing this embedded study was the identification of an appropriate outcome measure.

The measure needed to show several qualities. First, it needed to be able to detect changes brought by the trial intervention and thus, needed to assess functional tasks that were likely to be improved by a strengthening programme – like the FST- in both the upper and lower limbs.

Second, it should have good psychometric properties verified in the stroke population. Such as, validity, responsiveness and, most important for the repetitive nature of this procedure, reliability [266]. Reliability refers to the measure ability to provide results that are consistent and able to differentiate between participants. These characteristics are refereed as the test-retest (or intra-rater) reliability and the interrater reliability [307].

Third, to avoid potential learning effect with the trial primary efficacy measure [63,308], the measure for this embedded longitudinal study differed from the ones already implemented in the main trial.

Fourth, it should not be too long or require too much physical effort. In fact, it would not be desirable that participants become fatigued because of the length of time and effort required to complete the repeated assessment.

Finally, a pragmatic factor to consider was that the research therapist should be able to carry the equipment to undertake the measure alongside with other equipment needed to deliver the therapy during the home therapy sessions.

As a result of these key considerations, for this longitudinal embedded trial the *Fugl-Meyer assessment (FMA)* of paretic upper and lower limb [298] was chosen as additional repetitive assessment.

FMA showed good psychometric properties [309]. It has been validated among stroke survivors and is one of the most often used tool to evaluate stroke patients, in particular for upper limb extremity [309,310]. This give consistency of outcome measure across research.

Platz et al. (2005) rated the test-retest reliability of the upper limb motor score as excellent among patients with neurological conditions (Interclass correlation coefficient (ICC) is 0.97) [306]. Duncan et al. (1983) examined the test-retest and interrater reliability of the FMA among stroke survivors and found an excellent correlation (Intra-rater Pearson's correlation coefficients: (r) is 0.98-0.99 for the total score, $r = [0.995-0.996]$ for the upper extremity and $r = 0.96$ for the lower extremity; interrater $r [0.98-0.995]$ for the upper extremity and $r = [0.89-0.95]$ for the lower limb) [311].

The FMA is divided into five domains: motor function, sensory function, balance, joint range motion, and joint pain. Each domain contains multiple items, each scored on a 3-point ordinal scale (0=not able to perform; 1=partially performed; 2=fully performed). To limit the burden on participants, which were already engaged in a highly demanding physical intervention, only *the motor function and reflex domain items* were tested (see Table 6-1). The average time needed to administer the motor and reflex sections of the FMA was estimated between 15-30 minutes. The FMA protocol is available in Appendix T.

The FMA was undertaken weekly by therapists who were trained on the assessment beforehand. This time point appeared able to provide enough information to explore the therapy time course relationship as well as not too disruptive on the main trial. As standard procedure, the FMA for upper and lower limbs was taken on the same day every week before the intervention.

The FMA minimal clinically important difference (MCID) in stroke survivors has been estimated around 5.25 points [312,313] on the upper limb, and as 10% increments on the lower limb portion of the test [309].

Data were collected on a standardised FMA score sheet (see Appendix U) for each participant at each measure point assessment. Space for comments were available if needed in the score sheet. Blinding assessors was not possible because the therapist delivering the trial intervention also undertake the weekly assessment. The therapists' code was recorded in the FMA score sheet. People involved in the analysis were not involved in the outcome measures.

Other data available for all participants included in FeSTivALS trial were: participant's age, gender, time after stroke, side of stroke, and duration of each training session, missing of daily training session, and reasons for variation on the planned dose of daily training or for missing sessions.

Table 6-1: Fugl-Meyer Assessment: motor domain items

Upper Extremity (66 points)	Lower Extremity (34 points)
Shoulder retraction	Hip flexion
Shoulder elevation	Hip extension (supine)
Shoulder abduction	Hip adduction (supine)
Shoulder abduction to 90 degrees	Knee flexion (supine)
Shoulder adduction/internal rotation	Knee flexion (sitting)
Shoulder external rotation	Knee flexion (standing)
Shoulder flexion 0–90 degrees	Knee extension (supine)
Shoulder flexion 90–180 degrees	Ankle dorsiflexion (supine)
Elbow flexion	Ankle dorsiflexion (sitting)
Elbow extension	Ankle dorsiflexion (standing)
Forearm supination	Ankle plantar flexion (supine)
Forearm pronation	Heel-shin speed
Forearm supination/pronation (elbow at 0 degrees)	Heel-shin tremor
Forearm supination/pronation (elbow at 90 degrees, shoulder at 0 degrees)	Heel-shin dysmetria
Hand to lumbar spine	Knee reflex
Wrist flexion/extension (elbow at 0 degrees)	Hamstring reflex
Wrist flexion/extension (elbow at 90 degrees)	Ankle reflex
Wrist extension against resistance (elbow at 0 degrees)	
Wrist extension against resistance (elbow at 90 degrees)	
Wrist circumduction	
Finger flexion	
Finger extension	
Extension of MCP joints, flexion of PIPs/DIPs	
Thumb adduction	
Thumb opposition	
Grasp cylinder	
Grasp tennis ball	
Finger-nose speed	
Finger-nose tremor	
Finger-nose dysmetria	
Finger flexion reflex	
Biceps reflex	
Triceps reflex	

Note: see Fugl-Meyer et al. (1975) for details and scoring instructions. From: Gladstone D. et al. (2002).

6.3 Analysis

All participants' data were included in the analysis following an intention to treat procedure. This increased trustfulness of the trial results on study feasibility [291].

In this longitudinal study the feasibility of undertaking repetitive assessment procedure during a clinical efficacy trial was assessed using participants' adherence to the weekly measure (attrition rate). The possible impact of the FMA on the delivering of the trial intervention was also explored assessing if: *i*) the number of missing trial sessions, and *ii*) the amount of therapy (in minutes) undertaken by participants differed between the groups who did (assessed group) and the group who did not (not-assessed group) the additional FMA assessment.

The patients' responses over time –the time course relationships- were explored to support the appropriateness of the data collection on the decision on the appropriate length of the intervention. The relevance of data collection on the intervention time curve effect was explored by measuring the difference between FMA score at each weekly assessment, with confident interval (CI) constructed at 95%. Data were analyzed as a group effect over time for participants allocated to upper and lower limb training, as well as for each included participant.

The appropriateness of undertaking repetitive assessment in a weekly bases was explored based on the ability to construct the patients' responses over time with the retrieved data.

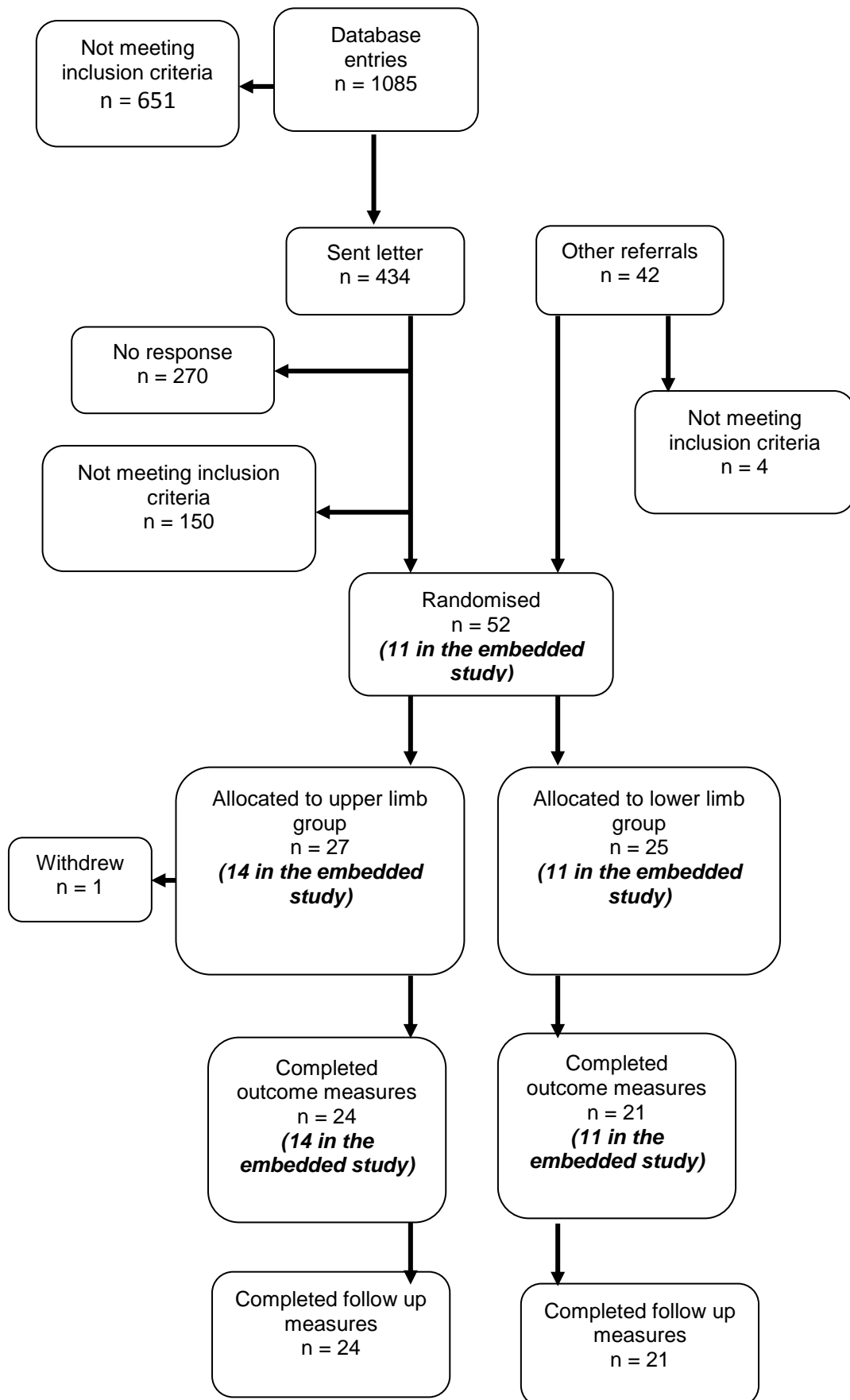
All analyses were undertaken using Stata 13 statistical software.

6.4 Results

6.4.1 Recruitment procedure

Figure 6-2 shows the flowchart of the recruitment and consent rate of FeSTivALS trial. A total of 52 participants were randomised to take part in FeSTivALS trial.

Figure 6-2: Flowchart of FeSTivALS trial recruitment and consent process.



From when this longitudinal embedded study started 25 participants were randomised and undertook the additional weekly FMA. Fourteen of them were allocated to FST-UL and eleven were allocated to FST-LL (highlighted in bolt).

One participant (ID=135), randomised to receive FST-LL, did not receive the FMA due to time constrain imposed by the day centre where he was living. He was allowed to receive a maximum of one hour training session from the researcher therapist. Intention to treat principles were followed and this participant is included in the analysis.

Table 6-2 shows participants’ characteristics at baseline (pre intervention) for all participants included in the longitudinal embedded study and disaggregated by their allocated intervention group (FMA_FST-UL; FMA_FST-LL).

On average, sample participants had a mean age of 71.5 years, observed after 1.7 months after stroke. The mean score for the upper limb (UL) part of the FMA was 27.1 (total possible score for UL section= 66). For the lower limb (LL) part of the FMA was 16 (total possible score for LL section = 34). All characteristics were almost balanced across the two groups.

Table 6-2: Summarised baseline characteristics for all participants who undertake the longitudinal study and by training groups

Subjects' characteristics	Overall FMA (n=25)		FMA_FST-UL (n=14)		FMA_FST-LL (n=11)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	71.5	12.2	70	13.7	73.2	10.6
Female (%)	0.2	0.4	0.3	0.5	0.2	0.4
Right side affected (%)	0.4	0.5	0.4	0.5	0.5	0.5
Time after stroke (months)	1.7	1.1	1.6	1	1.8	1.3
FMA(UL) score	27.1	21.8	35.5	15.4	23.6	20.5
FMA(LL) score	16	12	13.7	12	24.2	7
FAC score	2	1.4	1.8	1.5	2.3	1.3
ARAT score	16.6	12.3	17.8	13.6	15.3	11

Notes: SD= Standard Deviation; FAC= Functional ambulatory category; ARAT= Action research arm test; FMA (UL) score Fugl-Meyer motor function assessment; FMA (LL)= Lower limb score Fugl-Meyer motor function assessment; FMA_FST-UL= participants undertaking Fugl-Meyer motor function assessment and allocated to receive upper limb therapy; FMA_FST-LL= participants undertaking Fugl-Meyer motor function assessment and allocated to receive lower limb therapy.

Table 6-3 shows FeSTivALS participants’ characteristics at baseline for both, the group who did the weekly FMA in addition to the trial intervention (assessed group) (FMA_FST) and the group who did only the FeSTivALS trial intervention (non-assessed group) (FST).

All characteristics were balanced at baseline (pre intervention) across the two groups except for time since stroke and functional measures where statistically significant differences were found ($p < 0.05$). Overall, the group who undertook only the trial intervention (FST group) had a mean of 3.6 months after stroke; the group who undertook the additional assessment plus the trial intervention (FMA_FST group) had a mean of 1.7 months after stroke. The FST group achieved better FAC measure but had a lower ARAT measure compared to the FMA_FST group.

Table 6-3: Summarised baseline characteristics for all FeSTivALS participants by groups who undertake FST only (FST) (non-assessed group) and who undertake weekly FMA in addition to FST (FMA_FST) (assessed group)

Subjects' characteristics	FST (n=26)		FMA_FST (n=25)	
	Mean	SD	Mean	SD
Age (years)	65	13.5	71.5	12.2
Female (%)	0.4	0.5	0.2	0.4
Right side affected (%)	0.5	0.5	0.4	0.5
Time since stroke (months)	3.6*	1.5	1.7	1.1
FAC score	2.9*	1.3	2	1.4
ARAT score	14.5*	14.1	16.6	12.3

Notes: SD= Standard Deviation; FST= Functional strength training; FMA_FST= group undertaking Fugl-Meyer assessment before trial intervention; (*) significant difference < 0.05 .

6.5 Feasibility of the repetitive assessments procedure

6.5.1 Attrition rate

Feasibility of undertaking repetitive assessment procedure during a stroke rehabilitation clinical efficacy trial was assessed controlling for participants’ adherence to the weekly assessments (FMA).

Table 6-4 shows participants' adherence to the weekly assessments and trial intervention to all participants and by their allocated group (FST-UL; FST-LL). In detail:

- seven participants (28%) completed all the weekly assessments (highlighted in green). Four participants were on the intervention upper limb group (FST-UL) and three on the intervention lower limb group (FST-LL);
- ten participants (40%) missed one weekly measure. Six participants were on the FST-UL group and four on the FST-LL group. The reasons for missing the measure were: trial management⁶⁶ (8% of the total sample of 25 participants) (ID=139; 140); personal reasons not related to the trial (12% of the total sample of 25 participants) (ID=137; 147; 149); the research therapist considered participants too tired or weak to undertake the measures without affecting the delivery of the trial intervention (20% of the total sample of 25 participants) (ID=131; 134; 136; 143; 152);
- seven participants (28%) missed three or more assessments. Four belonged on the FST-UL group and three on the FST-LL group. The reasons for missing the measure were: lack of therapy time (12% of the total sample of 25 participants) (ID=145; 148; 151); personal reasons not related to the trial (8% of the total sample of 25 participants) (ID=132; 150); participants were considered too weak to do the measure and the training on the same training day (8% of the total sample of 25 participants) (ID=127; 129).
- one participant (4%) (ID=135) did not take the measures for restriction on the allowed therapy time by his care home.

⁶⁶ The therapists had not enough time to undertake both, the measure and the therapy so the priority was on delivering the study intervention.

Table 6-4: Participants' adherence to the weekly FMA and trial intervention by allocated group

Allocated therapy	Patient's Identifier ID	week of observation					
		1	2	3	4	5	6
UL	128	v	v	v	v	v	v
	129	v	v	x	x	x	x
	131	v	v	v	v	v	x
	132	v	x	x	x	x	x
	134	v	v	v	v	x	v
	137	v	x	v	v	v	v
	138	v	v	v	v	v	v
	141	v	v	v	v	v	v
	142	v	v	v	v	v	v
	143	v	x	v	v	v	v
	145	v	x	x	x	x	x
	147	v	v	x	v	v	v
	151	v	x	x	x	x	v
	152	v	v	x	v	v	v
	LL	127	v	x	v	x	x
130		v	v	v	v	v	v
135		x	x	x	x	x	x
136		v	v	x	v	v	v
139		v	v	v	x	v	v
140		v	v	x	v	v	v
144		v	v	v	v	v	v
146		v	v	v	v	v	v
148		v	v	x	x	x	v
149		v	v	v	x	v	v
150	v	v	x	x	x	x	

Notes: weekly sessions highlighted in light green (v) correspond to sessions where participant undertook both FMA and trial intervention successfully. The orange (x) highlights the session where participants had the trial intervention but not the FMA; whereas, the red (x) correspond to sessions where participants didn't undertake either FMA or trial intervention.

For this embedded longitudinal study one weekly assessment was planned for the 6 weeks of trial intervention. Considering the 25 enrolled participants, a total of 150 in assessments were planned. Of these overall 150 assessments, 105 (70%) were successfully undertaken (in light green) and 45 (30%) were missed (in red/orange). Considering now only the missing sessions, in 25 cases (55.5% of the total missing) the entire training session was missed. The therapist was unable to see participants, or participants were not available for reasons not related with the trial. In the remaining twenty cases (13.3% of the total sessions) (in orange) participants did not undertake only the FMA while, the trial intervention was successfully undertaken. Among these cases the reasons for not undertaking the FMA were:

- lack of therapist time or constraints imposed by the participant' care setting (nine cases, 45%);
- participants' personal reasons not related with the trial (four cases, 20%);
- participants considered too weak to do the motor assessment without affecting the trial intervention (seven cases, 35%).

6.5.2 Impact of the FMA on the trial intervention

The possible impact of the FMA on the trial intervention was explored comparing the groups who did the weekly FMA in addition to the trial intervention (assessed group) (FMA_FST) and the group who did only the FeSTivALS trial intervention (non-assessed group) (FST) on:

1. the number of missing therapy sessions;
2. the average daily amount of therapy (in minutes) undertaken by participants.

Table 6-5 shows the average missing sessions for the non-assessed group (FST) and the assessed group (FMA_FST). The allocated intervention group (UL/LL) is also highlighted in the table.

Table 6-5: Average missing sessions by the groups who did only the trial intervention (non-assessed group) (FST) and the group who did the additional weekly assessment and the trial intervention (assessed group) (FMA_FST) and by allocated intervention (UL/LL).

Group	Overall	UL	LL
FST (mean) (n=24)	3.2	3.1	3.4
FMA_FST (mean) (n=25)	4.1	4.7	3.3

Notes: FST= non-assessed group; FMA_FST= assessed group undertaking FMA before intervention; UL = allocated upper limb trial intervention; LL = allocated lower limb trial intervention

Overall, the non-assessed group (FST) missed less sessions, 3.2 sessions on average, compared to the participants in the assessed group (FMA_FST) who missed 4.1 sessions on average.

While acknowledging the small sample, further analyses were reported on the average of missing session by subgroups.

The average missing session rate slightly changed in favour of the assessed group (FMA_FST) if the participants who missed sessions for reasons not related with the trial intervention were excluded from the analysis: three participants in the assessed group (FMA_FST) compared to one in the non-assessed group (FST). With this new condition, on average, the assessed group (FMA_FST) missed 1.1 session against an average of 2.8 for the non-assessed group (FST).

Let now consider the allocated intervention groups. The non-assessed group allocated to upper limb training (FST) missed - on average - 3.1 therapy sessions against 4.7 sessions missed by the assessed group (FMA_FST). The non-assessed group allocated to lower limb training (FST) missed - on average- 3.4 sessions against 3.3 sessions missed by the assessed group (FMA_FST).

Table 6.6 visually shows the daily adherence to the therapy sessions for the FST and FMA_FST groups, by allocated intervention (UL/LL). Missing training sessions were highlighted in red and marked with an "x". Participants who completely adhered to the training session during the six weeks period were highlighted in green. In the table were reported the percentage of participants undertaking the daily training session for all training period by group who did and did not the FMA assessment.

One participant in the non-assessed group (FST) and five participants in the assessed group (FMA_FST) completely adhered to the training session during the six weeks training period (green line in Table 6.6).

Table 6-6: Adherence to the daily trial intervention for all FeSTivALS participants by groups who did and did not the FMA and by allocated training (UL, LL).

	Week1				Week2				Week3				Week4				Week5				Week6				Total missing
	Day1	Day2	Day3	Day4	Day1	Day2	Day3	Day4	Day1	Day2	Day3	Day4	Day1	Day2	Day3	Day4	Day1	Day2	Day3	Day4	Day1	Day2	Day3	Day4	
FST-UL Group																									
102	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	1
103	v	x	v	v	v	v	v	v	v	v	x	x	x	x	v	x	v	x	x	x	v	x	x	x	12
106	v	v	v	v	x	x	x	x	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	5
108	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	x	v	v	1
111	v	v	0	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	x	v	v	v	v	2
112	x	v	v	v	v	v	v	v	x	v	x	v	v	v	x	v	v	v	v	v	v	v	v	x	5
115	v	v	v	v	v	v	v	v	v	v	v	v	v	x	v	x	v	v	v	v	v	v	v	x	2
116	v	v	v	v	v	v	v	v	v	v	v	v	v	x	v	v	v	v	v	v	v	v	v	v	1
118	v	v	v	v	v	v	v	v	v	v	v	v	v	v	x	v	v	v	v	v	x	v	v	v	2
119	v	v	x	v	v	v	v	v	v	v	v	v	v	v	v	x	v	v	v	v	v	v	v	v	2
120	v	v	v	v	v	v	v	v	x	v	v	v	v	v	v	v	v	v	v	v	v	x	x	x	4
121	v	v	v	v	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	1
123	v	v	v	x	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	2
101	v	v	v	v	v	v	v	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	1
104	v	v	v	v	x	v	v	v	v	v	v	v	v	x	x	x	v	v	v	v	v	v	v	v	1
107	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	x	v	1
109	v	v	v	v	x	v	v	v	v	v	x	v	v	v	v	v	x	v	v	v	v	x	v	v	4
110	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	x	v	x	v	v	v	v	v	v	2
113	x	x	v	v	v	v	v	v	x	v	x	v	v	v	x	v	v	v	v	v	v	v	v	v	5
114	v	v	v	v	v	v	v	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	1
117	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	1
122	v	v	v	v	v	v	v	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	14
124	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	0
125	v	v	v	v	v	x	v	v	x	v	x	x	x	v	v	v	v	v	v	v	v	v	v	v	4
Daily %	87.5	91.7	91.7	95.8	83.3	87.5	95.8	91.7	66.7	100	87.5	83.3	87.5	87.5	83.3	79.2	87.5	87.5	87.5	87.5	95.8	79.2	79.2	75	
FST-LL Group																									
128	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	0
129	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	x	x	x	x	x	v	v	x	6
131	x	x	v	v	v	v	v	v	v	v	v	v	x	v	v	v	v	x	v	v	v	v	v	x	4
132	v	v	v	v	v	v	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	18
134	v	v	v	x	v	v	v	v	v	v	v	v	x	x	x	v	v	v	v	v	v	v	v	x	7
137	v	v	v	x	v	v	v	x	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	x	4
138	v	v	v	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	x	2
141	v	v	v	v	v	v	v	x	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	2
142	v	v	v	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	x	v	v	v	v	x	3
143	v	v	v	x	v	v	x	v	v	v	v	v	v	v	x	v	x	v	x	v	v	v	v	x	6
145	v	v	x	v	v	v	v	v	v	v	x	v	v	v	x	x	x	x	x	x	x	x	x	x	11
147	v	v	v	v	v	x	v	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	x	3
151	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	0
152	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	0
127	v	v	v	v	x	v	v	v	v	v	v	v	x	v	v	v	v	v	v	v	v	v	v	v	2
130	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	0
FMA_FST-UL Group																									
135	v	v	x	v	v	v	v	x	x	v	v	x	v	v	v	v	v	v	v	v	v	v	v	x	5
136	v	v	v	v	v	v	v	v	v	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	1
139	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	x	v	v	v	v	v	v	x	2
140	v	v	v	v	v	v	v	v	x	v	v	v	v	v	v	v	v	v	v	v	v	x	v	x	3
144	v	v	v	x	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	x	2
146	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	0
148	v	v	v	v	v	v	v	v	v	v	v	v	v	v	v	x	x	v	v	x	v	v	v	v	3
149	v	v	v	x	v	v	v	v	v	v	x	v	v	x	v	v	v	v	x	v	v	v	x	x	5
150	v	v	v	x	v	x	v	v	v	v	x	x	x	x	x	x	x	x	x	x	x	x	x	x	13
Daily %	91.7	95.8	91.7	66.7	95.8	91.7	91.7	91.7	79.2	83.3	83.3	87.5	79.2	87.3	95.8	79.2	79.2	58.3	58.3	62.5	79.2	87.5	79.2	16.7	

Note: ID= participant' identification code; x= missing training session; v= completed training session; FST= group undertaking trial intervention alone; FMA_FST= group undertaking Fugl-Meyer assessment before trial intervention; UL = allocated upper limb trial intervention; LL = allocated lower limb trial intervention; the light green band correspond to a participant who was compliant to a full week of training; the sessions highlighted in red correspond to a missed trial intervention session. The percentage of participants undertaking the daily training session is reported by group who did and did not the FMA assessment.

Table 6-7 shows the mean daily amount of therapy in minutes in the six weeks of training period for all sample by the assessed group (FMA_FST) and the non-assessed group (FST) and by allocation intervention group (UL/LL). A significant positive difference in the mean duration of daily therapy of 5.5 minutes was found in favour of the non-assessed group (FST). If the groups were disaggregated between those participants who receive upper (UL) or lower (LL) limb interventions, this difference remained highly statistically significant (at 1% level) only for the group who received UL training, with a mean of 7.7 minutes of more therapy.

Table 6-7: Participants' mean daily duration of therapy and standard deviation (SD) by the group who did the additional weekly assessment and the trial intervention (assessed group) (FMA_FST) and the groups who did only the trial intervention (control group) (FST) and by allocated intervention treatment (UL/LL)

GROUP	FMA_FST^a (mean)	SD	FST^a (mean)	SD	Diff.
UL	36.2 (n=14)	20.7	43.9 (n=13)	19.8	7.7*
LL	36.7 (n=11)	20.7	39.5 (n=11)	16.6	2.8
Overall	36.4 (n=25)	20.3	41.9 (n=24)	19	5.5*

Note: ^a= therapy duration in minutes UL= allocated upper limb trial intervention; LL= allocated lower limb trial intervention; FST= group undertaking trial intervention alone; FMA_FST= group undertaking Fugl-Meyer assessment before trial intervention; SD= standard deviation; (*) significant difference at 0.00001.

6.6 Informative nature of the repeated assessment procedure

The patients' response to the trial therapy was calculated at each week (six assessment points) of the intervention period, in terms of overall FMA value computed among all participants, by allocated intervention group.

Upper limb score

Table 6-8 shows, for participants allocated to receive FST-UL, the average value of FMA upper limb score (FMA-UL) at each measure time point.

Table 6-8: Mean FMA upper limb score (FMA-UL) and standard deviation for participants allocated to receive FST-UL at each weekly assessment.

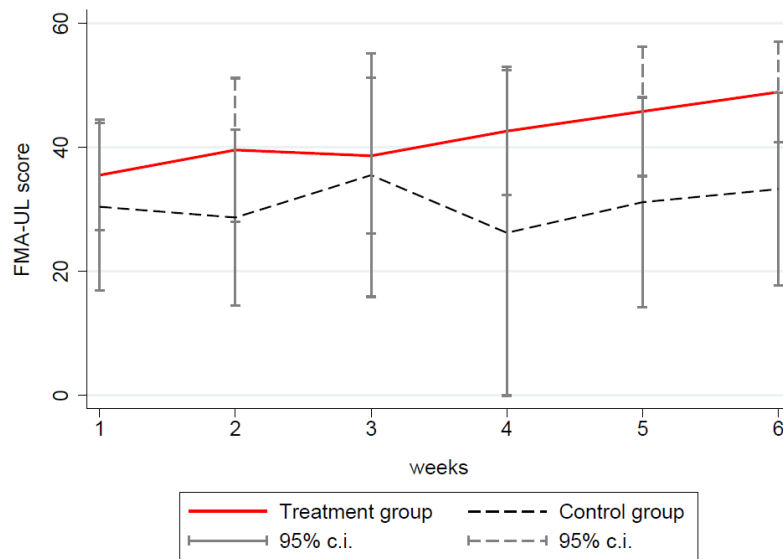
Weekly assessment	FMA-UL (mean)	SD	Participants assessed by week
1	35.5	15.4	14
2	39.6	15.1	9
3	38.6	15	8
4	42.6	14.4	10
5	45.8	13.6	9
6	48.9	11.3	10

Note: FMA-UL= Fugl-Meyer upper limb motor assessment score; SD=standard deviation; column on the right reports the number of participants assessed each week.

The mean value of FMA-UL observed at week 1 (pre intervention) was 35.5 points and 48.9 at week 6. The difference from week 1 was of 13.4 points, which was well above the 5.25 points MCID for the upper limb section of this measure.

Participants' attrition rate to the weekly assessments is reported in the right column of the table. Fourteen participants were enrolled and assessed at week 1. Four participants (28.6% of the original sample) were not observed at week 6.

Figure 6-3: Mean FMA-UL score trends over time for participants allocated to receive FST-UL (treatment group) and for participants allocated to receive FST-LL used as control groups



Note: x-axis=training weeks; y-axis= mean FMA-UL score observed in the group receiving FST-UL (treatment group) and in the group receiving FST-LL (control group). Vertical bars represent 95% confident interval (95% CI).

The red line in Figure 6-3 shows the mean of FMA upper limb score (FMA-UL) over the six weeks of therapy for the participants allocated to receive FST-UL (treatment group), with a confidence interval (CI) constructed at 95%. For comparison purpose, the same trend is also reported for the group of participants receiving FMA upper limb but, allocated to receive therapy for their lower limb (FST-LL) only (dash black line, defined as control group). It appeared that the upper limb therapy enhanced motor functions steadily for all training period of six weeks (red line). This could not be seen in the control group (dash black line), providing an indication that the improvement in upper limb functions was mainly due to the intervention. Besides, results pointed out that a stop in the improvement (therapy effect) was not reached at the end of the six week, providing an indication that further improvement could have been obtained with a longer therapy period. Subjects' trends over time are available in Appendix V.

This analysis also shown that a weekly assessment procedure provided enough and appropriate data to explore the intervention effect over time on upper limb.

Lower limb score

Table 6-9 shows the average value of FMA lower limb score (FMA-LL) at each measure time point for participants allocated to receive FST-LL.

Table 6-9: Mean FMA lower limb score (FMA-LL) and standard deviation for participants allocated to receive FST-LL at each weekly assessment.

Weekly assessment	FMA-LL (mean)	SD	participants assessed by week
1	24.2	7	10
2	24.4	7.5	9
3	25.3	6	6
4	27.6	5.5	5
5	28	4.8	7
6	26	7.8	8

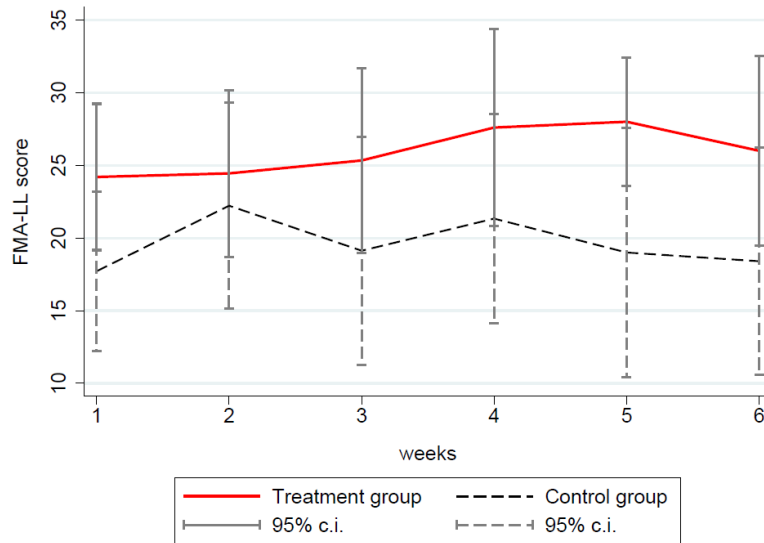
Note: FMA-UL= Fugl-Meyer upper limb motor assessment score; SD=standard deviation; column on the right reports the number of participants assessed each week.

Ten participants were enrolled to receive FST-LL and assessed by the FMA-LL at week one. The mean value of FMA-LL observed at week 1 (pre intervention) was 24.2 points and 26 at week 6, with an overall increase of less than 2 points. This increase was lower than the 10% increment required for the MCID for the lower limb section of this measure.

Participants' attrition rate to the weekly assessments is reported on the right column of the table. Two participants (about 20% of the original sample) were not observed at week 6.

The red line in Figure 6-5 shows the mean of FMA lower limb score (FMA-LL) over the six weeks of therapy for the participants allocated to receive FST-LL, with a confidence interval (CI) constructed at 95%. Figure 6-5 and Table 6-9 show that the therapy response over time for the group undertaking FST-LL had a slight increasing trend, with a better outcome saw at week 5. After week 5 a decrease of 2 points score was seen. As before, the same trend is also reported for the group allocated to receive therapy for their upper limb (FST-UL) (dash black line) and used as control group, confirming difficulties in deriving definitive conclusions. Subjects' trends over time are available in Appendix V.

Figure 6-4: Mean FMA-LL score trends over time for participants allocated to receive FST-LL (treatment group) and for participants allocated to receive FST-UL used as control groups



Note: x-axis=training weeks; y-axis= mean FMA-LL score observed in the in the group receiving FST-LL (treatment group) and in the group receiving FST-UL (control group). Vertical bars represent 95% confident interval (95% CI).

6.7 Discussion

This analysis pointed out the feasibility of applying a weekly assessment procedure in stroke rehabilitation clinical research.

About 68% of the sample (17 participants) successfully undertook the weekly assessments procedure or missed only one assessment. Among the remaining eight participants who had missed more than three assessments, only two were unable to undertake the weekly assessment while being able to perform the trial intervention. Therefore, attrition (the loss of eligible participants during the trial) seemed mainly related to the delivery of the trial intervention rather than on the added repetitive assessments. However, the repetitive assessment increased the burden of the trial. A significant positive difference in the mean duration of the daily intervention therapy was found in favour of the non-assessed group (the group who did only the intervention therapy). It also appeared that the length and physical effort required to undertake the additional Fugl-Meyer assessment could have impacted on the delivery of the

trial intervention for the weakest and frailer participants or, could have impacted on the amount of therapy that the therapists were able to deliver. Some adjustments of the undertaken assessment (e.g. using a less demanding assessment, or an assessment integrated into the therapy) might help in reducing these disadvantages. Examples of assessments integrated into the therapy could see the use of the Box and Blok test (or its modifications) for the upper limb and the five-minutes walking test or the “time up and go” test for the lower limb.

On a methodological point of view, this study was able to provide relevant information on stroke rehabilitation therapy effect over time. In detail, it was possible to derive longitudinal data potentially useful in determining the appropriate length of the applied intervention. The Fugl-Meyer assessment seemed to show that the therapy has enhanced motor function steadily over the six weeks of upper limb training protocol without reaching a reduced effect size.

Furthermore, this study indicated the potential of this repetitive procedure to undertake sub-group analysis. Disaggregating the data by groups of participants who have received upper limb intervention and those who have received lower limb interventions it was possible to illustrate a statistical significant difference on the mean duration of daily therapy only for the group receiving upper limb intervention.

STUDY STRENGTHS

This study highlighted the feasibility of applying multiple assessment procedure in stroke clinical research. The upcoming benefit of this procedure was the possibility to explore participants’ therapy response over time, informing on the appropriate length of intervention. This procedure could deliver more cost-effective therapies but also it could provide relevant information of participants’ response to specific therapies. For example this procedure could allow an early identification of the subgroup(s) of participants that could benefit more from the applied therapy or dose. The

development of rehabilitative programme to fit individual's needs is welcomed to the research community [67,131] and the application of repetitive assessments is a promising way to go forward. However, further research on this direction is required.

A further advantage of applying a multiple assessment procedure is a potential reduction of the bias induced by the loss of end-point data (attrition), often seen in clinical trials. With this procedure, the loss of one (or more) assessment point still allows data analysis, under less stringent assumptions than random attrition. For instance, if the latest observation becomes missing, the previous one (or the subsequent one) can be used instead to infer on the missing value. This would not be possible in a pre and post observation design where subjects with missing post observation (or pre observation) data will inevitably be eliminated from the analyses.⁶⁷

LIMITS OF THE STUDY

The small number of participants enrolled in this study could have impacted on the trial results. However, such a sample size is common with several feasibility studies [247,314] and in line with other feasibility studies (i.e. [315,316,317]). Besides, it was sufficient to derive participants and groups therapy effect curves over time. Appendix W gives the sample size calculation assuming that the Fugl-Meyer assessment was used as a primary outcome measure.

Another concern was the documented differences in baseline (pre intervention) characteristics found among participants who undertook only the trial intervention and participants who undertook the additional assessment before the trial intervention. This could have influenced our estimated impact of the Fugl-Meyer assessment. Unbalanced groups, however, was driven by the nature of this trial (i.e. an embedded study). The randomization procedure was only undertaken for allocating participants to

⁶⁷ Strictly speaking, we referred here to the “*listwise deletion*” method for handling missing data. According this method, an entire observation is excluded from analysis if any single value is missing.

the intervention groups and not for allocating those undertaking/not-undertaking the repetitive assessments. However, the main aim of this embedded study was to assess the feasibility of a repetitive assessment procedure in stroke clinical research, rather than providing data on the appropriate length of therapy.

Finally, the length and physical effort required to undertake the additional Fugl-Meyer assessment could have increased the burden associated with the trial. The decision to test only the motor function domains of the Fugl-Meyer was made to limit this burden, while preserving the scope of the trial assessment.

Chapter 7:

Conclusions and implications for future research

This research work reflected the attempt to make a contribution to the complex and challenging field of dose optimization in motor interventions, by fulfilling the knowledge gap on optimal intervention doses and protocols in stroke rehabilitation clinical research.

To fulfill this research breakthrough, three main aims were set:

1. to identify dose optimization approaches and designs that were suitable for use in stroke rehabilitation research;
2. to test the feasibility of a novel phase I dose optimization trial design for motor interventions after stroke; and
3. to assess the feasibility and acceptability of undertaking repetitive assessments to identify the appropriate length of stroke rehabilitative interventions in a clinical efficacy trial.

This chapter offers a discussion of the methodology used for this thesis and the results achieved. The project is ultimately placed within the wider context of stroke rehabilitation research.

The following section starts discussing how well the aims and objectives of this research project have been addressed.

1. Identification of suitable dose optimisation approaches and designs

The *first aim* of this research project was to identify dose optimization approaches suitable for use in stroke rehabilitation research. To do so, dose optimization approaches applied in exercise-based training research were investigated with a systematic review (Chapter 2). Results from this review highlighted that, despite the existence of a large number of studies pooled by guidelines on recommended training doses, only a small number of these studies investigated the intervention dose-response relationship to identify appropriate dose or protocol endpoints. Furthermore, even those studies which investigated the appropriate dose or protocol, they often applied sub-optimal designs and approaches towards dose optimization.

The lack of reliable and efficient dose optimization designs in exercise-based training literature drew the attention to pharmaceutical research which was identified as the field applying the “gold” standard dose optimization designs and approaches. A narrative systematic review on pharmaceutical dose optimization clinical research was undertaken (Chapter 3) and showed that, in this field, there is a clear, standardised and efficient research pathway towards the identification of optimal drugs doses and protocols. In brief, the first dose optimization studies are the so called dose-finding studies. These studies are small and used as precursor of clinical efficacy studies to suggest appropriate doses early in the research pathway. They are often followed by dose-ranging studies which aim at confirming and adjusting the optimal therapeutic dose and protocol in wider samples.

The information gathered from the reviews on dose optimization approaches in exercise-based training and pharmaceutical literature were then used to devise the novel phase I dose optimization trial design for motor intervention. Specifically, among the dose optimization designs applied in pharmaceutical research, a phase I 3+3 rule-based, outcome-adaptive dose-finding design was chosen to be adapted for use in stroke rehabilitation research. The development of this novel design was undertaken in the methodological chapter of this thesis (Chapter 4).

2. Testing feasibility and informative nature of a dose-finding trial design

The *second aim* of this research project was to test the feasibility and informative nature of the newly devised dose-finding design for motor interventions after stroke. In detail, the feasibility of the 3+3 dose-finding design and all its characteristic features were tested with moderately impaired stroke survivors undertaking an upper limb model-task intervention (Chapter 5).

All the operating characteristics of this novel trial design were found feasible with the selected group of stroke survivors. Cohorts of three participants were found to be adequate and efficient to guide the devised trial algorithm through the dose escalation and de-escalation procedures. The final sample size of 15 participants was appropriate and in line with existing literature on dose optimization in pharmaceutical research. The multi-stage recruitment allowed the recruitment of the needed sample in the foreseen time frame. The trial stopping rules were useful to avoid the delivery of similar doses between cohorts and to guarantee participants' safety. The relatively short length of the study (2 weeks), and the considerable effort made on engaging participants to the training and overall trial, allowed to achieve 100% of retention rate. The data collected from this trial enabled the use of standard statistical models for pharmaceutical dose-finding trials for their analysis. The use of these statistical models were found relevant for stroke rehabilitation research, allowing preliminary study on the training dose-response relationship. Acknowledging that the purpose of this trial was to test the informative nature of the design, and not to use the numerical data on the optimal dose further, the analysis enabled the derivation of the maximal tolerable dose as 209 repetitions and the recommended phase II dose as 162 repetitions of the applied model-task intervention.

Some refinements to the reported dose-finding design should be considered for further studies to enhance the appropriateness of dose optimization process on motor interventions. Firstly, the issues of heterogeneity on participants' characteristics among cohorts, highlighted in this trial, should be limited considering the possible interrelationship between optimal training

dose and subject' characteristics. Although the cohorts' heterogeneity did not affect the results of this trial on the feasibility of implementing a dose-finding design to stroke rehabilitation research, it could compromise results on doses. Secondly, the stopping rule limit of 10% difference between subsequent cohorts used in this trial could be overestimated when applied to a different intervention. Therefore, considering the rapid increments in the numbers of repetitions assigned by the escalation procedure, a 10% difference from the last beneficial dose between subsequent cohorts could be used instead. Thirdly, although the electronic counter was considered by participants as a good support to track high number of task repetitions, few issues were acknowledged with the implemented device causing some missing or incorrect data recording. A different or refined system to objectively record participants' achieved number of repetitions is therefore advisable. Finally, the use of a reliable and validated primary outcome measure should be used in further studies to increase reliability of results on dose.

3. Testing feasibility and acceptability of repetitive assessments in a clinical trial

To fulfill the *third aim* of this research, a repetitive assessment was embedded in a stroke rehabilitation clinical efficacy trial (Chapter 6). The results of this longitudinal study showed that it was feasible and acceptable to deliver a weekly repetitive assessments procedure in stroke rehabilitation efficacy trials without affecting the trial intervention outcomes. The data retrieved were sufficient to study the treatment effect over-time and to provide indication on the appropriate length of the applied intervention. Acknowledging that this trial was explorative on the feasibility to apply repetitive assessments in stroke rehabilitation research, it was able to indicate that participants receiving the trial upper limb intervention enhanced their motor functions steadily over the six weeks of intervention. This result could imply that more than six weeks of the trial upper limb intervention may be required to reach maximal therapy effect. Whereas, for participants receiving trial lower limb intervention, the peak of improvement was reached after five

weeks of intervention, although there was not a statistically significant difference.

The analysis on the impact of the additional repetitive assessment seemed to suggest that the assessment used in this trial, the Fugl-Meyer assessment, increased the burden of the trial. In fact, the length and physical effort required to undertake the additional Fugl-Meyer assessments appeared to have impacted on the delivery of the trial intervention for the weakest and frailer participants or, on the amount of therapy that the therapists were able to deliver. Some adjustments on the undertaken assessment (e.g. using a less demanding assessment, or an assessment integrated into the therapy) are therefore advisable to limit these upcoming issues.

How this thesis has contributed to stroke rehabilitation research

The systematic review in exercise-based training literature undertaken in this thesis had the innovative value to explore the methodological aspects of dose optimization in the primary trials upon which the guidelines and recommendations on appropriate dose of training were based. Understanding the designs and the approaches applied to dose optimization gave indication on the strength of results and recommendations on training dose and protocol. The studies' risk of bias assessment applied in this review focused on the dose optimization protocols, providing further information on the strength of results on optimal doses and protocols. The taxonomic study conducted in this review on the definition and use of the training dose and its components, alongside with the assessment of the current recommendations on training dose and protocol provided useful indication for further research trajectories for motor interventions.

Results from the systematic review in exercise-based training literature highlighted that only dose-ranging approaches had been applied to identify the appropriate training dose and protocol. These designs only allowed the limited investigation of pre-defined numbers and levels of dose. As a result,

the study's ability to investigate the dose-response relationships, and the ability to identify the appropriate dose of training was confined to the appropriateness of the tested doses. Dose-ranging approaches are therefore, inefficient and inadequate to improve the current gap of knowledge on the dose-response relationship in stroke rehabilitation research. This review also highlighted some important aspects to preserve reliability of data during dose optimization processes of motor interventions. Firstly, the importance of finding a meaningful definition of the “training dose”, which accounted for its multifactorial aspects. Secondly, the need to use a standardised and consistent terminology on dose to contrast the existing heterogeneity on the way key concepts of the training dose and protocol were defined. Finally, the need to use adequate and controlled procedures when manipulating the components of the training to increase reliability of the results on appropriate dose. Moreover, this review helped in understanding how the different components of the training dose and protocol were manipulated and which controls were undertaken in the existing practice of dose optimization in exercise-based training research.

The second review undertaken in this research project, a narrative systematic review on dose optimization approaches applied in pharmaceutical clinical research, was also the first of its kind with the specific aim of providing key features to inform dose optimisation methods for stroke rehabilitation research. Results from this review found that, in pharmaceutical clinical research dose-finding designs were commonly viewed as the best designs to target dose endpoints in the early stage of the research, given their adaptive nature in exploring the dose-response relationship and their elevate efficiency. Furthermore, this review highlighted that each stage of the pharmaceutical dose optimization research pathway saw the implementation of different approaches to answer different questions on dose as well as target different dose endpoint(s). The implementation of a standardised pathway to dose optimization increases the reliability of the research results allowing more control on the applied research procedure(s). This control has

the scope to preserve patients' safety, as well as monitor efficiency of the research.

The information gathered from the two aforementioned reviews helped to devise a novel dose-finding trial design expressly designed for use in stroke rehabilitation research. The methodological work behind this research thesis adopted, for the first time, a pharmaceutical dose-finding design to the specificities of the stroke rehabilitation field. The features of the developed dose-finding design reflected the attempt to establish a standardised and efficient procedure to dose optimization for motor interventions in general, and stroke rehabilitation research in particular.

During the writing-up period of this thesis, Dite and colleagues published a study implementing a different form of a pharmaceutical dose escalation design applied to stroke rehabilitation research [293]. However, the design implemented in Dite and colleagues' study raised concerns that brought critical difficulties in the evaluation of their results.

The dose-finding design presented in this research work differed significantly from that of Dite and colleagues' study and presented some methodological advantages. For instance, in the dose-finding trial used in this thesis, the training dose was consistent within participants of the same cohort and only one parameter of the dose, the amount of training, was manipulated among subsequent cohorts. This procedure was used to increase the understanding of the underline active training parameter(s) able to maximise therapy effect, besides enhancing the clarity on the dose-response relationship results. In Dite and colleagues' study the training protocol comprised more than one intervention which differed among training weeks and within participants. Additionally, dose increments were allowed within cohorts. This approach could bring uncertainty on the dose-response relationship and on the true effect of dose.

In the study reported in this thesis, an analysis on the recommended phase II dose was introduced, alongside with the study on the maximal tolerable dose, which is more common in pharmaceutical studies. This additional analysis

acknowledged that, in motor interventions, the interest is on the intervention effect, rather than on the dose toxicity. A dose-escalation procedure was also planned in this study allowing for a non-increasing dose-response relationship. This could help to closely target the recommended dose of motor interventions. In Dite and colleagues' study, the dose escalation plan was not based on clinical efficacy. Consequently, the dose-response relationship could not be studied and, the recommended phase II dose could not be determined. As in pharmaceutical dose-finding studies, in Dite and colleagues' study the dose-limiting tolerance (dose toxicity) was the guiding parameter for the dose-escalation procedure. A dose-escalation procedure was not planned. Following this approach, they made the assumption that the intervention efficacy increased monotonically with the dose and, therefore, the appropriate dose to use corresponded to the maximal tolerable dose. This assumption, however, has not been verified yet for motor interventions. Some safety issues can also arise implementing the maximal tolerable dose in subsequent trials. Interestingly, in the study reported in this thesis, the recommended dose was about 78% of the maximal tolerable dose. In clinical practice, this result could bring concerns for safety, as well as representing a considerable resources saving for the health system compared with the provision of the maximal tolerable dose.

Two checking rules were implemented in the study reported in this thesis to limit the issue of heterogeneity on participants' presentation and therapy response when using small sample size of participants as the ones commonly employed in dose-finding designs. In Dite and colleagues' study the possible issue brought by the small cohorts' size was addressed only by restricting the study inclusion criteria. This approach could improve the reliability of trial results on dose due to heterogeneity among and across cohorts but could reduce the generalisability of the results. Furthermore, if inclusion criteria were set too restrictive, the time and resources needed for the recruitment process could increase dramatically.

Unlike the study reported in this research project, in Dite and colleagues' study the starting dose was relatively high, which did not allowed any increase

of the dose. Only two cohorts were enrolled before the identification of the maximal tolerable dose.

To allow for a high level of control and restriction on both the trial intervention and the training dose, the dose-finding study reported in this thesis applied a model-task intervention. In a pharmaceutical dose-finding study, apart from the dose, the delivered treatment is identical across participants and among groups. The model-task intervention imitated this high controlled research setting. This approach, while increasing the reliability of results, could limit the generalisability of the results. In this respect, the study implemented by Dite and colleagues is promising when assessing the feasibility of dose-finding pharmaceutical approaches with complex stroke rehabilitation interventions. Both trials devised in this thesis and in Dite and colleagues' study should be seen as a call for further research to explore the use and relevance of dose optimization procedures in pilot studies implementing complex stroke rehabilitative therapies.

As the first project of its kind, the initial results of the study reported in this thesis successfully show the implementation of a dose-finding design derived from pharmaceutical literature to stroke rehabilitation research. This could make a step forward in the stroke rehabilitation research pathway tackling the issue of dose optimization for motor interventions. As shown in this study, the implementation of standardised dose-finding designs in stroke rehabilitation research is likely to provide empirical robust evidence to substantiate claims for appropriate dose of physical therapy proven to be feasible, safe and able to maximise motor recovery. The use of early dose-finding studies can help minimise the proliferation of inconclusive or divergent clinical studies, as studies will use more appropriate doses and hence increase their ability to find a significant difference. As an example, in 2008, a phase II study assessed the safety and feasibility of a very early mobilization (VEM) approach at high dose after stroke [79]. In 2011, Cunning et al. indicated that high dose of VEM was more effective than standard care mobilization in improving sooner, independent walking but failed to show statistical significant post-intervention differences in clinical scores [318].

Recently, the AVERT trial challenged these results [82] by finding that participants enrolled to receive a very early, high dose mobilization intervention did significantly worse than participants receiving early, lower dose mobilization. These findings were in line with our results which suggested that the more effective dose might be smaller than the maximal dose that participants were able to sustain and may warn against the use of high intensive training protocol before more evidence is available.

The use of small cohorts' sizes, typical of these designs, is likely to increase efficiency of stroke rehabilitation research and any other research that faces daunting challenges in the recruitment of participants and the associated costs.

The second study implemented in this research project assessed another uncommon optimization procedure in stroke rehabilitation research: the feasibility and its informative nature to deliver a repetitive assessments procedure. The use of repetitive assessment procedures, in early efficacy trials, could improve research outcomes by guiding the implementation of appropriate duration of the training intervention and therefore maximising the treatment efficacy, as currently happening in other medical research fields [130,131]. It is also worth highlighting that the implementation of repetitive assessment procedures can bring two additional advantages. Firstly, it can help in reducing the attrition bias, i.e. the bias induced by the loss of end-point data, often seen in clinical trials. With a repetitive assessments procedure, the loss of one (or more) assessment point(s) still allows data analysis. Secondly, it gives the possibility to analyse data on the therapy time course effect dividing participants in sub-groups depending on their abilities or characteristics. This could help to early identify participants that could benefit more (or less) from the applied therapy or dose tailoring personalised rehabilitation plans. As reported by Kwakkel and Dobkin, as well as being widely acknowledged by the research community, the development of rehabilitative programme to fit individual's specific needs is a goal to enhance stroke rehabilitation outcomes [67,131].

Further developments

The future steps of this research could see the implementation of the phase I 3+3 dose-finding design and the multiple assessments procedure to stroke rehabilitation research to seek confirmatory results. In detail, the dose-finding design will be set using a complex rehabilitative intervention providing information on the feasibility and relevance of this dose-finding design in the “real world” clinical research setting.

Whereas, a less wearying assessment could be implemented in a longitudinal study to gain further confirmatory results on the feasibility and tolerability of this repetitive assessments procedure in early efficacy rehabilitative trials with stroke survivors.

In conclusion, this methodological thesis has contributed to move the dose optimization process in stroke rehabilitation research forward. It showed that fixed designs and posterior analyses might not be the best approaches to maximise trial efficacy and to investigate the appropriate training dose and protocols. Interim analyses and flexible designs can be used instead to target the appropriate dose and length of training and to improve research efficiency.

The feasibility and relevance for stroke rehabilitation research of new and efficacious methodologies able to identify the appropriate dose and length of therapy presented in this thesis provided the groundwork for further research in this field.

The regular and standardised implementation of the dose optimization designs reported in this research thesis could improve the future of stroke rehabilitation research. The implementation, early on in the research pathway, of reliable doses which have been proven to be feasible, effective and safe could enhance patients’ motor recovery maximising training effect and increase research efficiency reducing the chance to deliver sub-therapeutic or dangerous doses in costly phase II efficacy trials.

References

1. Association S (2016) The state of the nation, stroke statistics. stroke.org.uk.
2. National Audit Office, Alex Scharaschkin, William Palmer *et al.* (2010) Progress in improving stroke care. In: Health Do, editor. London: Stationery Office Limited.
3. Ekman M Economic evidence in stroke: a review. *The European Journal of Health Economics* 2004; 5: s74-s83.
4. Young J, Forster A Review of stroke rehabilitation. *BMJ* 2007; 334: 86-90.
5. Mackay J, Mensah G (2004) The Atlas of Heart Disease and Stroke. The Atlas of Heart Disease and Stroke. Geneva, Switzerland,,: World Health Organization.
6. Kelly-Hayes M, Beiser A, Kase CS *et al.* The influence of gender and age on disability following ischemic stroke: the Framingham study. *J Stroke Cerebrovasc Dis* 2003; 12: 119-26.
7. Langhorne P, Coupar F, Pollock A Motor recovery after stroke: a systematic review. *Lancet Neurol* 2009; 8: 741-54.
8. Patel M, Coshall C, Rudd AG *et al.* Natural history of cognitive impairment after stroke and factors associated with its recovery. *Clinical Rehabilitation* 2003; 17: 158-66.
9. Lawrence ES, Coshall C, Dundas R *et al.* Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population. *Stroke* 2001; 32: 1279-84.
10. Martino R, Foley N, Bhogal S *et al.* Dysphagia After Stroke: Incidence, Diagnosis, and Pulmonary Complications. *Stroke* 2005; 36: 2756-63.
11. Warlow C, van Gijn J, et al. *Stroke: Practical Management*: Oxford: Blackwell Publishing, 2008.
12. Sainburg RL, Duff SV Does motor lateralization have implications for stroke rehabilitation? *J Rehabil Res Dev* 2006; 43: 311-22.
13. Gonzalez CL, Gharbawie OA, Williams PT *et al.* Evidence for bilateral control of skilled movements: ipsilateral skilled forelimb reaching deficits and functional recovery in rats follow motor cortex and lateral frontal cortex lesions. *Eur J Neurosci* 2004; 20: 3442-52.
14. Yarosh CA, Hoffman DS, Strick PL Deficits in movements of the wrist ipsilateral to a stroke in hemiparetic subjects. *J Neurophysiol* 2004; 92: 3276-85.
15. Wetter S, Poole JL, Haaland KY Functional implications of ipsilesional motor deficits after unilateral stroke. *Arch Phys Med Rehabil* 2005; 86: 776-81.
16. Nudo RJ Recovery after brain injury: mechanisms and principles. *Frontiers in Human Neuroscience* 2013; 7: 887.
17. Chen H, Epstein J, Stern E Neural plasticity after acquired brain injury: evidence from functional neuroimaging. *PM R* 2010; 2: S306-12.
18. Liu Z, Chopp M, Ding X *et al.* Axonal remodeling of the corticospinal tract in the spinal cord contributes to voluntary motor recovery after stroke in adult mice. *Stroke* 2013; 44: 1951-6.

19. Murphy TH, Corbett D Plasticity during stroke recovery: from synapse to behaviour. *Nat Rev Neurosci* 2009; 10: 861-72.
20. Nudo RJ. The mechanisms and neurophysiology of recovery from stroke. In: Stein J, Zorowitz R, Harvey R, *et al.*, ed.^editors. *Stroke Recovery & Rehabilitation*. ed. New York, NY: Demos Medical Publishing, 2009:123-34.
21. Ward NS, Brown MM, Thompson AJ *et al.* *Neural correlates of motor recovery after stroke: a longitudinal fMRI study*. 2476-96 p, 2003.
22. Kwakkel G, van Peppen R, Wagenaar RC *et al.* Effects of augmented exercise therapy time after stroke: a meta-analysis. *Stroke* 2004; 35: 2529-39.
23. Hosp JA, Luft AR Cortical plasticity during motor learning and recovery after ischemic stroke. *Neural Plast* 2011; 2011: 871296.
24. Langhorne P, Bernhardt J, Kwakkel G Stroke rehabilitation. *Lancet* 2011; 377: 1693-702.
25. Dobkin B, TS C. Principles of recovery after stroke. In: ed.^editors. *Recovery after stroke*. ed.: Cambridge: Cambridge University Press, 2005.
26. Kwakkel G, Kollen B, Lindeman E Understanding the pattern of functional recovery after stroke: facts and theories. *Restor Neurol Neurosci* 2004; 22: 281-99.
27. Wolf SL, Winstein CJ, Miller JP *et al.* Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA* 2006; 296: 2095-104.
28. Dean CM, Richards CL, Malouin F Task-related circuit training improves performance of locomotor tasks in chronic stroke: A randomized, controlled pilot trial. *Archives of Physical Medicine and Rehabilitation* 2000; 81: 409-17.
29. Hsieh YW, Wu CY, Lin KC *et al.* Dose-response relationship of robot-assisted stroke motor rehabilitation: the impact of initial motor status. *Stroke* 2012; 43: 2729-34.
30. Duncan PW, Horner RD, Reker DM *et al.* Adherence to postacute rehabilitation guidelines is associated with functional recovery in stroke. *Stroke* 2002; 33: 167-77.
31. Intercollegiate Stroke Working Party (2012) National clinical guideline for stroke. In: The Royal College of Physicians, editor. 4th ed. <http://www.rcplondon.ac.uk/sites/default/files/national-clinical-guidelines-for-stroke-fourth-edition.pdf>.
32. Liepert J, Miltner WH, Bauder H *et al.* Motor cortex plasticity during constraint-induced movement therapy in stroke patients. *Neurosci Lett* 1998; 250: 5-8.
33. Carey JR, Kimberley TJ, Lewis SM *et al.* Analysis of fMRI and finger tracking training in subjects with chronic stroke. *Brain* 2002; 125: 773-88.
34. Brainin M, Heiss W-D *Textbook of Stroke Medicine*: Cambridge University Press, 2010.
35. Chen MD, Rimmer JH Effects of exercise on quality of life in stroke survivors: a meta-analysis. *Stroke* 2011; 42: 832-7.

36. Kwakkel G, Kollen BJ, Krebs HI Effects of robot-assisted therapy on upper limb recovery after stroke: a systematic review. *Neurorehabil Neural Repair* 2008; 22: 111-21.
37. Page SJ, Schmid A, Harris JE Optimizing terminology for stroke motor rehabilitation: recommendations from the American Congress of Rehabilitation Medicine Stroke Movement Interventions Subcommittee. *Arch Phys Med Rehabil* 2012; 93: 1395-9.
38. Pollock A, St George B, Fenton M *et al.* Top ten research priorities relating to life after stroke. *Lancet Neurol* 2012; 11: 209.
39. Veerbeek JM, van Wegen E, van Peppen R *et al.* What Is the Evidence for Physical Therapy Poststroke? A Systematic Review and Meta-Analysis. *PLoS ONE* 2014; 9.
40. Barker RN, Brauer SG Upper limb recovery after stroke: The stroke survivors' perspective. *Disability and Rehabilitation* 2005; 27: 1213-23.
41. Cauraugh JH, Lodha N, Naik SK *et al.* Bilateral movement training and stroke motor recovery progress: a structured review and meta-analysis. *Hum Mov Sci* 2010; 29: 853-70.
42. French B, Thomas LH, Leathley MJ *et al.* Repetitive Task Training for Improving Functional Ability After Stroke. *Stroke* 2009; 40: e98-e99.
43. Kleim JA, Jones TA Principles of Experience-Dependent Neural Plasticity: Implications for Rehabilitation After Brain Damage. *J Speech Lang Hear Res* 2008; 51: S225-39.
44. DeJong G, Horn SD, Gassaway JA *et al.* Toward a taxonomy of rehabilitation interventions: using an inductive approach to examine the "black box" of rehabilitation. *Archives of Physical Medicine and Rehabilitation* 2004; 85: 678-86.
45. Ammann BC, Knols RH, Baschung P *et al.* Application of principles of exercise training in sub-acute and chronic stroke survivors: a systematic review. *BMC Neurol* 2014; 14: 167.
46. Winter J, Hunter S, Sim J *et al.* Hands-on therapy interventions for upper limb motor dysfunction following stroke. *Cochrane Database Syst Rev* 2011: CD006609.
47. Young J, Forster A *Review of stroke rehabilitation*. 86-90 p, 2007.
48. Laney J, Adali T, McCombe Waller S *et al.* Quantifying motor recovery after stroke using independent vector analysis and graph-theoretical analysis. *Neuroimage Clin* 2015; 8: 298-304.
49. Byl NN, Pitsch EA, Abrams GM Functional outcomes can vary by dose: Learning-based sensorimotor training for patients stable poststroke. *Neurorehabilitation and Neural Repair* 2008; 22: 494-504.
50. Hornby TG, Straube DS, Kinnaird CR *et al.* Importance of specificity, amount, and intensity of locomotor training to improve ambulatory function in patients poststroke. *Top Stroke Rehabil* 2011; 18: 293-307.
51. Kwakkel G Impact of intensity of practice after stroke: issues for consideration. *Disabil Rehabil* 2006; 28: 823 - 30.
52. Kwakkel G, Kollen BJ, Wagenaar RC Long term effects of intensity of upper and lower limb training after stroke: a randomised trial. *J Neurol Neurosurg Psychiatry* 2002; 72: 473-9.

53. Kwakkel G, Wagenaar RC, Koelman TW *et al.* Effects of intensity of rehabilitation after stroke. A research synthesis. *Stroke* 1997; 28: 1550 - 56.
54. Campbell NC, Murray E, Darbyshire J *et al.* Designing and evaluating complex interventions to improve health care. *BMJ* 2007; 334: 455-59.
55. Hoyer EH, Celnik PA Understanding and enhancing motor recovery after stroke using transcranial magnetic stimulation. *Restor Neurol Neurosci* 2011; 29: 395-409.
56. Teasell R, Bayona NA, Bitensky J Plasticity and reorganization of the brain post stroke. *Top Stroke Rehabil* 2005; 12: 11-26.
57. Ward NS, Brown MM, Thompson AJ *et al.* Neural correlates of outcome after stroke: a cross-sectional fMRI study. *Brain* 2003; 126: 1430-48.
58. Cortes M, Black-Schaffer RM, Edwards DJ Transcranial magnetic stimulation as an investigative tool for motor dysfunction and recovery in stroke: an overview for neurorehabilitation clinicians. *Neuromodulation* 2012; 15: 316-25.
59. Johansen-Berg H, Dawes H, Guy C *et al.* Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain* 2002; 125: 2731-42.
60. Liepert J, Graef S, Uhde I *et al.* Training-induced changes of motor cortex representations in stroke patients. *Acta Neurologica Scandinavica* 2000; 101: 321-26.
61. Marshall RS, Perera GM, Lazar RM *et al.* Evolution of cortical activation during recovery from corticospinal tract infarction. *Stroke* 2000; 31: 656-61.
62. Koski L, Mernar TJ, Dobkin BH Immediate and Long-Term Changes in Corticomotor Output in Response to Rehabilitation: Correlation with Functional Improvements in Chronic Stroke. *Neurorehabilitation and Neural Repair* 2004; 18: 230-49.
63. Krakauer JW Motor learning: its relevance to stroke recovery and neurorehabilitation. *Current Opinion in Neurology* 2006; 19: 84-90.
64. Bowden MG, Woodbury ML, Duncan PW Promoting neuroplasticity and recovery after stroke: future directions for rehabilitation clinical trials. *Curr Opin Neurol* 2013; 26: 37-42.
65. Byl N, Pitsch E, Abrams G Functional outcomes can vary by dose: learning-based sensorimotor training for patients stable poststroke. *Neurorehabilitation & Neural Repair* 2008; 22: 494 - 504.
66. Hornby TG, Straube DS, et al. Importance of Specificity, Amount, and Intensity of Locomotor Training to Improve Ambulatory Function in Patients Poststroke. *Top Stroke Rehabil* 2011; 18: 293-307.
67. Kwakkel G Impact of intensity of practice after stroke: issues for consideration. *Disability and Rehabilitation* 2006; 28: 823 - 30.
68. NICE (2013) NICE clinical guideline 162. In: NICE, editor. Level 1A, City Tower, Piccadilly Plaza, Manchester M1 4BT: NICE.
69. Birkenmeier RL, Prager EM, Lang CE Translating Animal Doses of Task-Specific Training to People With Chronic Stroke in 1-Hour Therapy Sessions: A Proof-of-Concept Study. *Neurorehabilitation and Neural Repair* 2010; 24: 620-35.

70. Kwakkel G, Wagenaar RC, Twisk JWR *et al.* Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. *Lancet* 1999; 354: 191-96.
71. Taub E, Uswatte G, Pidikiti R Constraint-Induced Movement Therapy: a new family of techniques with broad application to physical rehabilitation--a clinical review. *J Rehabil Res Dev* 1999; 36: 237-51.
72. Lohse KR, Lang CE, Boyd LA Is more better? Using metadata to explore dose-response relationships in stroke rehabilitation. *Stroke* 2014; 45: 2053-8.
73. Dobkin BH Rehabilitation and Functional Neuroimaging Dose-Response Trajectories for clinical trials. *Neurorehab and Neural Repair* 2005; 19: 276-82.
74. Dobkin BH Progressive staging of pilot studies to improve Phase III trials for motor interventions. *Neurorehabilitation & Neural Repair* 2009; 23: 197 - 206.
75. Pomeroy V, Aglioti SM, Mark VW *et al.* Neurological Principles and Rehabilitation of Action Disorders: Rehabilitative Interventions. *Neurorehab. and Neural Repair* 2011; 25: 33S-43S.
76. Schmidt RA, IL C *Motor learning and performance : from principles to application*: Champaign, IL : Human Kinetics, 2014.
77. Dayan E, Cohen LG Neuroplasticity subserving motor skill learning. *Neuron* 2011; 72: 443-54.
78. Ottenbacher KJ, Jannell S The results of clinical trials in stroke rehabilitation research. *Arch Neurol* 1993; 50: 37-44.
79. Bernhardt J, Dewey H, Thrift A *et al.* A very early rehabilitation trial for stroke (AVERT): phase II safety and feasibility. *Stroke* 2008; 39: 390-6.
80. Bernhardt J, Thuy MN, Collier JM *et al.* Very early versus delayed mobilisation after stroke. *Cochrane Database Syst Rev* 2009: CD006187.
81. Johansson BB Brain Plasticity and Stroke Rehabilitation: The Willis Lecture. *Stroke* 2000; 31: 223-30.
82. The AVERT Trial Collaboration group Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *The Lancet* 2015; 386: 46-55.
83. Foley N, Pereira S, Salter K *et al.* Are recommendations regarding inpatient therapy intensity following acute stroke really evidence-based? *Top Stroke Rehabil* 2012; 19: 96-103.
84. Duncan PW, Zorowitz R, Bates B *et al.* Management of Adult Stroke Rehabilitation Care: a clinical practice guideline. *Stroke* 2005; 36: e100-43.
85. Kleim JA, Jones TA Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J Speech Lang Hear Res* 2008; 51: S225-39.
86. Monfils MH, Teskey GC Skilled-learning-induced potentiation in rat sensorimotor cortex: a transient form of behavioural long-term potentiation. *Neuroscience* 2004; 125: 329-36.
87. Krakauer JW, Carmichael ST, Corbett D *et al.* Getting neurorehabilitation right: what can be learned from animal models? *Neurorehab Neural Repair* 2012; 26: 923-31.

88. Cha J, Heng C, Reinkensmeyer DJ *et al.* Locomotor Ability in Spinal Rats Is Dependent on the Amount of Activity Imposed on the Hindlimbs during Treadmill Training. *Journal of Neurotrauma* 2007; 24: 1000-12.
89. Kleim JA, Barbay S, Cooper NR *et al.* Motor learning-dependent synaptogenesis is localized to functionally reorganized motor cortex. *Neurobiol Learn Mem* 2002; 77: 63-77.
90. Nudo RJ, Wise BM, SiFuentes F *et al.* Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science* 1996; 272: 1791-94.
91. Kleim JA, Barbay S, Nudo RJ Functional Reorganization of the Rat Motor Cortex Following Motor Skill Learning. *J Neurophysiol* 1998; 80: 3321-25.
92. MacLellan CL, Keough MB, Granter-Button S *et al.* A critical threshold of rehabilitation involving brain-derived neurotrophic factor is required for poststroke recovery. *Neurorehabil Neural Repair* 2011; 25: 740-8.
93. Xerri C, Merzenich MM, Peterson BE *et al.* Plasticity of primary somatosensory cortex paralleling sensorimotor skill recovery from stroke in adult monkeys. *J Neurophysiol* 1998; 79: 2119-48.
94. Birkenmeier RL, Prager EM, Lang CE Translating animal doses of task-specific training to people with chronic stroke in 1-hour therapy sessions: a proof-of-concept study. *Neurorehabil Neural Repair* 2010; 24: 620-35.
95. Waddell KJ, Birkenmeier RL, Moore JL *et al.* Feasibility of high-repetition, task-specific training for individuals with upper-extremity paresis. *Am J Occup Ther* 2014; 68: 444-53.
96. Farrell R, Evans S, Corbett D Environmental enrichment enhances recovery of function but exacerbates ischemic cell death. *Neuroscience* 2001; 107: 585-92.
97. Humm JL, Kozlowski DA, James DC *et al.* Use-dependent exacerbation of brain damage occurs during an early post-lesion vulnerable period. *Brain Res* 1998; 783: 286-92.
98. Kerr AL, Cheng S-Y, Jones TA Experience-dependent neural plasticity in the adult damaged brain. *J Commun Disord* 2011; 44: 538-48.
99. Risedal A, Zeng J, Johansson B Early training may exacerbate brain damage after focal brain ischemia in the rat. *Journal of Cerebral Blood Flow and Metabolism* 1999; 19: 997 - 1003.
100. Hillier S, English C, Crotty M *et al.* Circuit class or seven-day therapy for increasing intensity of rehabilitation after stroke: protocol of the CIRCIT trial. *Int J Stroke* 2011; 6: 560-5.
101. Hsieh YW, Wu CY, Liao WW *et al.* Effects of treatment intensity in upper limb robot-assisted therapy for chronic stroke: a pilot randomized controlled trial. *Neurorehabil Neural Repair* 2011; 25: 503-11.
102. Ouellette MM, LeBrosseur NK, Bean JF *et al.* High-Intensity Resistance Training Improves Muscle Strength, Self-Reported Function, and Disability in Long-Term Stroke Survivors. *Stroke* 2004; 35: 1404-09.
103. Haines TP, Kuys S, Clarke J *et al.* Dose-response relationship between physiotherapy resource provision with function and balance improvements in patients following stroke: a multi-centre observational study. *Journal of Evaluation in Clinical Practice* 2011; 17: 136-42.

104. Canning CG, Shepherd RB, Carr JH *et al.* A randomized controlled trial of the effects of intensive sit-to-stand training after recent traumatic brain injury on sit-to-stand performance. *Clin Rehabil* 2003; 17: 355-62.
105. Ouellette MM, LeBrasseur NK, Bean JF *et al.* High-intensity resistance training improves muscle strength, self-reported function, and disability in long-term stroke survivors. *Stroke* 2004; 35: 1404-9.
106. Sunderland A, Tinson DJ, Bradley EL *et al.* Enhanced physical therapy improves recovery of arm function after stroke. A randomised controlled trial. *J Neurol Neurosurg Psychiatry* 1992; 55: 530-5.
107. Richards CL, Malouin F, Wood-Dauphinee S *et al.* Task-specific physical therapy for optimization of gait recovery in acute stroke patients. *Archives of Physical Medicine and Rehabilitation* 2008; 74: 612-20.
108. Haines TP, Kuys S, Clarke J *et al.* Dose-response relationship between physiotherapy resource provision with function and balance improvements in patients following stroke: a multi-centre observational study. *J Eval Clin Pract* 2011; 17: 136-42.
109. Moore JL, Roth EJ, Killian C *et al.* Locomotor training improves daily stepping activity and gait efficiency in individuals poststroke who have reached a "plateau" in recovery. *Stroke* 2010; 41: 129-35.
110. Carey JR, Durfee WK, Bhatt E *et al.* Comparison of finger tracking versus simple movement training via telerehabilitation to alter hand function and cortical reorganization after stroke. *Neurorehabil Neural Repair* 2007; 21: 216-32.
111. Han C, Wang Q, Meng PP *et al.* Effects of intensity of arm training on hemiplegic upper extremity motor recovery in stroke patients: a randomized controlled trial. *Clin Rehabil* 2013; 27: 75-81.
112. Hunter SM, Hammett L, Ball S *et al.* Dose-Response Study of Mobilisation and Tactile Stimulation Therapy for the Upper Extremity Early After Stroke: A Phase I Trial. *Neurorehabil Neural Repair* 2011; 25: 314-22.
113. Yang YR, Yen JG, Wang RY *et al.* Gait outcomes after additional backward walking training in patients with stroke: a randomized controlled trial. *Clin Rehabil* 2005; 19: 264-73.
114. Di Lauro A, Pellegrino L, Savastano G *et al.* A randomized trial on the efficacy of intensive rehabilitation in the acute phase of ischemic stroke. *J Neurol* 2003; 250: 1206-8.
115. Dromerick A, Lang C, Birkenmier R *et al.* Very early constraint-induced movement during stroke rehabilitation (VECTORS). *Neurology* 2009; 73: 195 - 201.
116. Rodgers H, Mackintosh J, Price C *et al.* Does an early increased-intensity interdisciplinary upper limb therapy programme following acute stroke improve outcome? *Clinical Rehabilitation* 2003; 17: 579 - 89.
117. The Glasgow Augmented Physiotherapy Study G Can augmented physiotherapy input enhance recovery of mobility after stroke? A randomized controlled trial. *Clinical Rehabilitation* 2004; 18: 529 - 37.
118. English C, Veerbeek J Is more physiotherapy better after stroke? *Int J Stroke* 2015; 10: 465-6.

119. Lang CE, Lohse KR, Birkenmeier RL Dose and timing in neurorehabilitation: prescribing motor therapy after stroke. *Curr Opin Neurol* 2015; 28: 549-55.
120. Altman IM, Swick S, Malec JF Effectiveness of home- and community-based rehabilitation in a large cohort of patients disabled by cerebrovascular accident: evidence of a dose-response relationship. *Arch Phys Med Rehabil* 2013; 94: 1837-41.
121. Page SJ Intensity versus task-specificity after stroke: how important is intensity? *Am J Phys Med Rehabil* 2003; 82: 730-2.
122. Galvin R, Murphy B, Cusack T *et al.* The impact of increased duration of exercise therapy on functional recovery following stroke - what is the evidence? *Topics in Stroke Rehabilitation* 2008; 15: 365 - 77.
123. Langhorne P, Wagenaar R, Partridge C Physiotherapy after stroke: more is better? *Physiotherapy Research International* 1996; 1: 75 - 88.
124. Van Peppen RP, Kwakkel G, Wood-Dauphinee S *et al.* The impact of physical therapy on functional outcomes after stroke: what's the evidence? *Clin Rehabil* 2004; 18: 833-62.
125. Veerbeek JM, Koolstra M, Ket JC *et al.* Effects of augmented exercise therapy on outcome of gait and gait-related activities in the first 6 months after stroke: a meta-analysis. *Stroke* 2011; 42: 3311-5.
126. Cooke EV, Mares K, Clark A *et al.* The effects of increased dose of exercise-based therapies to enhance motor recovery after stroke: a systematic review and meta-analysis. *BMC Med* 2010; 8: 60.
127. Han C, Wang Q, Meng P-p *et al.* Effects of intensity of arm training on hemiplegic upper extremity motor recovery in stroke patients: a randomized controlled trial. *Clinical Rehabilitation* 2013; 27: 75-81.
128. Jorgensen HS, Nakayama H, Raaschou HO *et al.* Outcome and time course of recovery in stroke. Part II: Time course of recovery. The Copenhagen Stroke Study. *Arch Phys Med Rehabil* 1995; 76: 406-12.
129. Stein J, Bishop J, Gillen G *et al.* A pilot study of robotic-assisted exercise for hand weakness after stroke. *IEEE Int Conf Rehabil Robot* 2011; 2011: 5975426.
130. Whitall J, Byl N Stroke rehabilitation research: time to answer more specific questions? *Neurorehab. and Neural Repair* 2004; 17: 176-91.
131. Dobkin B Progressive staging of pilot studies to improve Phase III trials for motor interventions. *Neurorehabilitation & Neural Repair* 2009; 23: 197 - 206.
132. Teasell R Challenges in the implementation of evidence in stroke rehabilitation. *Top Stroke Rehabil* 2012; 19: 93-5.
133. Scottish Intercollegiate Guidelines Network Management of Patients with Stroke: Rehabilitation, Prevention and Management of Complications, and Discharge Planning (SIGN 118). . 2010.
134. Craig P, Dieppe P, Macintyre S *et al.* Developing and evaluating complex interventions: The new Medical Research Council guidance. *International Journal of Nursing Studies* 2013; 50: 587-92.
135. Cheung YK Coherence principles in dose-finding studies. *Biometrika* 2005; 92: 863-73.

136. Whittall J Stroke rehabilitation research: time to answer more specific questions? *Neurorehabil Neural Repair* 2004; 18: 3-8; author reply 9-11.
137. Pomeroy VM, Tallis RC Need to focus research in stroke rehabilitation. *Lancet* 2000; 355: 836-7.
138. Craig P, Dieppe P, Macintyre S *et al.* Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008; 337.
139. Ting N *Dose Finding in Drug Development*; Gail M KK, Samet J, Tsiatis A, Wong W, editor. New London, Connecticut: Pfizer, Springer ed., 2006.
140. Buford TW, Roberts MD, Church TS Toward Exercise as Personalized Medicine. *Sports medicine (Auckland, N.Z.)* 2013; 43: 157-65.
141. Pate RR, Pratt M, Blair SN *et al.* Physical Activity and Public Health -- A Recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine *JAMA* 1995: 402-07.
142. Haskell LM, Lee I-Min, pate RR *et al.* Physical Activity and Public Health: Updated Recommendation for Adults From the American College of Sports Medicine and the American Heart Association. . *Circulation* 2007; 116: 1081-93.
143. Nelson ME, Rejeski WJ, Blair SN *et al.* Physical Activity and Public Health in Older Adults. Recommendation From the American College of Sports Medicine and the American Heart Association. *Circulation J of the AM Heart Ass* 2007; 116: 1094-105.
144. Ratamess NA, Alvar BA, WEvetoch TK *et al.* *Progression models in resistance training for healthy adults*. American College of sport medicine, 2009.
145. American College of Sport and Medicine *ACSM's Guidelines for Exercise Testing and Prescription*; Thompson WR, editor. Philadelphia: Wolters Kluwer, Lippincott Williams & Wilkins, 2010.
146. Higgins, Green (2011) *Cochrane Handbook for Systematic Reviews of Interventions* In: Sons JW, editor. *Cochrane Handbook for Systematic Reviews of Interventions*.
147. Holm L, Reitelseder S, Pedersen TG *et al.* Changes in muscle size and MHC composition in response to resistance exercise with heavy and light loading intensity. *J Appl Physiol (1985)* 2008; 105: 1454-61.
148. McDermott MM, Liu K, Ferrucci L *et al.* Physical Performance in Peripheral Arterial Disease: A Slower Rate of Decline in Patients Who Walk More. *Annals of Internal Medicine* 2006; 144: 10-20.
149. Cauraugh JH, Coombes SA, Lodha N *et al.* Upper extremity improvements in chronic stroke: coupled bilateral load training. *Restor Neurol Neurosci* 2009; 27: 17-25.
150. Dromerick AW, Lang CE, Birkenmier RL *et al.* Very early constraint-induced movement during stroke rehabilitation (VECTORS). *Neurology* 2009; 73: 195 - 201.
151. Jigami H, Sato D, Tsubaki A *et al.* Effects of weekly and fortnightly therapeutic exercise on physical function and health-related quality of life in individuals with hip osteoarthritis. *Journal of Orthopaedic Science* 2012; 17: 737-44.

152. Marzolini S, Oh PI, Thomas SG *et al.* Aerobic and resistance training in coronary disease: single versus multiple sets. *Med Sci Sports Exerc* 2008; 40: 1557-64.
153. Miszko TA, Cress ME, Slade JM *et al.* Effect of Strength and Power Training on Physical Function in Community-Dwelling Older Adults. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 2003; 58: M171-M75.
154. Sato D, Kaneda K, Wakabayashi H *et al.* Comparison of 2-year effects of once and twice weekly water exercise on activities of daily living ability of community dwelling frail elderly. *Archives of Gerontology & Geriatrics* 2009; 49: 123-8.
155. da Silva PB, Antunes FN, Graef P *et al.* Strength training associated with task-oriented training to enhance upper-limb motor function in elderly patients with mild impairment after stroke: a randomized controlled trial. *Am J Phys Med Rehabil* 2015; 94: 11-9.
156. Ahtiainen JP, Pakarinen A, Alen M *et al.* Short vs. long rest period between the sets in hypertrophic resistance training: influence on muscle strength, size, and hormonal adaptations in trained men. *J Strength Cond Res.* 2005; 19: 572-82.
157. Humburg H, Baars H, Schröder J *et al.* 1-SET VS. 3-SET RESISTANCE TRAINING: A CROSSOVER STUDY. *Journal of Strength & Conditioning Research (Allen Press Publishing Services Inc.)* 2007; 21: 578-82.
158. Kemmler WK, Lauber D, Engelke K *et al.* EFFECTS OF SINGLE- VS. MULTIPLE-SET RESISTANCE TRAINING ON MAXIMUM STRENGTH AND BODY COMPOSITION IN TRAINED POSTMENOPAUSAL WOMEN. *Journal of Strength & Conditioning Research (Allen Press Publishing Services Inc.)* 2004; 18: 689-94.
159. Berger RA Optimum repetitions for the development of strength. *Res Q.* 1962; 33: 334-38.
160. Abrahin O, Rodrigues RP, Nascimento VC *et al.* Single- and multiple-set resistance training improves skeletal and respiratory muscle strength in elderly women. *Clinical Interventions in Aging* 2014; 9: 1775-82.
161. Baker JS, Davies B, Cooper SM *et al.* Strength and Body Composition Changes in Recreationally Strength-Trained Individuals: Comparison of One versus Three Sets Resistance-Training Programmes. *BioMed Research International* 2013; 2013: 6.
162. Farinatti PT, Geraldes AA, Bottaro MF *et al.* Effects of different resistance training frequencies on the muscle strength and functional performance of active women older than 60 years. *J Strength Cond Res* 2013; 27: 2225-34.
163. Van Roie E, Delecluse C, Coudyzer W *et al.* Strength training at high versus low external resistance in older adults: Effects on muscle volume, muscle strength, and force-velocity characteristics. *Experimental Gerontology* 2013; 48: 1351-61.
164. Anderson T, Kearney JT Effects of three resistance training programs on muscular strength and absolute and relative endurance. *Res Q.* 1982; 53: 1-7.

165. Berger RA Optimum repetitions of three weight training programme. *Res Q.* 1963; 34: 396-98.
166. Borst SE, Dehoyos DV, Garzarella L *et al.* Effects of resistance training on insulin-like growth factor-1 and IGF binding proteins. *Med Sci Sports Exerc.* 2001; 33: 648-53.
167. Campos GE, Luecke TJ, Wendeln HK *et al.* muscular adaptation in response to three different resistance-training regimes: Specificity of repetition maximum training zones. *Eu J of Applied Phy* 2002; 88: 50-60.
168. Capen EK Study of four programs of heavy resistance exercises for development of muscular strength. *Res Q.* 1956; 27: 132-42.
169. de Souza TP, Fleck SL, Simao R *et al.* Comparison between constant and decreasing rest intervals: influence on maximal strength and hypertrophy. *Journal of Strength & Conditioning Research* 2010; 24: 1843-50.
170. De Vos NJ, Singh NA, Ross DA *et al.* Optimal load for increasing muscle power during explosive resistance training in older adults. . *J Gerontol.* 2005; 60A: 638-47.
171. DiFrancisco-Donoghue J, Werner W, Douris PC Comparison of once-weekly and twice-weekly strength training in older adults. *Br J Sports Med* 2007; 41: 19-22.
172. Ewing JL, Wolfe DR, Rogers MA *et al.* Effects of velocity of isokinetic training on strength, power, and quadriceps muscle fibre characteristics. . *Eur J Appl Physiol.* 1990; 60: 159-62.
173. Fatouros IG, Kambas A, Katrabasas I *et al.* Resistance training and detraining effects on flexibility performance in the elderly are intensity-dependent. . *J Strength Cond Res.* 2006; 20: 634-42.
174. Galvão DA, Taaffe DR Resistance Exercise Dosage in Older Adults: Single-Versus Multiset Effects on Physical Performance and Body Composition. *Journal of the American Geriatrics Society* 2005; 53: 2090-97.
175. Goto K, Nagasawa M, Yanagisawa O *et al.* Muscular adaptations to combinations of high- and low-intensity resistance exercises. *J Strength Cond Res.* 2004; 18: 730-7.
176. HARRIS C, DEBELISO MA, SPITZER-GIBSON TA *et al.* The Effect of Resistance-Training Intensity on Strength-Gain Response in the Older Adult. *The Journal of Strength & Conditioning Research* 2004; 18: 833-38.
177. HASS CJ, GARZARELLA L, DE HOYOS D *et al.* Single versus multiple sets in long-term recreational weightlifters. *Medicine & Science in Sports & Exercise* 2000; 32: 235.
178. Henwood TR, Riek S, Taaffe DR Strength versus muscle power-specific resistance training in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* 2008; 63: 83-91.
179. Hunter GR Changes in body composition, body build and performance associated with different weight training frequencies in males and females. *Strength & Conditioning Journal* 1985; 7: 26-28.
180. Hunter GR, Wetzstein CJ, McLafferty CL *et al.* High-resistance versus variable-resistance training in older adults. . *Med Sci Sports Exerc.* 2001; 33: 1759-64.

181. Kelly SB, Brown LE, Coburn JW *et al.* The effect of single versus multiple sets on strength. *J Strength Cond Res* 2007; 21: 1003-6.
182. Kraemer WJ, Nindl BC, Ratamess NA *et al.* Changes in muscle hypertrophy in women with periodized resistance training. *Med Sci Sports Exerc* 2004; 36: 697-708.
183. McBride J, Blaak J, Triplett-McBride T Effect of resistance exercise volume and complexity on EMG, strength, and regional body composition. *European Journal of Applied Physiology* 2003; 90: 626-32.
184. MUNN J, HERBERT RD, HANCOCK MJ *et al.* Resistance Training for Strength: Effect of Number of Sets and Contraction Speed. *Medicine & Science in Sports & Exercise* 2005; 37: 1622-26
10.249/01.mss.0000177583.41245.f8.
185. Neils CM, Udermann BE, Brice GA *et al.* INFLUENCE OF CONTRACTION VELOCITY IN UNTRAINED INDIVIDUALS OVER THE INITIAL EARLY PHASE OF RESISTANCE TRAINING. *Journal of Strength & Conditioning Research (Allen Press Publishing Services Inc.)* 2005; 19: 883-87.
186. O'Shea P Effects of selected weight training programs on the development of strength and muscle hypertrophy. . *Res Q.* 1966; 37: 95-102.
187. Onambele-Pearson GL, Breen L, Stewart CE Influences of carbohydrate plus amino acid supplementation on differing exercise intensity adaptations in older persons: skeletal muscle and endocrine responses. *Age* 2010; 32: 125-38.
188. Paulsen G, Mykkestad D, Raastad T The influence of volume of exercise on early adaptations to strength training. *J Strength Cond Res.* 2003; 17: 115-20.
189. Pollock ML, Graves JE, Bamman MM *et al.* Frequency and volume of resistance training: effect of cervical extension strength. *Arch Phys Med Rehabil.* 1993; 74: 1080-6.
190. Rana SR, Chleboun GS, Gilders RM *et al.* Comparison of early phase adaptations for traditional strength and endurance, and low velocity resistance training programs in college-aged women. *Journal of Strength & Conditioning Research (Lippincott Williams & Wilkins)* 2008; 22: 119-27.
191. RHEA MR, ALVAR BA, BALL SD *et al.* Three Sets of Weight Training Superior to 1 Set With Equal Intensity for Eliciting Strength. *The Journal of Strength & Conditioning Research* 2002; 16: 525-29.
192. RØNNESTAD BR, EGELAND W, KVAMME NH *et al.* Dissimilar Effects of One- and Three-Set Strength Training on Strength and Muscle Mass Gains in Upper and Lower Body in Untrained Subjects. *The Journal of Strength & Conditioning Research* 2007; 21: 157-63.
193. Schlumberger A, Stec J, Schmidtbleicher D Single- vs. multiple-set strength training in women. *J Strength Cond Res.* 2001; 15: 284-9.
194. Signorile JF, Carmel MP, Lai S *et al.* Early plateaus of power and torque gains during high- and low-speed resistance training of older women. *Journal of Applied Physiology* 2005; 98: 1213-20.
195. Starkey DB, Pollock ML, Ishida Y *et al.* Effect of resistance training volume on strength and muscle thickness. *Med Sci Sports Exerc* 1996; 28: 1311-20.

196. Stone WJ, Coulter SP Strength/Endurance Effects From Three Resistance Training Protocols With Women. *The Journal of Strength & Conditioning Research* 1994; 8: 231-34.
197. Vincent KR, Braith RW, Feldman RA *et al.* Improved cardiorespiratory endurance following 6 months of resistance exercise in elderly men and women. . *Arch Intern Med.* 2003; 162: 673-8.
198. WEISS LW, CONEX HD, CLARK FC Differential Functional Adaptations to Short-Term Low-, Moderate-, and High-Repetition Weight Training. *The Journal of Strength & Conditioning Research* 1999; 13: 236-41.
199. Candow DG, Burke DG Effect of Short-Term Equal-Volume Resistance Training With Different Workout Frequency on Muscle Mass and Strength in Untrained Men and Women. *The Journal of Strength & Conditioning Research* 2007; 21: 204-7.
200. de Paleville D T, Swank A M, Funk D *et al.* Adding weights to low intensity exercise increases isometric muscular strength and functional ability in healthy older adults. *International Journal of Fitness* 2009; 5: 51-59.
201. Nakamura Y, Tanaka K, Yabushita N *et al.* Effects of exercise frequency on functional fitness in older adult women. . *Arch Gerontol Geriatr.* 2007; 44: 163-73.
202. Kalapotharakos V, Michalopoulos M, Tokmakidis SP *et al.* Effects of a heavy and a moderate resistance training on functional performance in older adults. . *J Strength Cond Res.* 2005; 19: 652-7.
203. Nemoto K, Gen-no H, Masuki S *et al.* Effects of high-intensity interval walking training on physical fitness and blood pressure in middle-aged and older people. *Mayo Clin Proc* 2007; 82: 803-11.
204. Rang HP *Drug discovery and development. Technology in transition:* CHURCHILL LIVINGSTONE, ELSEVIER, 2006.
205. Bretz F, Dette H, Pinheiro J Practical considerations for optimal designs in clinical dose finding studies. *Statistics in medicine* 2010; 29: 10.1002/sim.3802.
206. Chang L, Ameen VZ, Dukes GE *et al.* A dose-ranging, phase II study of the efficacy and safety of alosetron in men with diarrhea-predominant IBS. *Am J Gastroenterol* 2005; 100: 115-23.
207. Sheiner LB, Beal SL, *al. e* Study designs for dose-ranging. *Clin Pharmacol Ther* 1989; 46: 63-77.
208. Bretz F, Hsu J, Pinheiro J *et al.* Dose finding - a challenge in statistics. *Biom J* 2008; 50: 480-504.
209. Piantadosi S *CLINICAL TRIALS a methodologic perspective.* New Jersey: John Wiley & Son, 2005.
210. Pinheiro J, Bornkamp B, Glimm E *et al.* Model-based dose finding under model uncertainty using general parametric models. *Statistics in Medicine* 2014; 33: 1646-61.
211. Pinheiro J, Sax F, Antonijevic Z *et al.* Adaptive and Model-Based Dose-Ranging Trials: Quantitative Evaluation and Recommendations. White Paper of the PhRMA Working Group on Adaptive Dose-Ranging Studies. *Statistics in Biopharmaceutical Research* 2010; 2: 435-54.
212. Oberg E Physical Activity Prescription: Our Best Medicine. *Integrative Medicine* 2007; 6: 18-22.

213. Yeatts SD Novel Methodologic Approaches to Phase I, II, and III Trials. *Stroke; a journal of cerebral circulation* 2013; 44: S116-S18.
214. Campbell M, Fitzpatrick R, Haines A *et al.* Framework for design and evaluation of complex interventions to improve health. *BMJ* 2000; 321: 694-96.
215. Whelan HT, Cook JD, Amlie-Lefond CM *et al.* Practical Model-Based Dose Finding in Early-Phase Clinical Trials Optimizing Tissue Plasminogen Activator Dose for Treatment of Ischemic Stroke in Children. *Stroke* 2008; 39: 2627.
216. Redfern J, McKeivitt C, Wolfe CD Development of complex interventions in stroke care: a systematic review. *Stroke* 2006; 37: 2410-9.
217. Collins JA, Fauser BCJM Balancing the strengths of systematic and narrative reviews. *Human Reproduction Update* 2005; 11: 103-04.
218. Rother ET Revisão sistemática X revisão narrativa. *Acta Paulista de Enfermagem* 2007; 20: v-vi.
219. Hempel G *Drug monitoring and clinical chemistry*; RM S, editor. Amsterdam, The Netherland: Elsevier Ltd., 2004.
220. Rick NG *DRUGS from Discovery to Approval*. New Jersey: Wiley-Blackwell, 2009.
221. Fox E, Curt GA, Balis FM Clinical Trial Design for Target-Based Therapy. *Oncologist* 2002; 7: 401-09.
222. Bunnage EM Getting pharmaceutical R&D back on target. *Nature Chemical Biology* 2011; 7: 335–39.
223. LoRusso PM, Jones SF, Koch KM *et al.* Phase I and Pharmacokinetic Study of Lapatinib and Docetaxel in Patients With Advanced Cancer. *J Clin Oncol* 2008; 26: 3051-56.
224. Huang X, Biswas S, Oki Y *et al.* A Parellel Phase I/II Trial Design for Combination Therapies. *Biometrics* 2007; 63: 429-36.
225. Jahanzeb M, Mortimer JE, Yunus F *et al.* Phase II Trial of Weekly Vinorelbine and Trastuzumab as First-Line Therapy in Patients with HER2+ Metastatic Breast Cancer. *Oncologist* 2002; 7: 410-17.
226. U.S. Department of Health and Human Services. *Guidance for Industry, Investigators, and Reviewers. Exploratory IND Studies*. 5600 Fishers Lane, Rockville, MD 20857, (Tel) 301-827-4573: Food and Drug Administration, Center for Drug Evaluation and Research (CDER), 2006.
227. Thompson WR On the Likelihood that One Unknown Probability Exceeds Another in View of the Evidence of Two Samples. *Biometrika* 1933; 25: 285-94.
228. Stein C A Two-Sample Test for a Linear Hypothesis Whose Power is Independent of the Variance. *The Annals of Mathematical Statistics* 1945; 16: 243-58.
229. Robbins H, Sutton M A Stochastic Approximation Method. *The Annals of Mathematical Statistics* 1951; 22: 400-07.
230. Wages NA, Conaway MR, O'Quigley J Using the time-to-event continual reassessment method in the presence of partial orders. *Stat Med* 2013; 32: 131-41.
231. Le Tourneau C, Lee JJ, Siu LL Dose Escalation Methods in Phase I Cancer Clinical Trials. *Journal of the National Cancer Institute* 2009.

232. Storer BE Small-Sample Confidence Sets for the MTD in a Phase I Clinical Trial. *Biometrics* 1993; 49: 1117-25.
233. Berry DA Adaptive Clinical Trials: The Promise and the Caution. *Journal of Clinical Oncology* 2011; 29: 606-09.
234. O'Quigley J, Pepe M, Fisher L Continual reassessment method: a practical design for phase 1 clinical trials in cancer. *Biometrics* 1990; 46: 33-48.
235. O'Quigley J, Conaway M Continual Reassessment and Related Dose-Finding Designs. *Statistical science : a review journal of the Institute of Mathematical Statistics* 2010; 25: 202-16.
236. Hansen AR, Graham DM, Pond GR *et al.* Phase 1 trial design: is 3 + 3 the best? *Cancer Control* 2014; 21: 200-8.
237. Rogatko A, Schoeneck D, Jonas W *et al.* Translation of Innovative Designs Into Phase I Trials. *Journal of Clinical Oncology* 2007; 25: 4982.
238. Bretz F, Hsu J, Pinheiro J *et al.* Dose Finding – A Challenge in Statistics. *Biometrical Journal* 2008; 50: 480-504.
239. Steinfeld J, Yiu G, Miller SD Dose-Ranging Study to Evaluate the Efficacy and Safety of Four Doses of Fluticasone Propionate/Salmeterol Multidose Dry Powder Inhaler (FS MDPI) Compared with Fluticasone Propionate (Fp) Mdpi and FS DPI in Subjects with Persistent Asthma. *Journal of Allergy and Clinical Immunology* 2015; 135: AB6.
240. Krams M, Less KR, Berry DA The past is the future: Innovative designs in Acute Stroke Therapy trials. *Stroke* 2005; 36: 1341-47.
241. Guo SW, Evers JL Lack of transparency of clinical trials on endometriosis. *Obstet Gynecol* 2013; 121: 1281-90.
242. Miller JE, Korn D, Ross JS Clinical trial registration, reporting, publication and FDAAA compliance: a cross-sectional analysis and ranking of new drugs approved by the FDA in 2012. *BMJ Open* 2015; 5.
243. Penel N, Kramar A What does a modified-Fibonacci dose-escalation actually correspond to? *BMC Medical Research Methodology* 2012; 12: 1-5.
244. Holleran CL, Rodriguez KS, Echaz A *et al.* Potential contributions of training intensity on locomotor performance in individuals with chronic stroke. *J Neurol Phys Ther* 2015; 39: 95-102.
245. Hunter SM, Hammett L, Ball S *et al.* Dose–Response Study of Mobilisation and Tactile Stimulation Therapy for the Upper Extremity Early After Stroke: A Phase I Trial. *Neurorehabilitation and Neural Repair* 2011; 25: 314-22.
246. Arnold DM, Burns KE, Adhikari NK *et al.* The design and interpretation of pilot trials in clinical research in critical care. *Crit Care Med* 2009; 37: S69-74.
247. Lancaster GA, Dodd S, Williamson PR Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract* 2004; 10: 307-12.
248. Whitehead AL, Sully BG, Campbell MJ Pilot and feasibility studies: is there a difference from each other and from a randomised controlled trial? *Contemp Clin Trials* 2014; 38: 130-3.
249. Thabane L, Ma J, Chu R *et al.* A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol* 2010; 10: 1.

250. Penel N, Isambert N, Leblond P *et al.* "Classical 3 + 3 design" versus "accelerated titration designs": analysis of 270 phase 1 trials investigating anti-cancer agents. *Investigational New Drugs* 2009; 27: 552-56.
251. Brannath W, Bauer P, Posch M On the efficiency of adaptive designs for flexible interim decisions in clinical trials. *Journal of Statistical Planning and Inference* 2006; 136: 1956-61.
252. Tsiatis AA, Mehta C On the inefficiency of the adaptive design for monitoring clinical trials. *Biometrika* 2003; 90: 367-78.
253. Le Tourneau C, Gan HK, Razak ARA *et al.* Efficiency of New Dose Escalation Designs in Dose-Finding Phase I Trials of Molecularly Targeted Agents. *PLoS ONE* 2012; 7: e51039.
254. Bretz F, Dette H, Pinheiro JC Practical considerations for optimal designs in clinical dose finding studies. *Statistics in Medicine* 2010; 29: 731-42.
255. Tighiouart M, Rogatko A, #xe9 Number of Patients per Cohort and Sample Size Considerations Using Dose Escalation with Overdose Control. *Journal of Probability and Statistics* 2012; 2012: 16.
256. Harris JE, Eng JJ Paretic Upper-Limb Strength Best Explains Arm Activity in People With Stroke. *Physical Therapy* 2007; 87: 88-97.
257. Alberts JL, Butler AJ, Wolf SL The effects of constraint-induced therapy on precision grip: A preliminary study. *Neurorehabilitation and Neural Repair* 2004; 18: 250-58.
258. Dromerick AW, Edwards DF, Hahn M Does the Application of Constraint-Induced Movement Therapy During Acute Rehabilitation Reduce Arm Impairment After Ischemic Stroke? *Stroke* 2000; 31: 2984-88.
259. Ro T, Noser E, Boake C *et al.* Functional reorganization and recovery after constraint-induced movement therapy in subacute stroke: case reports. *Neurocase* 2006; 12: 50-60.
260. Kleim JA, Barbay S, Nudo RJ Functional Reorganization of the Rat Motor Cortex Following Motor Skill Learning. *Journal of Neurophysiology* 1998; 80: 3321-25.
261. Nudo RJ, Wise BM, SiFuentes F *et al.* Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science* 1996; 272: 1791-4.
262. Cooke E, Mares K, Clark A *et al.* The effects of increased dose of exercise-based therapies to enhance motor recovery after stroke: a systematic review and meta-analysis. *BMC Medicine* 2010; 8: 60.
263. Donaldson C, Tallis R, Miller S *et al.* Effects of Conventional Physical Therapy and Functional Strength Training on Upper Limb Motor Recovery After Stroke: A Randomized Phase II Study *Neurorehabil Neural Repair* 2009; 23: 389-97.
264. Kwakkel G, Wagenaar RC, Koelman TW *et al.* Effects of intensity of rehabilitation after stroke. A research synthesis. *Stroke* 1997; 28: 1550 - 56.
265. Veerbeek JM, Koolstra M, Ket JCF *et al.* Effects of Augmented Exercise Therapy on Outcome of Gait and Gait-Related Activities in the First 6 Months After Stroke: A Meta-Analysis. *Stroke* 2011; 42: 3311-15.
266. Barak S, Duncan PW Issues in selecting outcome measures to assess functional recovery after stroke. *NeuroRx* 2006; 3: 505-24.

267. Recommendations for clinical trial evaluation of acute stroke therapies. *Stroke* 2001; 32: 1598-606.
268. Bertrand AM, Mercier C, Bourbonnais D *et al.* Reliability of maximal static strength measurements of the arms in subjects with hemiparesis. *Clinical Rehabilitation* 2007; 21: 248-57.
269. Boissy P, Bourbonnais D, Carlotti MM *et al.* Maximal grip force in chronic stroke subjects and its relationship to global upper extremity function. *Clinical Rehabilitation* 1999; 13: 354-62.
270. Hammer A, Lindmark B Test-retest intra-rater reliability of grip force in patients with stroke. *J Rehabil Med* 2003; 35: 189-94.
271. Salter K, Jutai JW, Teasell R *et al.* Issues for selection of outcome measures in stroke rehabilitation: ICF Body Functions. *Disabil Rehabil* 2005; 27: 191-207.
272. Salter K, Jutai JW, Teasell R *et al.* Issues for selection of outcome measures in stroke rehabilitation: ICF Participation. *Disabil Rehabil* 2005; 27: 507-28.
273. Salter K, Jutai JW, Teasell R *et al.* Issues for selection of outcome measures in stroke rehabilitation: ICF activity. *Disabil Rehabil* 2005; 27: 315-40.
274. Hendricks HT, Pasman JW, Merx JL *et al.* Analysis of recovery processes after stroke by means of transcranial magnetic stimulation. *J Clin Neurophysiol* 2003; 20: 188-95.
275. Nitschke JE, McMeeken JM, Burry HC *et al.* When is a change a genuine change?: A clinically meaningful interpretation of grip strength measurements in healthy and disabled women. *Journal of Hand Therapy* 1999; 12: 25-30.
276. Lang CE, Edwards DF, Birkenmeier RL *et al.* Estimating Minimal Clinically Important Differences of Upper-Extremity Measures Early After Stroke. *Archives of Physical Medicine and Rehabilitation* 2008; 89: 1693-700.
277. Fasoli SE, Trombly CA, Tickle-Degnen L *et al.* Effect of Instructions on Functional Reach in Persons With and Without Cerebrovascular Accident. *American Journal of Occupational Therapy* 2002; 56: 380-90.
278. Mathiowetz V, Volland G, Kashman N *et al.* Adult norms for the Box and Block Test of manual dexterity. *Am J Occup Ther* 1985; 39: 386-91.
279. Salter K, Campbell N, Richardson M *et al.* (2013) Outcome Measures in Stroke Rehabilitation. EBR SR [Evidence-Based Review of Stroke Rehabilitation].
280. Desrosiers J, Bravo G, Hebert R *et al.* Validation of the Box and Block Test as a measure of dexterity of elderly people: reliability, validity, and norms studies. *Arch Phys Med Rehabil* 1994; 75: 751-5.
281. Platz T, Pinkowski C, van Wijck F *et al.* Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study. *Clinical Rehabilitation* 2005; 19: 404-11.
282. Salter K, Lutai j, Zettler L *et al.* (2011) Outcome measures in stroke rehabilitation. In: Teasell DR, editor. The Evidence-Based Review of Stroke Rehabilitation (EBRSR) reviews current practices in stroke rehabilitation. www.ebrsr.com: EBR SR.

283. Carey JR, Kimberley TJ, Lewis SM *et al.* Analysis of fMRI and finger tracking training in subjects with chronic stroke. *Brain* 2002; 125: 773-88.
284. Higgins J, Salbach NM, Wood-Dauphinee S *et al.* The effect of a task-oriented intervention on arm function in people with stroke: a randomized controlled trial. *Clinical Rehabilitation* 2006; 20: 296-310.
285. Butler AJ, Wolf SL Putting the Brain on the Map: Use of Transcranial Magnetic Stimulation to Assess and Induce Cortical Plasticity of Upper-Extremity Movement. *Physical Therapy* 2007; 87: 719-36.
286. Dimyan MA, Cohen LG Contribution of transcranial magnetic stimulation to the understanding of mechanisms of functional recovery after stroke. *Neurorehabilitation and neural repair* 2010; 24: 125-35.
287. Calautti C, Baron J-C Functional Neuroimaging Studies of Motor Recovery After Stroke in Adults: A Review. *Stroke* 2003; 34: 1553-66.
288. Rossi S, Hallett M, Rossini PM *et al.* Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009; 120: 2008-39.
289. Rossini PM, Barker AT, Berardelli A *et al.* Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology* 1994; 91: 79-92.
290. Delvaux V, Alagona G, Gerard P *et al.* Post-stroke reorganization of hand motor area: a 1-year prospective follow-up with focal transcranial magnetic stimulation. *Clin Neurophysiol* 2003; 114: 1217-25.
291. Gupta SK Intention-to-treat concept: A review. *Perspectives in Clinical Research* 2011; 2: 109-12.
292. Nevo B FACE VALIDITY REVISITED. *Journal of Educational Measurement* 1985; 22: 287-93.
293. Dite W, Langford ZN, Cumming TB *et al.* A Phase 1 exercise dose escalation study for stroke survivors with impaired walking. *Int J Stroke* 2015; 10: 1051-6.
294. Mares K, Cross J, Clark A *et al.* The FeSTivaLS trial protocol: A randomized evaluation of the efficacy of functional strength training on enhancing walking and upper limb function later post stroke. *International Journal of Stroke* 2013; 8: 374-82.
295. Scott NW, McPherson GC, Ramsay CR *et al.* The method of minimization for allocation to clinical trials. a review. *Control Clin Trials* 2002; 23: 662-74.
296. Pocock SJ, Simon R Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; 31: 103-15.
297. Hill KD, Bernhardt J, McGann AM *et al.* A New Test of Dynamic Standing Balance for Stroke Patients: Reliability, Validity and Comparison with Healthy Elderly. *Physiotherapy Canada* 1996; 48: 257-62.
298. Fugl-Meyer AR, Jaasko L, Leyman I *et al.* The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance. *Scand J Rehabil Med* 1975; 7: 13-31.

299. van der Lee JH, Beckerman H, Lankhorst GJ *et al.* The responsiveness of the Action Research Arm test and the Fugl-Meyer Assessment scale in chronic stroke patients. *J Rehabil Med* 2001; 33: 110-3.
300. Trew M, Everett T *Human Movement an Introductory Text*: Churchill Livingstone, 2005.
301. Holden MK, Gill KM, Magliozzi MR Gait assessment for neurologically impaired patients. Standards for outcome assessment. *Phys Ther* 1986; 66: 1530-9.
302. Yozbatiran N, Der-Yeghiaian L, Cramer SC A standardized approach to performing the action research arm test. *Neurorehabil Neural Repair* 2008; 22: 78-90.
303. Teasell R, Foley NC, Salter K *EBRSR: Evidence-Based Review of Stroke Rehabilitation*; EBRSR, editor, 2011.
304. Mehrholz J, Wagner K, Rutte K *et al.* Predictive validity and responsiveness of the functional ambulation category in hemiparetic patients after stroke. *Arch Phys Med Rehabil* 2007; 88: 1314-9.
305. Lang CE, Wagner JM, Dromerick AW *et al.* Measurement of upper-extremity function early after stroke: properties of the action research arm test. *Arch Phys Med Rehabil* 2006; 87: 1605-10.
306. Platz T, Pinkowski C, van Wijck F *et al.* Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study. *Clin Rehabil* 2005; 19: 404-11.
307. Finch E, Brooks D, Stratford P *et al.* *Physical Rehabilitation Outcome Measures: A Guide to Enhanced Clinical Decision Making*: Canadian Physiotherapy Association, 2002.
308. Doyon J, Benali H Reorganization and plasticity in the adult brain during learning of motor skills. *Curr Opin Neurobiol* 2005; 15: 161-7.
309. Gladstone DJ, Danells CJ, Black SE The Fugl-Meyer Assessment of Motor Recovery after Stroke: A Critical Review of Its Measurement Properties. *Neurorehabilitation and Neural Repair* 2002; 16: 232-40.
310. Sullivan KJ, Tilson JK, Cen SY *et al.* Fugl-Meyer Assessment of Sensorimotor Function After Stroke. *Stroke* 2011; 42: 427-32.
311. Duncan PW, Propst M, Nelson SG Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident. *Phys Ther* 1983; 63: 1606-10.
312. Wagner JM, Rhodes JA, Patten C Reproducibility and minimal detectable change of three-dimensional kinematic analysis of reaching tasks in people with hemiparesis after stroke. *Phys Ther* 2008; 88: 652-63.
313. Page SJ, Fulk GD, Boyne P Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. *Phys Ther* 2012; 92: 791-8.
314. Lancaster GA, Campbell MJ, Eldridge S *et al.* Trials in primary care: statistical issues in the design, conduct and evaluation of complex interventions. *Stat Methods Med Res* 2010; 19: 349-77.
315. Dahl A, Askim T, Stock R *et al.* Short- and long-term outcome of constraint-induced movement therapy after stroke: a randomized controlled feasibility trial. *Clinical Rehabilitation* 2008; 22: 436-47.

316. Page SJ, Levine P, Sisto SA *et al.* A randomized efficacy and feasibility study of imagery in acute stroke. *Clinical Rehabilitation* 2001; 15: 233-40.
317. Saposnik G, Teasell R, Mamdani M *et al.* Effectiveness of Virtual Reality Using Wii Gaming Technology in Stroke Rehabilitation: A Pilot Randomized Clinical Trial and Proof of Principle. *Stroke* 2010; 41: 1477-84.
318. Cumming TB, Thrift AG, Collier JM *et al.* Very early mobilization after stroke fast-tracks return to walking: further results from the phase II AVERT randomized controlled trial. *Stroke* 2011; 42: 153-8.
319. Malcolm MP, Triggs WJ, Light KE *et al.* Reliability of motor cortex transcranial magnetic stimulation in four muscle representations. *Clin Neurophysiol* 2006; 117: 1037-46.
320. Sale MV, Ridding MC, Nordstrom MA Factors influencing the magnitude and reproducibility of corticomotor excitability changes induced by paired associative stimulation. *Exp Brain Res* 2007; 181: 615-26.
321. Riecker A, Gröschel K, Ackermann H *et al.* Functional significance of age-related differences in motor activation patterns. *NeuroImage* 2006; 32: 1345-54.
322. Ward NS, Frackowiak RS Age-related changes in the neural correlates of motor performance. *Brain* 2003; 126: 873-88.
323. Martin PG, Gandevia SC, Taylor JL Theta burst stimulation does not reliably depress all regions of the human motor cortex. *Clin Neurophysiol* 2006; 117: 2684-90.
324. Takatsuru Y, Fukumoto D, Yoshitomo M *et al.* Neuronal circuit remodeling in the contralateral cortical hemisphere during functional recovery from cerebral infarction. *J Neurosci* 2009; 29: 10081-6.
325. Rossini PM, Altamura C, Ferreri F *et al.* Neuroimaging experimental studies on brain plasticity in recovery from stroke. *Eura Medicophys* 2007; 43: 241-54.
326. Hummel FC, Cohen LG Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? *Lancet Neurol* 2006; 5: 708-12.

Appendix A :

Electronic search strategies for dose optimization approaches in Exercise-based training

MEDLINE SEARCH STRATEGY

1. exp Exercise Therapy/
2. exercise/ or resistance training/
3. *Motor Activity/
4. *Robotics/ or robot-assisted therapy.mp.
5. (dose* adj2 relationship).ti,ab.
6. dose-response.ti,ab.
7. dose-finding.ti,ab.
8. ((dose or dosage or intensit* or frequenc* or duration* or time or amount or power or how much or repetition* or set* or load* or volume or work) adj3 (training or therap* or protocol* or activit* or program* or exercise*)).ti,ab.
9. 1 or 2 or 3 or 4
10. 8 or 5 or 6 or 7
11. 10 and 9
12. ((functional or motor) adj2 (abilit* or recovery)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. (musc* adj (strength or abilit* or function* power or work or torque or force)).ti,ab.
14. *"Quality of Life"/
15. *Heart Rate/
16. exp cardiovascular physiological processes/ or exp hemodynamics/ or exp respiratory physiological phenomena/
17. exp Oxygen Consumption/ or oxygen uptake.mp.
18. 17 or 15 or 16
19. "Activities of Daily Living"/
20. functional limitation.ti,ab.
21. ((motor or muscular) adj performance).ti,ab.
22. 14 or 12 or 13 or 21 or 19 or 20
23. 18 or 22
24. 22 and 11
25. evaluation.mp.
26. effec*.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
27. controlled clinical trial.mp.

28. (((controlled before and after) or cohort or case-control or longitudinal or observational or case or qualitative) adj3 stud*).mp.
29. *program evaluation/
30. program evaluation.tw.
31. intervention studies/
32. experiment*.tw.
33. (time adj series).tw.
34. (pre test or pretest or (post test or posttest)).tw.
35. impact.tw.
36. intervention*.tw.
37. chang*.tw.
38. compar*.tw.
39. (controlled before and after stud*).mp.
40. comparative study.sh.
41. exp Evaluation Studies/
42. follow up studies.sh.
43. prospective studies.sh.
44. (control* or prospective* or volunteer*).ti,ab.
45. 44 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
46. 24 and 45
47. 22 and 11
48. 47 and 45
49. limit 48 to yr="2007 -Current"

EMBASE SEARCH STRATEGY

1. Exercise therapy/
2. exp exercise/ or weight training/
3. Physical fitness/
4. resistance training/
5. *Robotics/ or robot-assisted therapy.mp.
6. 1 or 2 or 3 or 4 or 5
7. ((dose or dosage or intensit* or frequenc* or duration* or time or amount or power or how much or repetition* or set* or load* or volume or work) adj3 (training or therap* or protocol* or activit* or program* or exercise*)).ti,ab.
8. (musc* adj (strength or abilit* or recovery or function* power or work or torque or force)).ti,ab.
9. exp Oxygen Consumption/ or oxygen uptake.mp.
10. ((motor or muscular) adj performance).ti,ab.
11. functional limitation.ti,ab.
12. evaluation.mp.
13. effec*.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. controlled clinical trial.mp.

15. (((controlled before and after) or cohort or case-control or longitudinal or observational or case or qualitative) adj3 stud*).mp.
16. program evaluation.tw.
17. experiment*.tw.
18. (time adj series).tw.
19. (pre test or pretest or (post test or postest)).tw.
20. impact.tw.
21. intervention*.tw.
22. chang*.tw.
23. compar*.tw.
24. (controlled before and after stud*).mp.
25. comparative study.sh.
26. follow up studies.sh.
27. prospective studies.sh.
28. (control* or prospective* or volunteer*).ti,ab.
29. dose-finding\$.ti,ab.
30. dose-ranging.ab,ti.
31. dos\$ relationship.ti,ab.
32. dose-response.ti,ab.
33. hemodynamic processes/ or blood pressure/ or cardiac output/ or heart rate/ or regional blood flow/ or vascular resistance/ or vasodilation/
34. oxygen consumption/
35. Heart rate/
36. "Activities of daily living"/ or Disability evaluation/
37. quality of life.mp.
38. ((functional or motor) adj (abilit* or recovery)).ti,ab.
39. Program evaluation/
40. intervention studies.ti,ab.
41. research design/ or case report/ or clinical trials/ or randomized controlled trials/ or comparative study/
42. 7 or 29 or 30 or 31 or 32
43. 6 and 42
44. 8 or 10 or 11 or 36 or 37
45. 9 or 33 or 34 or 35
46. 43 and 45
47. limit 46 to yr="2007 -Current"

CHINAL SEARCH STRATEGY

1. (MH "Exercise+")
2. (MM "Therapeutic Exercise") or ("robot-assisted therapy")
3. exercise therapy
4. (MM "Physical Education and Training") OR (MM "Recreation") OR (MM "Sports") OR (MM "Leisure Activities") OR (MH "Physical Fitness+")
5. 1 or 2 or 3 or 4

6. dose-finding
7. dose-response
8. (MM "Dose-Response Relationship")
9. dose relationship
10. 6 or 7 or 8 or 9
11. training* N3 dose or training* N3 dosage or training* N3 intensit* or training* N3 frequenc* or training* N3 duration or training* N3 amount or training* N3 power or training* N3 how much or training* N3 repetition* or training* N3 set* or training* N3 load* or training* N3 volume
12. therap* N3 dose or therap* N3 dosage or therap* N3 intensit* or therap* N3 frequenc* or therap* N3 duration or therap* N3 amount or therap* N3 power or therap* N3 how much or therap* N3 repetition* or therap* N3 set* or therap* N3 load* or therap* N3 volume or therap* N3 work or therap* N3 time
13. protocol* N3 dose or protocol* N3 dosage or protocol* N3 intensit* or protocol* N3 frequenc* or protocol* N3 duration or protocol* N3 amount or protocol* N3 power or protocol* N3 how much or protocol* N3 repetition* or protocol* N3 set* or protocol* N3 load* or protocol* N3 volume
14. activit* N3 dose or activit* N3 dosage or activit* N3 intensit* or activit* N3 frequenc* or activit* N3 duration or activit* N3 amount or activit* N3 power or activit* N3 how much or activit* N3 repetition* or activit* N3 set* or activit* N3 load* or activit* N3 volume
15. program* N3 dose or program* N3 dosage or program* N3 intensit* or program* N3 frequenc* or program* N3 duration or program* N3 amount or program* N3 power or program* N3 how much or program* N3 repetition* or program* N3 set* or program* N3 load* or program* N3 volume
16. exercise* N3 dose or exercise* N3 dosage or exercise* N3 intensit* or exercise* N3 frequenc* or exercise* N3 duration or exercise* N3 amount or exercise* N3 power or exercise* N3 how much or exercise* N3 repetition* or exercise* N3 set* or exercise* N3 load* or exercise* N3 volume
exercise* N3 work or program* N3 work or activit* N3 work or protocol* N3 work or training* N3 work or exercise* N3 time or program* N3 time or activit* N3 time or protocol* N3 time or training* N3 time
17. 16 or 15 or 14 or 13 or 12 or 11 or 10
18. 5 and 17
19. Muscle N1 performance or Muscular N1 performance
20. musc* N1 strength or musc* N1 abilit* or musc* N1 torque or musc* N1 force or musc* N1 work or musc* N1 power or musc* N1 function* or musc* N1 recovery

21. (MH "Oxygen Consumption+") OR (MH "Heart Function Tests+")
22. (MM "Functional Status") OR (MM "Functional Assessment") OR "functional ability" or functional recovery or motor recovery
23. (MH "Hemodynamics+")
24. (MH "Activities of Daily Living+")
25. "functional limitation" OR (MM "Quality of Live")
26. 19 or 20 or 22 or 24 or 25
27. 26 AND 18
28. (MH "Clinical Trials+") OR (MH "Random Sample+") OR "randomized controlled trial" OR (MH "Intervention Trials") OR "controlled clinical trial" OR (MH "Comparative Studies") OR "evaluation stud*" OR "clinical stud*" OR "clinical article*"
29. (MM "Evaluation Research") OR (MM "Cross Sectional Studies") OR (MM "Experimental Studies") OR (MM "Nonexperimental Studies") OR "Evaluation Studies"
30. impact or intervention* or experiment* or chang*
31. (MH "Case Control Studies+")
32. effect*
33. (MH "Prospective Studies+") OR (MM "Postexposure Follow-Up")
34. 28 or 29 or 30 or 31 or 32 or 33
35. S28 AND S34

S37. S36 Limiters - Published Date from: 2001-2012;

Appendix B : Exercise-based therapy review

REFERENCE LIST OF INCLUDED ARTICLES

1. *Ahtiainen JP, Pakarinen A, Alen M, Kraemer WJ, Häkkinen K. (2005)* "Short vs. long rest period between the sets in hypertrophic resistance training: influence on muscle strength, size, and hormonal adaptations in trained men. *J Strength Cond Res.*, 19, 572-82.
2. *Anderson T & Kearney JT (1982)*. "Effects of three resistance training programs on muscular strength and absolute and relative endurance". *Res Q.*, 53, 1-7.
3. *Berger RA (1962)*. "Optimum repetitions for the development of strength". *Res Q.* , 33, 334-338.
4. *Berger RA (1963)*. "Optimum repetitions of three weight training programme". *Res Q.*, 34, 396-398.
5. *Borst SE, Dehoyos DV, Garzarella L & et al. (2001)*. "Effects of resistance training on insulin-like growth factor-1 and IGF binding proteins". *Med Sci Sports Exerc.* , 33, 648–53.
6. *Campos GE, Luecke TJ, Wendeln HK et al. (2002)*. "Muscular adaptation in response to three different resistance-training regimes: Specificity of repetition maximum training zones". *Eu J of Applied Phy*, 88, 50-60.
7. *Candow DG & Burke DG (2007)*. Effect of Short-Term Equal-Volume Resistance Training With Different Workout Frequency on Muscle Mass and Strength in Untrained Men and Women. *The Journal of Strength & Conditioning Research*, 21, 204-7.
8. *Capen EK (1956)*. Study of four programs of heavy resistance exercises for development of muscular strength. *Res Q.*, 27, 132–42.
9. *Cauraugh JH, Coombes SE et al. (2009)*. "Upper extremity improvements in chronic stroke: coupled bilateral load training." *Restorative Neurology & Neuroscience* 27(1): 17-25.
10. *de Paleville DT., Swank AM, et al. (2009)*. "Adding weights to low intensity exercise increases isometric muscular strength and functional ability in healthy older adults." *International Journal of Fitness* 5(1): 51-59.
11. *de Souza RP, Fleck SJ, et al. (2010)*. "Comparison Between constant and decreasing rest intervals: influence on maximal strength and hypertrophy." *Journal of Strength & Conditioning Research* 24(7): 1843-1850.
12. *de Vos NJ, Singh NA, Ross DA et al. (2005)*. "Optimal load for increasing muscle power during explosive resistance training in older adults". *J Gerontol.* , 60A, 638–47.

13. *DiFrancisco-Donoghue, J., W. Werner, et al. (2007). "Comparison of once-weekly and twice-weekly strength training in older adults." British Journal of Sports Medicine 41(1): 19-22.*
14. *Dromerick AW, Land CE, Birkenmier RL, Wanger, JM, et al. (2009). "Very early constraint-induced movement during stroke rehabilitation (VECTORS) ". Neurology, 73, 195 - 201.*
15. *Ewing JL, Wolfe DR, Rogers MA, Amundson ML & Stull GA (1990). "Effects of velocity of isokinetic training on strength, power, and quadriceps muscle fibre characteristics". Eur J Appl Physiol., 60, 159–62.*
16. *Fatouros IG, Kambas A, Katrabasas I, et al. (2006). "Resistance training and detraining effects on flexibility performance in the elderly are intensity-dependent". J Strength Cond Res., 20, 634-642.*
17. *Goto Nagasawa M, Yanagisawa O, et al., (2004). "Muscular adaptations to combinations of high- and low-intensity resistance exercises.", J Strength Cond Res., 18:730-7.*
18. *Galvao DA and Taaffe DR, (2005), "Resistance exercise dosage in older adults: single- versus multiple sets effect on physical performance and body composition", J AM Geriatr Soc., 53:2090-7.*
19. *Harris C, Debelisa, MA. et al., (2004), "The Effect of Resistance-Training Intensity on Strength-Gain Response in the Older Adult.", J Strength Cond Res, 18:833-8.*
20. *Hass GJ et al. (2000), "Single versus multiple sets in long-term recreational weightlifters." Med Sci Sport Exerc., 32:235-42.*
21. *Hsieh, Y.-w., C.-y. Wu, et al. (2011). "Effects of Treatment Intensity in Upper Limb Robot-Assisted Therapy for Chronic Stroke." Neurorehabilitation and Neural Repair 25(6): 503-511.*
22. *Humburg H et al. (2007), "1-SET VS. 3-SET RESISTANCE TRAINING: A CROSSOVER STUDY.", J Strength Cond Res., 21:578-82.*
23. *Hunter GR. (1988), "Changes in body composition, body built, and performance associated with different weight training frequencies in males and females" NSCA J., 7:26-8.*
24. *Hunter GR et al., (2001), "High-resistance versus variable-resistance training in older adults.", Med Sci Sport Exerc., 33:1759-64.*
25. *Holm, L., S. Reitelseder, et al. (2008). "Changes in muscle size and MHC composition in response to resistance exercise with heavy and light loading intensity." Journal of Applied Physiology 105(5): 1454-1461.*
26. *Henwood, T. R., S. Riek, et al. (2008). "Strength versus muscle power-specific resistance training in community-dwelling older adults." Journals of Gerontology Series A-Biological Sciences & Medical Sciences 63(1): 83-91.*

27. *Kalapotharakos V et al.*, (2005), "Effects of a heavy and a moderate resistance training on functional performance in older adults.", J Strength Cond Res, 19:652-7.
28. *Kelly SB, Brown LE, et al.* (2007). "The effect of single versus multiple sets on strength." J Strength Cond Res. **21**(4): 1003-1006.
29. *Kemmler WK et al.*, (2004), "EFFECTS OF SINGLE- VS. MULTIPLE-SET RESISTANCE TRAINING ON MAXIMUM STRENGTH AND BODY COMPOSITION IN TRAINED POSTMENOPAUSAL WOMEN.", J Strength Cond Res., 18:689-94.
30. *Kraemer WJ, et al.*, (2004), "Changes in muscle hypertrophy in women with periodized resistance training.", Med Sci Sport Exerc., 36:697-708.
31. *MARZOLINI S, OH PI, et al.* (2008). "Aerobic and Resistance Training in Coronary Disease: Single versus Multiple Sets." Medicine & Science in Sports & Exercise **40**(9): 1557-1564 1510.1249/MSS.1550b1013e318177eb318177f.
32. *McBride JM et al.*, (2003), "Effect of resistance exercise volume and complexity on EMG, strength, and regional body composition.", Eur J Appl Physiol., 90:626-32.
33. *McDermot et al.*, (2006), "Physical Performance in Peripheral Arterial Disease: A Slower Rate of Decline in Patients Who Walk More.", Annual of Int. Med.,
34. *Miszko TA et al.*, (2003), "Effect of Strength and Power Training on Physical Function in Community-Dwelling Older Adults.", J Geront A Biol Sci Med., 58:171-5.
35. *Munn J et al.*, (2005), "Resistance training for strength: effect of number of set and concentration in women.", Medicine & Science in Sports & Exercise 37:1622-6.
36. *Nakamura Y et al.*, (2007), "Effects of exercise frequency on functional fitness in older adult women.", Arch Gerontol Geriatr., 44:163-73.
37. *Neils CM et al.* (2005), "INFLUENCE OF CONTRACTION VELOCITY IN UNTRAINED INDIVIDUALS OVER THE INITIAL EARLY PHASE OF RESISTANCE TRAINING." J Strength Cond Res., 19:883-7.
38. *Nemoto, K. I., H. Gen-No, et al.* (2007). "Effects of high-intensity interval walking training on physical fitness and blood pressure in middle-aged and older people." Mayo Clinic Proceedings **82** (7): 803-811
39. *Onambele-Pearson, G. L., L. Breen, et al.* "Influence of exercise intensity in older persons with unchanged habitual nutritional intake: skeletal muscle and endocrine adaptations." Age 32(2): 139-153.
40. *O'Shea P.* (1966), "Effect of selected weight training programs on the development of strength and muscle hypertrophy", Res Q., 37:95-102.
41. *Paulsen et al.* (2003), "The influence of volume of exercise on early adaptations to strength training.", J Strength Cond Res., 17:115-20.

42. *Pollock ML et al.* (1003), "Frequency and volume of resistance training: effect of cervical extension strength.", Arch Phys Med Rehabil. 74:1080-6.
43. *Rana SR, ChlebounGS, et al.* (2008). "Comparison of Early Phase Adaptations for Traditional Strength and Endurance, and Low Velocity Resistance Training Programs in College-Aged Women." The Journal of Strength & Conditioning Research 22(1): 119-127 110.1519/JSC.1510b1013e31815f31830e31817.
44. *Rhea MR et al.* (2002), "Three Sets of Weight Training Superior to 1 Set With Equal Intensity for Eliciting Strength.", Res Q. Exerc Sport, 16:525-9.
45. *Rønnestad BR, et al.,* (2007), "Dissimilar Effects of One- and Three-Set Strength Training on Strength and Muscle Mass Gains in Upper and Lower Body in Untrained Subjects.", J Strength Cond Res 21:157-63.
46. *Sato, D., K. Kaneda, et al.* (2009). "Comparison of 2-year effects of once and twice weekly water exercise on activities of daily living ability of community dwelling frail elderly." Archives of Gerontology & Geriatrics 49(1): 123-128.
47. *Schlumberger A et al.* (2001), "Single- vs. multiple-set strength training in women.", J Strength Cond Res., 15:284-9.
48. *Signorile JF et al.* (2005), "Early plateaus of power and torque gains during high- and low-speed resistance training of older women.", J Appl Physiol. 98:1213-20.
49. *Starkey DB et al.* (1996), "Effect of resistance training volume on strength and muscle thickness", Med Sci Sport Exerc, 28:1311-20.
50. *Stone WJ et al.* (1994), "Strength/Endurance Effects From Three Resistance Training Protocols With Women.", J Strength Cond Res., 8:231-4.
51. *Vincent KR et al.* (2003) "Improved cardiorespiratory endurance following 6 months of resistance exercise in elderly men and women. ", Arch Intern Med., 154:560-6.
52. *Weiss LW et al.* (1999), "Differential Functional Adaptations to Short-Term Low-, Moderate-, and High-Repetition Weight Training.", The Journal of Strength & Conditioning Research 13:236-41

INCLUDED STUDIES FROM UPDATING SEARCH

53. *Abraham O., Rodrigues R. P., et al.* (2014) "Single- and multiple-set resistance training improves skeletal and respiratory muscle strength in elderly women.", Clinical Interventions in Aging, 9, 1775-1782.
54. *Baker J. S., Davies B., et al.* (2013) "Strength and Body Composition Changes in Recreationally Strength-Trained Individuals: Comparison of One versus Three Sets Resistance-Training Programmes.", BioMed Research International, 2013, 6.

55. *Da Silva P. B., Antunes et al.* (2015) "Strength training associated with task-oriented training to enhance upper-limb motor function in elderly patients with mild impairment after stroke: a randomized controlled trial." Am J Phys Med Rehabil, 94, 11-9.
56. *Farinatti P. T., Gerdles A. A., et al.* (2013) "Effects of different resistance training frequencies on the muscle strength and functional performance of active women older than 60 years.", J Strength Cond Res, 27, 2225-34.
57. *Han C, Wang Q, Meng PP & Qi MZ* (2013). "Effects of intensity of arm training on hemiplegic upper extremity motor recovery in stroke patients: a randomized controlled trial". Clinical Rehabilitation, 27, 75-81.
58. *Jigami H, Sato D, Tsubaki A, Tokunaga Y et al.,* (2012). "Effects of weekly and fortnightly therapeutic exercise on physical function and health-related quality of life in individuals with hip osteoarthritis" Journal of Orthopaedic Science. **17**(6): 737-744.
59. *Van Roie E., Delecluse C., et al.* (2013) "Strength training at high versus low external resistance in older adults: Effects on muscle volume, muscle strength, and force–velocity characteristics.", Experimental Gerontology, 48, 1351-1361.

Appendix C :

Exercise-based therapy review. Reference list of excluded articles

STUDIES EXCLUDED VIA ABSTRACT:

1. (2010) "Home-based activity program for older people with depressive symptoms: DeLLITE-- a randomized controlled trial." *Annals of family medicine*. **Single dose.**
2. ÅsterÅys, H, Torstensen TA, et al. (2009). "Dose response effects of graded therapeutic exercises in patients with long-standing subacromial pain." *Advances in Physiotherapy* **11**(4): 199-209. **No population of interest.**
3. Abe T, Sakamaki M, et al. (2010) "Effects of low-intensity walk training with restricted leg blood flow on muscle strength and aerobic capacity in older adults." *Journal of geriatric physical therapy* (2001). **Single dose.**
4. Acslam Å B, Toraman NF, et al. (2008). "The effect of a 12-week supervised multicomponent exercise program on knee OA in Turkish women." *Journal of Back & Musculoskeletal Rehabilitation* **21**(2): 121-128. **Single dose.**
5. Adamsen, L., M. Quist, et al. (2009) "Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial." *BMJ (Clinical research ed.)*, b3410. **No population of interest.**
6. Alp, A., S. Cansever, et al. (2009) "Effects of Tai Chi exercise on functional and life quality assessments in senile osteoporosis." *Turkiye Klinikleri Journal of Medical Sciences*, 687-695. **No dose-response relationship.**
7. Andersen LL, Andersen JL, et al. "Early and late rate of force development: differential adaptive responses to resistance training?" *Scandinavian Journal of Medicine & Science in Sports* **20**(1): e162-169. **Single dose.**
8. Andersen, L. L., M. Kjaer, et al. (2008) "Effect of two contrasting types of physical exercise on chronic neck muscle pain." *Arthritis and rheumatism*, 84-91. **No population of interest.**
9. Anderson, C. E., G. A. Sforzo, et al. (2008) "The effects of combining elastic and free weight resistance on strength and power in athletes." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 567-574. **Different modalities of training.**
10. Arampatzis, A., K. Karamanidis, et al. (2007). "Mechanical properties of the triceps surae tendon and aponeurosis in relation to intensity of sport activity." *Journal of Biomechanics* **40** (9): 1946-1952. **No outcome of Interest.**
11. Arampatzis, A., A. Peper, et al. "Exercise of mechanisms for dynamic stability control increases stability performance in the elderly." *Journal of Biomechanics* **44**(1): 52-58. **Different modalities of training.**
12. Arce Esquivel AA and Welsch MA (2007). "High and low volume resistance training and vascular function." *Int J Sports Med*. **28**(3): 217-221. **No outcome of Interest.**
13. Ask, T., L. I. Strand, et al. (2009). "The effect of two exercise regimes; motor control versus endurance/strength training for patients with whiplash-associated disorders: a randomized controlled pilot study." *Clinical Rehabilitation* **23**(9): 812-823. **No population of interest.**
14. Avila, J. J., J. A. Gutierrez, et al. (2010) "Effect of moderate intensity resistance training during weight loss on body composition and physical performance in overweight older adults." *European Journal of Applied Physiology*. **No outcome of Interest.; Single dose.**
15. Bäck, M., B. Wennerblom, et al. (2008) "Effects of high frequency exercise in patients before and after elective percutaneous coronary intervention." *European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology*, 307-313. **No population of interest.**
16. Baker, M. K., D. J. Kennedy, et al. (2007). "Efficacy and feasibility of a novel tri-modal robust exercise prescription in a retirement community: a randomized, controlled trial." *Journal of the American Geriatrics Society* **55**(1): 1-10. **Single dose.**

17. Balboa-Castillo, T., P. Guallar-Castillon, et al. "Physical activity and mortality related to obesity and functional status in older adults in Spain." *American Journal of Preventive Medicine* **40 (1)**: 39-46. **No outcome of Interest.**
18. Bale, M. and L. Inger Strand (2008). "Does functional strength training of the leg in subacute stroke improve physical performance? A pilot randomized controlled trial." *Clinical Rehabilitation* **22 (10-11)**: 911-921. **Different modalities of training.**
19. Beck, A. M., K. Damkjaer, et al. "Physical and social functional abilities seem to be maintained by a multifaceted randomized controlled nutritional intervention among old (>65 years) Danish nursing home residents." *Archives of Gerontology & Geriatrics* **50(3)**: 351-355. **No outcome of Interest.**
20. Begnoche, D. M. and K. H. Pitetti (2007). "Effects of traditional treatment and partial body weight treadmill training on the motor skills of children with spastic cerebral palsy. A pilot study." *Pediatric Physical Therapy* **19(1)**: 11-19. **Different modalities of training.**
21. Bergeron, M. F. "Improving health through youth sports: is participation enough?" *New Directions for Youth Development*(115): 27-41. **No population of interest. No dose-response relationship investigated.**
22. Bernasconi, S., N. Tordi, et al. (2007). "Changes in oxygen uptake, shoulder muscles activity, and propulsion cycle timing during strenuous wheelchair exercise." *Spinal Cord* **45(7)**: 468-474. **No outcome of Interest.**
23. Bernhardt, J., J. Chan, et al. (2007) "Little therapy, little physical activity: rehabilitation within the first 14 days of organized stroke unit care." *Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine*, 43-48. **No dose-relationship investigated.**
24. Bevan, H. R., P. J. Bunce, et al. "Optimal loading for the development of peak power output in professional rugby players." *Journal of strength and conditioning research / National Strength & Conditioning Association* **24 (1)**: 43-47. **no population of interest (Athlete).**
25. Blacklock, R. E., R. E. Rhodes, et al. (2007). "Relationship Between Regular Walking, Physical Activity, and Health-Related Quality of Life." *Journal of Physical Activity & Health* **4(2)**: 138-152. **No dose-response relationship investigated.; No outcome of Interest.**
26. Blonc, S., S. Perrot, et al. (2010) "Effects of 5 weeks of training at the same time of day on the diurnal variations of maximal muscle power performance." *Journal of strength and conditioning research / National Strength & Conditioning Association*. **Same dose.**
27. Boake, C., E. A. Noser, et al. (2007) "Constraint-induced movement therapy during early stroke rehabilitation." *Neurorehabilitation and neural repair*, 14-24. **Single dose.**
28. Boudreau, S. A., K. Hennings, et al. (2010) "The effects of training time, sensory loss and pain on human motor learning." *Journal of oral rehabilitation*, 704-718. **No dose-relationship investigated.**
29. Bray, S. R., K. A. Martin Ginis, et al. (2008) "Effects of self-regulatory strength depletion on muscular performance and EMG activation." *Psychophysiology*, 337-343. **Single dose.**
30. Brechue, W. F. and J. L. Mayhew (2009). "Upper-body work capacity and 1RM prediction are unaltered by increasing muscular strength in college football players." *Journal of Strength & Conditioning Research* **23(9)**: 2477-2486. **No dose-response relationship investigated.; No outcome of Interest.**
31. Brenner, I. (2009). "Effects of passive exercise training on physical and psychological variables of elderly participants living in long-term care: a cross sectional study." *Perspectives* **33(4)**: 7-14. **no meet inclusion for training modality.**
32. Brentano, M. A., E. L. Cadore, et al. (2008). "Physiological adaptations to strength and circuit training in postmenopausal women with bone loss." *Journal of Strength & Conditioning Research* **22(6)**: 1816-1825. **Different training modalities (Order and dose).**
33. Brodin, N., E. Eurenus, et al. (2008) "Coaching patients with early rheumatoid arthritis to healthy physical activity: a multicenter, randomized, controlled study." *Arthritis and rheumatism*, 325-331. **No dose-response relationship investigated.**
34. Brown, S. H., C. A. Lewis, et al. (2010) "The effects of Internet-based home training on upper limb function in adults with cerebral palsy." *Neurorehabilitation and neural repair*, 575-583. **Single dose.**

35. Buchner, D. M. (2009). "Physical Activity and Prevention of Cardiovascular Disease in Older Adults." *Clinics in Geriatric Medicine* **25** (4): 661-675. **No dose-response relationship investigated.**
36. Buchowski, M. S., L. Choi, et al. (2009). "Seasonal Changes in Amount and Patterns of Physical Activity in Women." *Journal of Physical Activity & Health* **6**(2): 252-261. **No dose-relationship investigated.**
37. Burtin, C., B. Clerckx, et al. (2009) "Early exercise in critically ill patients enhances short-term functional recovery." *Critical care medicine*, 2499-2505. **No population of interest. No dose-relationship investigated.**
38. Buss, T., K. de Walden-Galuszko, et al. "Kinesitherapy alleviates fatigue in terminal hospice cancer patients-an experimental, controlled study." *Supportive Care in Cancer* **18**(6): 743-749. **No population of interest. No dose-response relationship investigated.**
39. Bustamante, V., E. López de Santa María, et al. (2010) "Muscle training with repetitive magnetic stimulation of the quadriceps in severe COPD patients." *Respiratory Medicine*. **no meet inclusion for training modality.**
40. Cairney, J., G. Faulkner, et al. (2009). "Changes over time in physical activity and psychological distress among older adults." *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie* **54**(3): 160-169. **No dose-relationship investigated.**
41. Cakir-Atabek, H., S. Demir, et al. (2010) "Effects of different resistance training intensity on indices of oxidative stress." *Journal of strength and conditioning research / National Strength & Conditioning Association*. **No outcome of Interest.; Different modalities of training.**
42. Cakt, B. D., B. Nacir, et al. (2010) "Cycling progressive resistance training for people with multiple sclerosis: a randomized controlled study." *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists*. **No population of interest.**
43. Camargo, M. D., R. Stein, et al. (2008) "Circuit weight training and cardiac morphology: a trial with magnetic resonance imaging." *British Journal of Sports Medicine*, 141-145; discussion 145. **No dose-response relationship investigated.**
44. Cancela Carral, J. M. and C. Ayán Pérez (2007) "Effects of high-intensity combined training on women over 65." *Gerontology*, 340-346. **Single dose.**
45. Cancela, J. M., S. Varela, et al. (2008). "Effects of High Intensity Training on Elderly Women: A Pilot Study." *Physical & Occupational Therapy in Geriatrics* **27**(2): 160-169. **Single dose.**
46. Capodaglio, P., M. Capodaglio Edda, et al. (2007) "Long-term strength training for community-dwelling people over 75: impact on muscle function, functional ability and life style." *European Journal of Applied Physiology*, 535-542. **Single dose.**
47. Carlson, M. C., J. S. Saczynski, et al. (2008) "Exploring the effects of an "everyday" activity program on executive function and memory in older adults: Experience Corps." *The Gerontologist*, 793-801. **Single dose.**
48. Carregaro, R. L., P. Gentil, et al. "Effects of antagonist pre-load on knee extensor isokinetic muscle performance." *Journal of Sports Sciences* **29**(3): 271-278. **No outcome of Interest.**
49. Carvalho, J., E. Marques, et al. "Isokinetic strength benefits after 24 weeks of multicomponent exercise training and combined exercise training in older adults." *Aging-Clinical & Experimental Research* **22**(1): 63-69. **Different modalities of training.**
50. Caserotti, P., P. Aagaard, et al. (2008). "Explosive heavy-resistance training in old and very old adults: changes in rapid muscle force, strength and power." *Scandinavian Journal of Medicine & Science in Sports* **18**(6): 773-782. **Single dose.**
51. Cauraugh, J., S. A. Coombes, et al. (2007). "Stroke motor recovery evidence: Bilateral coordination training with an extra load on the unimpaired hand." *Journal of Sport & Exercise Psychology* **29**: S60-S60. **No dose-response relationship investigated.**
52. Chan, H., S. Inoue, et al. (2007) "Residential program for long-term hospitalized persons with **mental illness** in Japan: Randomized controlled trial." *Psychiatry and clinical neurosciences*, 515-521. **Single dose.**
53. Cheah, B. C., R. A. Boland, et al. (2009) "INSPIRATIOnAL--INSPIRatory muscle training in amyotrophic lateral sclerosis." *Amyotrophic lateral sclerosis : official publication of the World Federation of Neurology Research Group on Motor Neuron Diseases*, 384-392. **No population of interest.**

54. Cheung, L. and A. Jones (2007). "Effect of Acu-TENS on recovery heart rate after treadmill running exercise in subjects with normal health." *Complementary Therapies in Medicine* **15**(2): 109-114. **no meet inclusion criteria.**
55. Chiappa, G. R., J. P. Ribeiro, et al. (2009). "Inspiratory resistive loading after all-out exercise improves subsequent performance." *European Journal of Applied Physiology* **106**(2): 297-303. **No outcome of Interest.**
56. Chin APJM, van Uffelen JGZ, et al. (2008). "The functional effects of physical exercise training in frail older people : a systematic review." *Sports Medicine* **38**(9): 781-793. **systematic review.**
57. Chludilova, V., L. Mifkova, et al. (2007). "Functional capacity in men after coronary artery bypass surgery influenced by physical training." *Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae* **80** (5): 203-210. **No outcome of Interest.**
58. Choi, L., K. Y. Chen, et al. "Distributed lag and spline modeling for predicting energy expenditure from accelerometry in youth." *Journal of Applied Physiology* **108**(2): 314-327. **No population of interest.**
59. Choo, J., L. E. Burke, et al. (2007). "Improved quality of life with cardiac rehabilitation for post-myocardial infarction patients in Korea." *European Journal of Cardiovascular Nursing* **6**(3): 166-171. **No outcome of Interest.;**
60. Chtara, M., A. Chaouachi, et al. (2008) "Effect of concurrent endurance and circuit resistance training sequence on muscular strength and power development." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 1037-1045. **Different modalities of training.**
61. Colado, J. C., V. Tella, et al. (2009). "Effects of a short-term aquatic resistance program on strength and body composition in fit young men." *Journal of Strength & Conditioning Research* **23**(2): 549-559. **Single dose.**
62. Conradsson, M., H. Littbrand, et al. (2010) "Effects of a high-intensity functional exercise programme on depressive symptoms and psychological well-being among older people living in residential care facilities: A cluster-randomized controlled trial." *Aging & Mental Health*. **Single dose; No outcome of Interest.**
63. Coote, S., B. Murphy, et al. (2008). "The effect of the GENTLE/s robot-mediated therapy system on arm function after stroke." *Clinical Rehabilitation* **22**(5): 395-405. **Different modalities of training.**
64. Cormie, P., M. R. McGuigan, et al. (2010) "Changes in the eccentric phase contribute to improved stretch-shorten cycle performance after training." *Medicine and science in sports and exercise*. **No outcome of Interest.**
65. Cormie, P., M. R. McGuigan, et al. (2010) "Influence of strength on magnitude and mechanisms of adaptation to power training." *Medicine and science in sports and exercise*. **No outcome of Interest.**
66. Courneya, K. S., A.-L. Tamburrini, et al. "The Alberta Physical Activity and Breast Cancer Prevention Trial: quality of life outcomes." *Preventive Medicine* **52**(1): 26-32. **No outcome of Interest.**
67. Cousins, J. M., M. A. Petit, et al. "Muscle power and physical activity are associated with bone strength in older men: The osteoporotic fractures in men study." *Bone* **47** (2): 205-211. **No outcome of Interest.**
68. Craddock, M. "Testing the Theory." *Activities, Adaptation & Aging* **34**(3): 232-235. **no meet inclusion criteria.**
69. Cramp, M. C., R. J. Greenwood, et al. "Effectiveness of a community-based low intensity exercise programme for ambulatory stroke survivors." *Disability & Rehabilitation* **32**(3): 239-247. **Single dose.**
70. Croisier, J. L., M. Foidart-Dessalle, et al. (2007). "An isokinetic eccentric programme for the management of chronic lateral epicondylar tendinopathy." *British Journal of Sports Medicine* **41** (4): 269-275. **Single ExBt intervention (dose).**
71. Crossley, K. M., B. Vicenzino, et al. (2008) "Targeted physiotherapy for patellofemoral joint osteoarthritis: a protocol for a randomised, single-blind controlled trial." *BMC Musculoskeletal Disorders*, 122. **Single ExBt intervention (dose).**
72. Csapo, R., C. Gormasz, et al. (2009). "Functional performance in community-dwelling and institutionalized elderly women." *Wiener Klinische Wochenschrift* **121**(11-12): 383-390. **Single dose.**

73. da Silva, D. P., V. M. Curty, et al. "COMPARISON OF DELORME WITH OXFORD RESISTANCE TRAINING TECHNIQUES: EFFECTS OF TRAINING ON MUSCLE DAMAGE MARKERS." *Biology of Sport* **27**(2): 77-81. **no meet inclusion criteria.**
74. da Silva, J. G. F. B., S. A. Cader, et al. (2009). "Strength training, level of muscular strength and functional autonomy in a population of elderly women. [Spanish]." *Revista Espanola de Geriatria y Gerontologia* **44** (5): 256-261. **Single dose.**
75. Da Silva, R. L., M. A. Brentano, et al. (2010) "Effects of different strength training methods on postexercise energetic expenditure." *Journal of strength and conditioning research / National Strength & Conditioning Association.* **No outcome of Interest.**
76. Dalgas, U., E. Stenager, et al. (2009) "Resistance training improves muscle strength and functional capacity in multiple sclerosis." *Neurology*, 1478-1484. **Single dose.**
77. Daly, R. M., H. G. Ahlborg, et al. (2008). "Association between changes in habitual physical activity and changes in bone density, muscle strength, and functional performance in elderly men and women." *Journal of the American Geriatrics Society* **56**(12): 2252-2260. **Different modalities of PA.**
78. Daussin, F. N., J. Zoll, et al. (2008) "Effect of interval versus continuous training on cardiorespiratory and mitochondrial functions: relationship to aerobic performance improvements in sedentary subjects." *American journal of physiology. Regulatory, integrative and comparative physiology*, R264-272. **No outcome of Interest.**
79. Davis, W. J., D. T. Wood, et al. (2008) "Concurrent training enhances athletes' cardiovascular and cardiorespiratory measures." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 1503-1514. **No outcome of Interest.**
80. Davis, W. J., D. T. Wood, et al. (2008) "Concurrent training enhances athletes' strength, muscle endurance, and other measures." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 1487-1502. **Same dose** (differing only in the timing and sequence of exercises).
81. De Backer, I. C., E. Van Breda, et al. (2007). "High-intensity strength training improves quality of life in cancer survivors." *Acta Oncologica* **46**(8): 1143-1151. **Single dose.**
82. De Backer, I. C., G. Vreugdenhil, et al. (2008). "Long-term follow-up after cancer rehabilitation using high-intensity resistance training: persistent improvement of physical performance and quality of life." *British Journal of Cancer* **99**(1): 30-36. **Single dose.**
83. de Jong, J., K. A. P. M. Lemmink, et al. (2007). "Twelve-month effects of the Groningen active living model (GALM) on physical activity, health and fitness outcomes in sedentary and underactive older adults aged 55-65." *Patient Education & Counseling* **66**(2): 167-176. **Single dose.**
84. de Jong, Z., M. Munneke, et al. (2009). "Long-term follow-up of a high-intensity exercise program in patients with rheumatoid arthritis." *Clinical Rheumatology* **28**(6): 663-671. **No dose specification.**
85. de Salles, B. F., R. Simao, et al. (2009). "Rest interval between sets in strength training." *Sports Medicine* **39**(9): 765-777. **Systematic rew.**
86. de Souza-Teixeira, F., S. Costilla, et al. (2009). "Effects of resistance training in multiple sclerosis." *International Journal of Sports Medicine* **30** (4): 245-250. **No population of interest.**
87. de Villarreal, E. S., J. J. González-Badillo, et al. (2008) "Low and moderate plyometric training frequency produces greater jumping and sprinting gains compared with high frequency." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 715-725. **No outcome of Interest.**
88. de Vreede, P. L., N. L. van Meeteren, et al. (2007) "The effect of functional tasks exercise and resistance exercise on health-related quality of life and physical activity. A randomised controlled trial." *Gerontology*, 12-20. **Different modalities of training.**
89. Dechamps, A., P. Diolez, et al. (2010) "Effects of exercise programs to prevent decline in health-related quality of life in highly deconditioned institutionalized elderly persons: a randomized controlled trial." *Archives of internal medicine.* **No outcome of Interest.**
90. Decramer, M. (2009). "Response of the respiratory muscles to rehabilitation in COPD." *Journal of Applied Physiology* **107**(3): 971-976. **No outcome of Interest.**
91. Deley, G., G. Kervio, et al. (2007) "Effects of a one-year exercise training program in adults over 70 years old: a study with a control group." *Aging clinical and experimental research*, 310-315. **Single dose.**

92. Deley, G., G. Kervio, et al. (2008). "Neuromuscular adaptations to low-frequency stimulation training in a patient with chronic heart failure." *American Journal of Physical Medicine and Rehabilitation* **87 (6)**: 502-509. **Single dose. No outcome of Interest.**
93. Dereli, E. E. and A. Yaliman "Comparison of the effects of a physiotherapist-supervised exercise programme and a self-supervised exercise programme on quality of life in patients with Parkinson's disease." *Clinical Rehabilitation* **24(4)**: 352-362. . **Different modalities of training.**
94. Dias, I., B. F. de Salles, et al. (2010) "Influence of exercise order on maximum strength in untrained young men." *Journal of science and medicine in sport / Sports Medicine Australia*.**Same dose diff order.**
95. Dillon, E. R., K. F. Bjornson, et al. (2009). "Ambulatory activity in youth with arthrogyposis: a cohort study." *Journal of Pediatric Orthopedics* **29(2)**: 214-217. **No population of interest.**
96. Dolmage, T. and R. Goldstein (2008). "Effects of One-Legged Exercise Training of Patients With COPD." *Chest* **133(2)**: 370-376. **Single dose.**
97. Dourado, V. S., S. E. Tanni, et al. (2009). "Effect of three exercise programs on patients with chronic obstructive pulmonary disease." *Brazilian Journal of Medical and Biological Research* **42 (3)**: 263-271. **Different modalities of training.**
98. Dourado, V. Z., L. C. Antunes, et al. (2009) "Factors associated with the minimal clinically important difference for health-related quality of life after physical conditioning in patients with COPD." *Jornal brasileiro de pneumologia : publicação oficial da Sociedade Brasileira de Pneumologia e Tisiologia*, 846-853. **no meet inclusion criteria.**
99. Driller, M. W., J. W. Fell, et al. (2009) "The effects of high-intensity interval training in well-trained rowers." *International journal of sports physiology and performance*, 110-121. **Single dose.**
100. Dronkers, J. J., H. Lamberts, et al. (2010) "Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study." *Clinical Rehabilitation*, 614-622. **No population of interest.**
101. Dubbert, P. M., M. C. Morey, et al. (2008) "Counseling for home-based walking and strength exercise in older primary care patients." *Archives of internal medicine*, 979-986. **no meet inclusion criteria.**
102. Duffield, R., J. Edge, et al. (2007). "The relationship between the V02 slow component, muscle metabolites and performance during very-heavy exhaustive exercise." *Journal of Science and Medicine in Sport* **10(3)**: 127-134. **Single dose.**
103. Duffield, R., R. Green, et al. (2010) "Precooling can prevent the reduction of self-paced exercise intensity in the heat." *Medicine and science in sports and exercise*, 577-584. **No outcome of Interest.**
104. Duffield, R., M. King, et al. (2009). "Recovery of Voluntary and Evoked Muscle Performance Following Intermittent-Sprint Exercise in the Heat." *International journal of sports physiology & performance* **4(2)**: 254-268. **No dose-responce ralationship investigated.**
105. Duschau-Wicke, A., A. Caprez, et al. (2010) "Patient-cooperative control increases active participation of individuals with SCI during robot-aided gait training." *Journal of neuroengineering and rehabilitation*. **No dose-responce ralationship investigated.**
106. Egerton, T. and S. G. Brauer (2009). "Temporal Characteristics of Habitual Physical Activity Periods Among Older Adults." *Journal of Physical Activity & Health* **6(5)**: 644-650. **No dose-responce ralationship investigated.**
107. Egerton, T., S. G. Brauer, et al. "Dynamic postural stability is not impaired by moderate-intensity physical activity in healthy or balance-impaired older people." *Human Movement Science* **29(6)**: 1011-1022. **No dose-responce ralationship investigated.**
108. Egerton, T., S. G. Brauer, et al. (2009). "Fatigue After Physical Activity in Healthy and Balance-Impaired Elderly." *Journal of Aging & Physical Activity* **17(1)**: 89-105. **No outcome of Interest.**
109. Elavsky, S. (2009). "Physical activity, menopause, and quality of life: The role of affect and self-worth across time." *Menopause* **16 (2)**: 265-271. **No outcome of Interest.**
110. Elliott, M., P. Wagner, et al. (2007). "Power Athletes and Distance Training: Physiological and Biomechanical Rationale for Change." *Sports Medicine (Auckland)* **37(1)**: 47-57. **No dose-responce ralationship investigated.**

111. English, C. K., S. L. Hillier, et al. (2007). "Circuit class therapy versus individual physiotherapy sessions during inpatient stroke rehabilitation: a controlled trial.[Erratum appears in Arch Phys Med Rehabil. 2007 Oct;88(10):1364]." Archives of Physical Medicine & Rehabilitation **88**(8): 955-963. **Different modalities of training.**
112. Esteve-Lanao, J., C. Foster, et al. (2007) "Impact of training intensity distribution on performance in endurance athletes." Journal of strength and conditioning research / National Strength & Conditioning Association, 943-949. **No outcome of Interest. (Athlete).**
113. Estrada, M., A. Kleppinger, et al. (2007) "Functional impact of relative versus absolute sarcopenia in healthy older women." Journal of the American Geriatrics Society, 1712-1719. **no meet inclusion criteria.**
114. Evangelista, L. S., M. A. Hamilton, et al. "Is exercise adherence associated with clinical outcomes in patients with advanced heart failure?" Physician & Sportsmedicine **38**(1): 28-36. **No outcome of Interest.**
115. Fahlman, M., A. Morgan, et al. (2007). "Combination Training and Resistance Training as Effective Interventions to Improve Functioning in Elders." Journal of Aging & Physical Activity **15**(2): 195-205. **Different modalities of training.**
116. Fahlman, M. M., N. McNevin, et al. "Effects of Resistance Training on Functional Ability in Elderly Individuals." American Journal of Health Promotion **25**(4): 237-243. **Single dose.**
117. Fahlman, M. M., R. Topp, et al. (2007) "Structured exercise in older adults with limited functional ability." Journal of gerontological nursing, 32-39. **Single dose.**
118. Faigenbaum, A. D., N. A. Ratamess, et al. (2008). "Effect of Rest Interval Length on Bench Press Performance in Boys, Teens, and Men." Pediatric Exercise Science **20**(4): 457-469. **No outcome of Interest.**
119. Falla, D., G. Jull, et al. (2008). "Training the cervical muscles with prescribed motor tasks does not change muscle activation during a functional activity." Manual Therapy **13** (6): 507-512. **No outcome of Interest.**
120. Falvo, M. J., B. K. Schilling, et al. (2007) "Efficacy of prior eccentric exercise in attenuating impaired exercise performance after muscle injury in resistance trained men." Journal of strength and conditioning research / National Strength & Conditioning Association, 1053-1060. **No dose-response relationship investigated.**
121. Farr, J. N., S. B. Going, et al. (2010) "Progressive resistance training improves overall physical activity levels in patients with early osteoarthritis of the knee: a randomized controlled trial." Physical Therapy, 356-366. **Single dose.**
122. Fatone, C., M. Guescini, et al. "Two weekly sessions of combined aerobic and resistance exercise are sufficient to provide beneficial effects in subjects with Type 2 diabetes mellitus and metabolic syndrome." Journal of Endocrinological Investigation **33**(7): 489-495. **No outcome of Interest.**
123. Fatouros, I. G., A. Chatzinikolaou, et al. (2009) "Intensity of resistance exercise determines adipokine and resting energy expenditure responses in overweight elderly individuals." Diabetes Care, 2161-2167. **No outcome of Interest.**
124. Feiereisen, P., C. Delagardelle, et al. (2007) "Is strength training the more efficient training modality in chronic heart failure?" Medicine and science in sports and exercise, 1910-1917. **Different modalities of training.**
125. Ferguson, C., B. J. Whipp, et al. (2007). "Effects of prior very-heavy intensity exercise on indices of aerobic function and high-intensity exercise tolerance." Journal of Applied Physiology **103**(3): 812-822. **No outcome of Interest.**
126. Ferrauti, A., M. Bergermann, et al. (2010) "Effects of a concurrent strength and endurance training on running performance and running economy in recreational marathon runners." Journal of strength and conditioning research / National Strength & Conditioning Association. **No outcome of Interest. (Athlete).**
127. Ferrazza, A., D. Martolini, et al. (2009). "Cardiopulmonary exercise testing in the functional and prognostic evaluation of patients with pulmonary diseases." Journal of Prosthetics and Orthotics **21**(1): 3-17. **No dose-response relationship investigated.**
128. Fielding, R. A., J. Katula, et al. (2007). "Activity Adherence and Physical Function in Older Adults with Functional Limitations." Medicine & Science in Sports & Exercise **39**(11): 1997-2004. **Single dose.**

129. Filippin, N. T., P. H. L. da Costa, et al. "Effects of treadmill-walking training with additional body load on quality of life in subjects with Parkinson's disease." *Revista Brasileira de Fisioterapia* **14**(4): 344-350. **Different modalities of training.**
130. Fimland, M. S., J. Helgerud, et al. (2010) "Enhanced neural drive after maximal strength training in multiple sclerosis patients." *European Journal of Applied Physiology*. **No outcome of Interest.**
131. Fisher, B. E., A. D. Wu, et al. (2008). "The Effect of Exercise Training in Improving Motor Performance and Corticomotor Excitability in People With Early Parkinson's Disease." *Archives of Physical Medicine and Rehabilitation* **89** (7): 1221-1229. **Different modalities of training.**
132. Flint-Wagner, H. G., J. Lisse, et al. (2009). "Assessment of a sixteen-week training program on strength, pain, and function in rheumatoid arthritis patients." *JCR: Journal of Clinical Rheumatology* **15**(4): 165-171. **No outcome of Interest.**
133. Ford, M. P., L. A. Malone, et al. "Step Activity in Persons With Parkinson's Disease." *Journal of Physical Activity & Health* **7**(6): 724-729. **No dose-response relationship investigated.**
134. Foroughi, N., R. M. Smith, et al. "Progressive resistance training and dynamic alignment in osteoarthritis: A single-blind randomised controlled trial." *Clinical Biomechanics* **26**(1): 71-77. **Single dose.**
135. Forrester, L. W., L. A. Wheaton, et al. (2008). "Exercise-mediated locomotor recovery and lower-limb neuroplasticity after stroke." *Journal of Rehabilitation Research & Development* **45**(2): 205-220. **No dose-response relationship investigated.**
136. Fox, K., A. Stathi, et al. (2007). "Physical activity and mental well-being in older people participating in the Better Ageing Project." *European Journal of Applied Physiology* **100**(5): 591-602. **No outcome of Interest.**
137. Franko, O. I., D. Zurakowski, et al. (2008) "Functional disability of the wrist: direct correlation with decreased wrist motion." *The Journal of hand surgery*, 485-492. **no meet inclusion criteria.**
138. French B, Thomas JH, et al. (2009). "Repetitive Task Training for Improving Functional Ability After Stroke." *Stroke* **40**(4): e98-99. **Systematic rew.**
139. Friedenreich, C. M., L. S. Cook, et al. "Case-control study of lifetime total physical activity and endometrial cancer risk." *Cancer Causes & Control* **21**(7): 1105-1116. **No population of interest.**
140. Gacesa, J. Z. P., D. B. Kozic, et al. (2009). "Changes of functional status and volume of triceps brachii measured by magnetic resonance imaging after maximal resistance training." *Journal of Magnetic Resonance Imaging* **29** (3): 671-676. **No outcome of Interest.**
141. Galvão, D. A., D. R. Taaffe, et al. (2010) "Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial." *Journal of clinical oncology* : official journal of the American Society of Clinical Oncology. **No outcome of Interest.**
142. Galvin, R., B. Murphy, et al. (2008). "The impact of increased duration of exercise therapy on functional recovery following stroke--what is the evidence?" *Topics in Stroke Rehabilitation* **15**(4): 365-377. **Systematic rew.**
143. Garcia-Lopez, D., A. J. Herrero, et al. (2010). "Influence of "In Series" Elastic Resistance on Muscular Performance During a Biceps-curl Set on the Cable Machine." *Journal of Strength & Conditioning Research* **24**(9): 2449-2455. **No population of interest.**
144. Garg, P. K., K. Liu, et al. (2009). "Physical activity during daily life and functional decline in peripheral arterial disease." *Circulation* **119**(2): 251-260. **No outcome of Interest.**
145. Gaudin, P., S. Leguen-Guegan, et al. (2008). "Is dynamic exercise beneficial in patients with rheumatoid arthritis?" *Joint, Bone, Spine: Revue du Rhumatisme* **75**(1): 11-17. **Systematic rew.**
146. Gayan-Ramirez, G. and M. Decramer (2009). "[Pulmonary rehabilitation in patients with chronic obstructive pulmonary disease]." *Presse Medicale* **38**(3): 452-461. **Reccomendations**
147. Geithner, C. A. and D. R. McKenney "Strategies for Aging Well." *Strength & Conditioning Journal* (Lippincott Williams & Wilkins) **32**(5): 36-52. **No dose-response relationship investigated.**
148. Girold, S., D. Maurin, et al. (2007) "Effects of dry-land vs. resisted- and assisted-sprint exercises on swimming sprint performances." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 599-605. **Different modalities of training.**

149. Gitlin, L. N., W. W. Hauck, et al. (2009) "Long-term effect on mortality of a home intervention that reduces functional difficulties in older adults: results from a randomized trial." *Journal of the American Geriatrics Society*, 476-481. **Single dose.**
150. Glass, S. C. (2008) "Effect of a learning trial on self-selected resistance training load." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 1025-1029. **No outcome of Interest.**
151. Glinsky, J., L. Harvey, et al. (2008) "Short-term progressive resistance exercise may not be effective at increasing wrist strength in people with tetraplegia: a randomised controlled trial." *The Australian journal of physiotherapy*, 103-108. **No population of interest.**
152. Gonzales, J. U. and J. S. Williams "Effects of acute exercise on inspiratory muscle strength and endurance in untrained women and men." *Journal of Sports Medicine & Physical Fitness* **50(3): 268-273. No outcome of Interest.**
153. González-Ravé, J. M., L. Machado, et al. (2009) "Acute effects of heavy-load exercises, stretching exercises, and heavy-load plus stretching exercises on squat jump and countermovement jump performance." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 472-479. **no meet inclusion criteria.**
154. Goodpaster, B. H., P. Chomentowski, et al. (2008) "Effects of physical activity on strength and skeletal muscle fat infiltration in older adults: a randomized controlled trial." *Journal of applied physiology (Bethesda, Md. : 1985)*, 1498-1503. **No dose-response relationship investigated.**
155. Gopalakrishnan, R., K. O. Genc, et al. "Muscle volume, strength, endurance, and exercise loads during 6-month missions in space." *Aviation Space & Environmental Medicine* **81(2): 91-102. no meet inclusion criteria. (SPACE)**
156. Goto, K., K. Tanaka, et al. "A single versus multiple bouts of moderate-intensity exercise for fat metabolism." *Clinical Physiology & Functional Imaging* **31(3): 215-220. No outcome of Interest.**
157. Granacher, U., L. Zahner, et al. (2008). "Strength, power, and postural control in seniors: Considerations for functional adaptations and for fall prevention." *European Journal of Sport Science* **8(6): 325-340. No dose-response relationship investigated.**
158. Granados, C., M. Izquierdo, et al. (2008). "Effects of an entire season on physical fitness in elite female handball players." *Medicine and Science in Sports and Exercise* **40 (2): 351-361. No dose-response relationship investigated.**
159. Guilhem, G., C. Cornu, et al. "A new device to study isoload eccentric exercise." *Journal of Strength & Conditioning Research* **24(12): 3476-3483. no meet inclusion criteria.**
160. Gupta, S. (2009). "Endurance and strength training have different benefits for people with peripheral arterial disease, but both improve quality of life." *Australian Journal of Physiotherapy* **55(1): 63-63. No dose-response relationship investigated.**
161. Hagedorn, D. K. and E. Holm "Effects of traditional physical training and visual computer feedback training in frail elderly patients. A randomized intervention study." *European Journal of Physical and Rehabilitation Medicine* **46 (2): 159-168. Different modalities of training.**
162. Hakkinen, A., A. Kukka, et al. (2009). "Health-related quality of life and physical activity in persons at high risk for type 2 diabetes." *Disability & Rehabilitation* **31(10): 799-805. No dose-response relationship investigated.**
163. Hamberg-van Reenen, H. H., B. Visser, et al. (2009) "The effect of a resistance-training program on muscle strength, physical workload, muscle fatigue and musculoskeletal discomfort: an experiment." *Applied ergonomics*, 396-403. **Single dose**
164. Hammer, A. and B. Lindmark (2009). "Is forced use of the paretic upper limb beneficial? A randomized pilot study during subacute post-stroke recovery." *Clinical Rehabilitation* **23(5): 424-433. Different modalities of training.**
165. Hamre, H. J., C. M. Witt, et al. (2007). "Eurythmy therapy in chronic disease: a four-year prospective cohort study." *BMC public health* **7: 61. Single dose**
166. Han, C. E., M. A. Arbib, et al. (2008). "Stroke rehabilitation reaches a threshold." *PLoS Computational Biology* **4(8): e1000133. No dose-response relationship investigated.**
167. Hansen, D., P. Dendale, et al. "Long-term effect of rehabilitation in coronary artery disease patients: randomized clinical trial of the impact of exercise volume." *Clinical* **24(4): 319-327. No outcome of Interest.**

168. Hansen, D., P. Dendale, et al. "The impact of training modalities on the clinical benefits of exercise intervention in patients with cardiovascular disease risk or type 2 diabetes mellitus." *Sports* **40**(11): 921-940. **No outcome of Interest.**
169. Hanson, E. D., S. Leigh, et al. (2007) "Acute effects of heavy- and light-load squat exercise on the kinetic measures of vertical jumping." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 1012-1017. **No outcome of Interest.**
170. Harness, E. T., N. Yozbatiran, et al. (2008). "Effects of intense exercise in chronic spinal cord injury." *Spinal Cord* **46**(11): 733-737. **No population of interest.**
171. Harris, C., M. DeBeliso, et al. (2007) "Detraining in the older adult: effects of prior training intensity on strength retention." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 813-818. **No training applied**
172. Harris, J. E., J. J. Eng, et al. (2009). "A self-administered Graded Repetitive Arm Supplementary Program (GRASP) improves arm function during inpatient stroke rehabilitation: a multi-site randomized controlled trial." *Stroke* **40**(6): 2123-2128. **Single dose**
173. Harris, N., J. Cronin, et al. (2007). "Contraction force specificity and its relationship to functional performance." *Journal of Sports Sciences* **25**(2): 201-212. **Systematic rew.**
174. Harts, C. C., P. H. Helmhout, et al. (2008). "A high-intensity lumbar extensor strengthening program is little better than a low-intensity program or a waiting list control group for chronic low back pain: a randomised clinical trial." *Australian Journal of Physiotherapy* **54**(1): 23-31. **No population of interest.**
175. Haykowsky, M., D. Taylor, et al. (2009). "Exercise training improves aerobic capacity and skeletal muscle function in heart transplant recipients." *American Journal of Transplantation* **9**(4): 734-739. **No population of interest.**
176. Hazell, T., K. Kenno, et al. (2007). "Functional benefit of power training for older adults." *Journal of Aging & Physical Activity* **15**(3): 349-359. **Systematic rew.**
177. He, J., H. Li, et al. (2007). "Real-time daily activity classification with wireless sensor networks using Hidden Markov Model." *Conference Proceedings: .. Annual International Conference of the IEEE Engineering in Medicine & Biology Society* **2007**: 3192-3195. **no meet inclusion criteria.**
178. Helgerud, J., T. Karlsen, et al. "Interval and Strength Training in CAD Patients." *International Journal of Sports Medicine* **32**(1): 54-59. **Different modalities of training.**
179. Hendriks, M. R. C., M. H. C. Bleijlevens, et al. (2008). "Lack of effectiveness of a multidisciplinary fall-prevention program in elderly people at risk: a randomized, controlled trial." *Journal of the American Geriatrics Society* **56**(8): 1390-1397. **no meet inclusion criteria.**
180. Henwood, T. R. and D. R. Taaffe (2008). "Detraining and retraining in older adults following long-term muscle power or muscle strength specific training." *Journals of Gerontology Series A-Biological Sciences & Medical Sciences* **63**(7): 751-758. **Same protocol.**
181. Herrero, F., A. F. San Juan, et al. (2007). "Effects of Detraining on the Functional Capacity of Previously Trained Breast Cancer Survivors." *International Journal of Sports Medicine* **28**(3): 257-264. **No dose-response relationship investigated.**
182. Hirsch, C. H., P. Diehr, et al. "Physical activity and years of healthy life in older adults: results from the cardiovascular health study." *Journal of Aging & Physical Activity* **18**(3): 313-334. **No outcome of Interest.**
183. Hiruntrakul, A., R. Nanagara, et al. (2010) "Effect of once a week endurance exercise on fitness status in sedentary subjects." *Journal of the Medical Association of Thailand = Chotmaihet thangphaet*. **Single dose**
184. Hodges, L. D., G. R. Sandercock, et al. (2008) "Randomized controlled trial of supervised exercise to evaluate changes in cardiac function in patients with peripheral atherosclerotic disease." *Clinical physiology and functional imaging*, 32-37. **No outcome of Interest.**
185. Hoff, J., A. E. Tjønnna, et al. (2007) "Maximal strength training of the legs in COPD: a therapy for mechanical inefficiency." *Medicine and science in sports and exercise*, 220-226. **Different modalities of training.**
186. Hoffman, J. R., N. A. Ratamess, et al. (2009) "Comparison between different off-season resistance training programs in Division III American college football players." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 11-19. **No population of interest. (Athlete).**

187. Holiat, J., M. Fiuit, et al. (2009). "Recreational Exercise in Rheumatic Diseases." *International Journal of Sports Medicine* **30**(11): 814-820. **No outcome of Interest. (QoL).**
188. Holmgren, E., B. Lindström, et al. "What is the benefit of a high intensive exercise program? A randomized controlled trial." *Advances in Physiotherapy* **12**(3): 115-124. **No dose-response relationship investigated.**
189. Holtermann, A., K. Søgaard, et al. (2008) "The influence of biofeedback training on trapezius activity and rest during occupational computer work: a randomized controlled trial." *European Journal of Applied Physiology*, 983-989. **no meet inclusion criteria.**
190. Hongo, M., E. Itoi, et al. (2007) "Effect of low-intensity back exercise on quality of life and back extensor strength in patients with osteoporosis: a randomized controlled trial." *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, 1389-1395. **Single dose.**
191. Hoogboom, T. J., M. J. Stukstette, et al. (2010) "Non-pharmacological care for patients with generalized osteoarthritis: design of a randomized clinical trial." *BMC Musculoskeletal Disorders*. **no meet inclusion criteria.**
192. Howe, T. E. and D. Rafferty (2009). "Quadriceps activity and physical activity profiles over long durations in patients with osteoarthritis of the knee and controls." *Journal of Electromyography & Kinesiology* **19**(2): e78-83. **no meet inclusion criteria.**
193. Hsieh, L. F., S. C. Chen, et al. (2009) "Supervised aerobic exercise is more effective than home aerobic exercise in female chinese patients with rheumatoid arthritis." *Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine*, 332-337. **Same dose.**
194. Hsieh, M. J., C. C. Lan, et al. (2007). "Effects of high-intensity exercise training in a pulmonary rehabilitation programme for patients with chronic obstructive pulmonary disease." *Respirology* **12** (3): 381-388. **Single dose**
195. Hu, M., T. Finni, et al. (2009). "Effects of strength training on work capacity and parasympathetic heart rate modulation during exercise in physically inactive men." *International Journal of Sports Medicine* **30**(10): 719-724. **No outcome of Interest.**
196. Huang, C. H. (2009) "High Intensity Inspiratory Training Improves Dyspnoea, Functional Status, and Quality of Life in Older Subjects [Abstract]." *Respirology*, A190 [PD 105‐103]. **No outcome of Interest.**
197. Hughes, S. L., R. B. Seymour, et al. (2009) "Best-practice physical activity programs for older adults: findings from the national impact study." *American journal of public health*, 362-368. **Reccomendation**
198. Hulmi, J. J., V. Kovanen, et al. (2009) "Acute and long-term effects of resistance exercise with or without protein ingestion on muscle hypertrophy and gene expression." *Amino acids*, 297-308. **no meet inclusion criteria.**
199. Hunt, K. J., B. A. Saunders, et al. (2007). "Energetics of paraplegic cycling: a new theoretical framework and efficiency characterisation for untrained subjects." *European Journal of Applied Physiology* **101**(3): 277-285. **No dose-response relationship investigated.**
200. Hurkmans, E. J., M. H. van den Berg, et al. "Maintenance of physical activity after Internet-based physical activity interventions in patients with rheumatoid arthritis." *Rheumatology (Oxford, England)* **49** (1): 167-172. **No dose-response relationship investigated.**
201. Hwa-Jin, L., P. Hi-Joon, et al. (2009). "Tai Chi Qigong for the quality of life of patients with knee osteoarthritis: a pilot, randomized, waiting list controlled trial." *Clinical Rehabilitation* **23**(6): 504-511. **Single dose.**
202. Iaia, F. M., J. Perez-Gomez, et al. "Effect of previous exhaustive exercise on metabolism and fatigue development during intense exercise in humans." *Scandinavian Journal of Medicine & Science in Sports* **20**(4): 619-629. **No outcome of Interest.**
203. Ibanez, J., E. M. Gorostiaga, et al. (2008). "Lower muscle strength gains in older men with type 2 diabetes after resistance training." *Journal of Diabetes & its Complications* **22**(2): 112-118. **Same dose diff population**
204. Ingrid, B. and A. Marsella (2008). "Factors influencing exercise participation by clients in long-term care." *Perspectives* **32**(4): 5-11. **No outcome of Interest.**

205. Ishikawa-Takata, K., H. Tanaka, et al. "Beneficial effect of physical activity on blood pressure and blood glucose among Japanese male workers." *Diabetes Research & Clinical Practice* **87**(3): 394-400. **No outcome of Interest.**
206. Ivey, F. M., C. E. Hafer-Macko, et al. (2008). "Task-oriented treadmill exercise training in chronic hemiparetic stroke." *Journal of Rehabilitation Research & Development* **45**(2): 249-259. **Single dose.**
207. Izquierdo-Gabarren, M., R. Gonzalez De Txabarri Exposito, et al. "Concurrent endurance and strength training not to failure optimizes performance gains." *Medicine and Science in Sports and Exercise* **42** (6): 1191-1199. **no population of interest. (high trained athlete)**
208. Iwamoto, J., H. Suzuki, et al. (2009). "Preventative effect of exercise against falls in the elderly: A randomized controlled trial." *Osteoporosis International* **20** (7): 1233-1240. **Single dose.**
209. Iwamoto, J., T. Takeda, et al. (2007). "Effect of muscle strengthening exercises on the muscle strength in patients with osteoarthritis of the knee." *Knee* **14**(3): 224-230. **Single dose.**
210. Izawa, K., S. Watanabe, et al. "Age-related differences in physiologic and psychosocial outcomes after cardiac rehabilitation." *American* **89**(1): 24-33. **No outcome of Interest.**
211. Izquierdo, M., J. Ibañez, et al. (2009) "Neuromuscular fatigue after resistance training." *International Journal of Sports Medicine*, 614-623. **No outcome of Interest.**
212. Izquierdo, M., J. Ibanez, et al. (2007). "Detraining and tapering effects on hormonal responses and strength performance." *Journal of Strength and Conditioning Research* **21** (3): 768-775. **No outcome of Interest.**
213. Jørgensen, J. r. R., D. T. Bech-Pedersen, et al. "Effect of Intensive Outpatient Physical Training on Gait Performance and Cardiovascular Health in People With Hemiparesis After Stroke." *Physical Therapy* **90**(4): 527-537. **Single dose.**
214. Jacobi, D., M.-A. Charles, et al. (2009). "Relationships of self-reported physical activity domains with accelerometry recordings in French adults." *European Journal of Epidemiology* **24**(4): 171-179. **Different modalities of training, reported**
215. Jacobs, P. L. (2009). "Effects of resistance and endurance training in persons with paraplegia." *Medicine & Science in Sports & Exercise* **41**(5): 992-997. **No population of interest.**
216. Jang, E.-J. and H.-S. Kim (2009). "[Effects of exercise intervention on physical fitness and health-related quality of life in hemodialysis patients]." *Journal of Korean Academy of Nursing* **39**(4): 584-593. **No population of interest.**
217. Jo E, Judelson DA, et al. (2010). "Influence of Recovery Duration After a Potentiating Stimulus on Muscular Power in Recreationally Trained Individuals." *Journal of Strength & Conditioning Research* **24**(2): 343-347.
218. Johnson, N. A., L. L. Y. Lim, et al. (2009). "Multicenter randomized controlled trial of a home walking intervention after outpatient cardiac rehabilitation on health-related quality of life in women." *European Journal of Cardiovascular Prevention & Rehabilitation* **16**(5): 633-637. **No outcome of Interest.**
219. Johnson, T. K. and M. H. Woollacott "NEUROMUSCULAR RESPONSES TO PLATFORM PERTURBATIONS IN POWER- VERSUS ENDURANCE-TRAINED ATHLETES." *Perceptual & Motor Skills* **112**(1): 3-20. **Different modalities of training.**
220. Judge, L. W. and J. R. Burke "The effect of recovery time on strength performance following a high-intensity bench press workout in males and females." *International journal of sports physiology & performance* **5**(2): 184-196. **Single dose.**
221. Jullien, H., C. Bisch, et al. (2008) "Does a short period of lower limb strength training improve performance in field-based tests of running and agility in young professional soccer players?" *Journal of strength and conditioning research / National Strength & Conditioning Association*, 404-411. **Single dose.**
222. Kakabeek, T., P. Hofer, et al. (2008). "Training and detraining of a tetraplegic subject: High-volume FES cycle training." *American Journal of Physical Medicine and Rehabilitation* **87**(1): 56-64. **No population of interest.**
223. Kalapotharakos, V. (2007). "Aerobic Exercise in Older Adults: Effects on VO₂-max and Functional Performance." *Critical Reviews in Physical and Rehabilitation Medicine* **19**(3): 213-225. **REview**

224. Kall, L. B. (2009). "Psychological determinants of quality of life in patients with whiplash associated disorders-a prospective study." *Disability & Rehabilitation* **31**(3): 227-236. **No population of interest.**
225. Kampshoff, C. S., L. M. Buffart, et al. "Design of the Resistance and Endurance exercise After ChemoTherapy (REACT) study: a randomized controlled trial to evaluate the effectiveness and cost-effectiveness of exercise interventions after chemotherapy on physical fitness and fatigue." *BMC Cancer* **10**: 658. **No population of interest.**
226. Karabulut, M., T. Abe, et al. "The effects of low-intensity resistance training with vascular restriction on leg muscle strength in older men." *European Journal of Applied Physiology* **108**(1): 147-155. **Single dose.; No outcome of Interest.**
227. Karinkanta, S., A. Heinonen, et al. (2009). "Maintenance of exercise-induced benefits in physical functioning and bone among elderly women." *Osteoporosis International* **20**(4): 665-674. **No dose-response relationship; No outcome of Interest.**
228. Karvinen, K. H., K. S. Courneya, et al. (2007). "Associations between exercise and quality of life in bladder cancer survivors: a population-based study." *Cancer Epidemiology, Biomarkers & Prevention* **16**(5): 984-990. **No population of interest.**
229. Kawahira, K., T. Noma, et al. (2009). "Improvements in limb kinetic apraxia by repetition of a newly designed facilitation exercise in a patient with corticobasal degeneration." *International Journal of Rehabilitation Research* **32**(2): 178-183. **Single dose.;**
230. Kell, R. T. and G. J. Asmundson (2009) "A comparison of two forms of periodized exercise rehabilitation programs in the management of chronic nonspecific low-back pain." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 513-523. **No population of interest.**
231. Kemi, O. J. and U. Wisloff "High-intensity aerobic exercise training improves the heart in health and disease." *Journal of Cardiopulmonary Rehabilitation & Prevention* **30**(1): 2-11. **No dose-response relationship; No outcome of Interest.**
232. Kemmler, W., S. von Stengel, et al. "Exercise, body composition, and functional ability: a randomized controlled trial." *American Journal of Preventive Medicine* **38**(3): 279-287. **No dose-response relationship; No outcome of Interest.**
233. Kendall, K. L., A. E. Smith, et al. (2009) "Effects of four weeks of high-intensity interval training and creatine supplementation on critical power and anaerobic working capacity in college-aged men." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 1663-1669. **No dose-response relationship; No outcome of Interest.**
234. Keogh, J. W., S. Morrison, et al. (2007). "Strength training improves the tri-digit finger-pinch force control of older adults." *Archives of Physical Medicine & Rehabilitation* **88**(8): 1055-1063. **No dose-response relationship; No outcome of Interest.**
235. Kerse, N., K. J. Hayman, et al. "Home-based activity program for older people with depressive symptoms: DeLLITE--a randomized controlled trial." *Annals of Family Medicine* **8**(3): 214-223. **Single dose.;**
236. Kerse, N., K. Peri, et al. (2008). "Does a functional activity programme improve function, quality of life, and falls for residents in long term care? Cluster randomised controlled trial." *BMJ* **337**: a1445. **Single dose.**
237. Keteyian, S. J., J. L. Fleg, et al. "Role and benefits of exercise in the management of patients with heart failure." *Heart Failure Reviews* **15**(6): 523-530. **Review.**
238. Kibele, A. and D. G. Behm (2009). "Seven weeks of instability and traditional resistance training effects on strength, balance and functional performance." *Journal of Strength & Conditioning Research* **23**(9): 2443-2450. **Single dose.;**
239. Kidgell, D. J., M. A. Stokes, et al. (2010) "Neurophysiological responses after short-term strength training of the biceps brachii muscle." *Journal of strength and conditioning research / National Strength & Conditioning Association*. **Single dose.**
240. Kilding, A., M. Fysh, et al. (2007). "Relationships between pulmonary oxygen uptake kinetics and other measures of aerobic fitness in middle- and long-distance runners." *European Journal of Applied Physiology* **100**(1): 105-114. **No outcome of Interest.**
241. Kilding, A. E., S. Brown, et al. (2010) "Inspiratory muscle training improves 100 and 200 m swimming performance." *European Journal of Applied Physiology*. **No outcome of Interest.**
242. Kiliç, F. (2008) "An intensive combined training program modulates physical, physiological, biomotoric, and technical parameters in women basketball players." *Journal of*

- strength and conditioning research / National Strength & Conditioning Association, 1769-1778. **No outcome of Interest.**
243. Kim, H., T. Suzuki, et al. (2007). "Effectiveness of multidimensional exercises for the treatment of stress urinary incontinence in elderly community-dwelling Japanese women: a randomized, controlled, crossover trial." *Journal of the American Geriatrics Society* **55**(12): 1932-1939. **No dose-response relationship; No population of interest.**
244. Kimura, K., S. Obuchi, et al. (2010) "The influence of short-term strength training on health-related quality of life and executive cognitive function." *Journal of Physiological Anthropology*, 95-101. **Single dose.; No outcome of Interest.**
245. King, J. A. and D. J. Cipriani (2010) "Comparing preseason frontal and sagittal plane plyometric programs on vertical jump height in high-school basketball players." *Journal of strength and conditioning research / National Strength & Conditioning Association*. **No outcome of Interest.**
246. Kirk, E. P., R. A. Washburn, et al. (2007) "Six months of supervised high-intensity low-volume resistance training improves strength independent of changes in muscle mass in young overweight men." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 151-156. **No outcome of Interest.**
247. Klusiewicz, A., L. Borkowski, et al. (2008). "The inspiratory muscle training in elite rowers." *Journal of Sports Medicine & Physical Fitness* **48**(3): 279-284. **No outcome of Interest.**
248. Koltyn, K. F. and M. Umeda (2007) "Contralateral attenuation of pain after short-duration submaximal isometric exercise." *The journal of pain : official journal of the American Pain Society*, 887-892. **No population of interest.**
249. Konecny, L., P. Pospisil, et al. "Combination of aerobic and resistant training in multiple sclerosis." *Scripta Medica Facultatis Medicae Universitatis Brunensis Masarykianae* **83** (2): 98-106. **No population of interest.**
250. Koninckx, E., M. Van Leemputte, et al. (2010) "Effect of isokinetic cycling versus weight training on maximal power output and endurance performance in cycling." *European Journal of Applied Physiology*. **Different modalities of training.**
251. Koval'chuk, V. V. and A. A. Skoromets (2007). "Therapeutic exercise in functional recovery of poststroke patients. [Russian]." *Voprosy kurortologii, fizioterapii, i lechebnoi fizicheskoi kultury* (4): 26-28. **no meet inclusion criteria. (Russian I.).**
252. Krebs, D. E., D. M. Scarborough, et al. (2007). "Functional vs. strength training in disabled elderly outpatients." *American Journal of Physical Medicine & Rehabilitation* **86**(2): 93-103. **Different modalities of training.**
253. Krentz, J. R. and J. P. Farthing "Neural and morphological changes in response to a 20-day intense eccentric training protocol." *European Journal of Applied Physiology* **110**(2): 333-340. **Single dose.; No outcome of Interest.**
254. Krieger, J. W. (2009). "Single versus multiple sets of resistance exercise: a meta-regression." *Journal of Strength & Conditioning Research* **23**(6): 1890-1901. **Review.**
255. Kubo, K., T. Ikebukuro, et al. "Effects of training on muscle and tendon in knee extensors and plantar flexors in vivo." *Journal of Applied Biomechanics* **26**(3): 316-323. **No dose-response relationship;**
256. Kutner, N. G., R. Zhang, et al. (2010) "Quality-of-life change associated with robotic-assisted therapy to improve hand motor function in patients with subacute stroke: a randomized clinical trial." *Physical Therapy*, 493-504. **No outcome of Interest.**
257. Lachman, M. E. and S. Agrigoroaei "Promoting functional health in midlife and old age: long-term protective effects of control beliefs, social support, and physical exercise." *PLoS ONE [Electronic Resource]* **5**(10): e13297. **No dose-response relationship investigated.;**
258. Lamas, G. A., J. D. Knight, et al. (2007). "Impact of rate-modulated pacing on quality of life and exercise capacity--evidence from the Advanced Elements of Pacing Randomized Controlled Trial (ADEPT)." *Heart Rhythm* **4**(9): 1125-1132. **Different modalities of training.**
259. Lamotte, M., F. Fleury, et al. (2010) "Acute cardiovascular response to resistance training during cardiac rehabilitation: effect of repetition speed and rest periods." *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*. **No outcome of Interest.**

260. Landi, F., A. Russo, et al. (2007). "Physical activity and risk of cognitive impairment among older persons living in the community." *Aging-Clinical & Experimental Research* **19**(5): 410-416. **No outcome of Interest.**
261. Lange, A. K., B. Vanwanseele, et al. (2009). "Resistive Exercise for Arthritic Cartilage Health (REACH): a randomized double-blind, sham-exercise controlled trial." *BMC Geriatrics* **9**: 1. **No population of interest. Single dose.;**
262. Langhammer, B., J. K. Stanghelle, et al. (2009) "An evaluation of two different exercise regimes during the first year following stroke: a randomised controlled trial." *Physiotherapy theory and practice*, 55-68. **Different modalities of training.**
263. Larsen, M. K., A. Samani, et al. (2009) "Short-term effects of implemented high intensity shoulder elevation during computer work." *BMC Musculoskeletal Disorders*, 101. **No dose-responce relationship investigated.**
264. Lee, C. K. (2007). "[Effects of an inpatient pulmonary rehabilitation program on dyspnea, exercise capacity, and health related quality of life for patients with chronic lung disease]." *Daehan Ganho Haghoeji* **37**(3): 343-352. **No outcome of Interest.**
265. Lee, H. J., H. J. Park, et al. (2009). "Tai Chi Qigong for the quality of life of patients with knee osteoarthritis: A pilot, randomized, waiting list controlled trial." *Clinical Rehabilitation* **23** (6): 504-511. **Single dose.**
266. Lee, M.-J., S. L. Kilbreath, et al. "Effect of progressive resistance training on muscle performance after chronic stroke." *Medicine & Science in Sports & Exercise* **42**(1): 23-34. **Different modalities of training.**
267. Lee, M.-J., S. L. Kilbreath, et al. (2008). "Comparison of effect of aerobic cycle training and progressive resistance training on walking ability after stroke: a randomized sham exercise-controlled study." *Journal of the American Geriatrics Society* **56**(6): 976-985. **Different modalities of training.(Same protocol.)**
268. Lee, M. J., S. L. Kilbreath, et al. (2010) "Effect of progressive resistance training on muscle performance after chronic stroke." *Medicine and science in sports and exercise.* **Duplicate.**
269. Lee, M. J., S. L. Kilbreath, et al. (2008) "Comparison of effect of aerobic cycle training and progressive resistance training on walking ability after stroke: a randomized sham exercise-controlled study." *Journal of the American Geriatrics Society*, 976-985. **Duplicate.**
270. Lemmey, A. B., S. M. Marcora, et al. (2009) "Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial." *Arthritis and rheumatism*, 1726-1734. **Different modalities of training.**
271. Lennon, O., A. Carey, et al. (2008). "A pilot randomized controlled trial to evaluate the benefit of the cardiac rehabilitation paradigm for the non-acute ischaemic stroke population." *Clinical Rehabilitation* **22**(2): 125-133. **Single dose.**
272. Leung, R. W. M., J. A. Alison, et al. "Ground walk training improves functional exercise capacity more than cycle training in people with chronic obstructive pulmonary disease (COPD): a randomised trial." *Journal of Physiotherapy* **56**(2): 105-112. **Different modalities of training.**
273. Levinger, I., C. Goodman, et al. (2007) "The effect of resistance training on functional capacity and quality of life in individuals with high and low numbers of metabolic risk factors." *Diabetes Care*, 2205-2210. **No population of interest. Single dose.**
274. Lexell, J. and U. B. Flansbjer (2008). "Muscle strength training, gait performance and physiotherapy after stroke." *Minerva Medica* **99**(4): 353-368. **Review.**
275. Li, W.-C., Y.-C. Chen, et al. (2009). "Effects of exercise programmes on quality of life in osteoporotic and osteopenic postmenopausal women: a systematic review and meta-analysis." *Clinical Rehabilitation* **23**(10): 888-896. **Review.**
276. Li, Z. G. (2009) "[Effect of an exercise prescription of intensive strength training on physical function in aged males]." *Journal of Clinical Rehabilitative Tissue Engineering Research*, 3966-3971. **Single dose.;**
277. Limke, J. C., J. Rainville, et al. (2008) "Randomized trial comparing the effects of one set vs two sets of resistance exercises for outpatients with chronic low back pain and leg pain." *European journal of physical and rehabilitation medicine*, 399-405. **No population of interest.**
278. Lin, D. H., C. H. Lin, et al. (2009) "Efficacy of 2 non-weight-bearing interventions, proprioception training versus strength training, for patients with knee osteoarthritis: a

- randomized clinical trial." *The Journal of orthopaedic and sports physical therapy*, 450-457. **Different modalities of training.**
279. Lin, K.-c., C.-y. Wu, et al. (2009). "Constraint-induced therapy versus dose-matched control intervention to improve motor ability, basic/extended daily functions, and quality of life in stroke." *Neurorehabilitation & Neural Repair* **23**(2): 160-165. **Different modalities of training.**
280. Lin, K. C., C. Y. Wu, et al. (2008) "A randomized controlled trial of constraint-induced movement therapy after stroke." *Acta neurochirurgica. Supplement*, 61-64. **Different modalities of training.**
281. Littbrand, H., L. Lundin-Olsson, et al. (2009). "The effect of a high-intensity functional exercise program on activities of daily living: a randomized controlled trial in residential care facilities." *Journal of the American Geriatrics Society* **57**(10): 1741-1749. **Single dose.**
282. Liu, C.-J. and N. Latham "Adverse events reported in progressive resistance strength training trials in older adults: 2 sides of a coin." *Archives of Physical Medicine & Rehabilitation* **91**(9): 1471-1473. **Review.**
283. Lo, A. C., P. Guarino, et al. (2009) "Multicenter randomized trial of robot-assisted rehabilitation for chronic stroke: methods and entry characteristics for VA ROBOTICS." *Neurorehabilitation and neural repair*, 775-783. **Different modalities of training.**
284. Lo, A. C., P. D. Guarino, et al. (2010) "Robot-assisted therapy for long-term upper-limb impairment after stroke." *The New England journal of medicine*, 1772-1783. **Different modalities of training.** (Same protocol.)
285. Lobo, A., P. Santos, et al. (2008). "Relationship between intensity of physical activity and health-related quality of life in Portuguese institutionalized elderly." *Geriatrics & gerontology international* **8**(4): 284-290. **No outcome of Interest.**
286. Lovell, D. I., R. Cuneo, et al. (2010) "The effect of strength training and short-term detraining on maximum force and the rate of force development of older men." *European Journal of Applied Physiology*, 429-435. **Single dose.**
287. Lustosa, L. P., F. M. Coelho, et al. "The effects of a muscle resistance program on the functional capacity, knee extensor muscle strength and plasma levels of IL-6 and TNF-alpha in pre-frail elderly women: a randomized crossover clinical trial--a study protocol." *Trials [Electronic Resource]* **11**: 82. **Single dose.; No outcome of Interest.**
288. Lynch, B. M., E. Cerin, et al. (2007). "Associations of leisure-time physical activity with quality of life in a large, population-based sample of colorectal cancer survivors." *Cancer Causes & Control* **18**(7): 735-742. **No outcome of Interest.**
289. Machado, G. P. M., M. A. M. Gignac, et al. (2008). "Participation restrictions among older adults with osteoarthritis: a mediated model of physical symptoms, activity limitations, and depression." *Arthritis & Rheumatism* **59**(1): 129-135. **No dose-response relationship investigated.**
290. Madarame, H., M. Neya, et al. (2008) "Cross-transfer effects of resistance training with blood flow restriction." *Medicine and science in sports and exercise*, 258-263. **No dose-response relationship investigated.**
291. Madariaga, V. B., J. B. Iturri, et al. (2007) "[Comparison of 2 methods for inspiratory muscle training in patients with chronic obstructive pulmonary disease]." *Archivos de bronconeumología*, 431-438. **Different modalities of training.**
292. Maeland, S., R. Jahnsen, et al. (2009). "No effect on gait function of progressive resistance exercise in adults with cerebral palsy A single-blind randomized controlled trial." *Advances in Physiotherapy* **11** (4): 227-233. **No population of interest. Single dose.**
293. Maior, A. S., T. Menuci, et al. (2008). "Variation of the training overload in the behavior of the muscular force and subjective perception of pain in sedentary female. [Portuguese]." *Medicina* **41** (2): 168-176. **No outcome of Interest.**
294. Maksymowych, W. P., K. L. Gooch, et al. (2010) "Impact of age, sex, physical function, health-related quality of life, and treatment with adalimumab on work status and work productivity of patients with ankylosing spondylitis." *The Journal of rheumatology*. **No population of interest.**
295. Mandic, S., W. Tymchak, et al. (2009) "Effects of aerobic or aerobic and resistance training on cardiorespiratory and skeletal muscle function in heart failure: a randomized controlled pilot trial." *Clinical Rehabilitation*, 207-216. **Different modalities of training.**

296. Manini, T., M. Marko, et al. (2007). "Efficacy of resistance and task-specific exercise in older adults who modify tasks of everyday life." *Journals of Gerontology Series A-Biological Sciences & Medical Sciences* **62**(6): 616-623. **Different modalities of training.**
297. Marangoni, A. H. (2010) "Effects of intermittent stretching exercises at work on musculoskeletal pain associated with the use of a personal computer and the influence of media on outcomes." *Work (Reading, Mass.)*, 27-37. **no meet inclusion criteria.**
298. Marcora, S. M. and W. Staiano (2010) "The limit to exercise tolerance in humans: mind over muscle?" *European Journal of Applied Physiology*, 763-770. **No outcome of Interest.**
299. Marini, M., E. Sarchielli, et al. (2008). "Role of adapted physical activity to prevent the adverse effects of the sarcopenia. A pilot study." *Italian Journal of Anatomy & Embryology* **113**(4): 217-225. **No outcome of Interest.**
300. Markovic, G., I. Jukic, et al. (2007) "Effects of sprint and plyometric training on muscle function and athletic performance." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 543-549. **Different modalities of training.**
301. Marquesste, T., B. Giannesini, et al. (2008). "Comparative MRI analysis of T2 changes associated with single and repeated bouts of downhill running leading to eccentric-induced muscle damage." *Journal of Applied Physiology* **105**(1): 299-307. **No dose-response relationship investigated.**
302. Martin Ginis, K. A., K. P. Arbour-Nicitopoulos, et al. "Leisure Time Physical Activity in a Population-Based Sample of People With Spinal Cord Injury Part II: Activity Types, Intensities, and Durations." *Archives of Physical Medicine & Rehabilitation* **91**(5): 729-733. **No population of interest.**
303. Marzolini, S., B. Jensen, et al. (2009) "Feasibility and effects of a group-based resistance and aerobic exercise program for individuals with **severe schizophrenia**: a multidisciplinary approach." *Mental Health and Physical Activity*, 29-36. **No population of interest. No dose-response relationship investigated.**
304. Marzolini, S., P. I. Oh, et al. (2008). "Aerobic and resistance training in coronary disease: single versus multiple sets." *Medicine & Science in Sports & Exercise* **40**(9): 1557-1564. **Duplicate.**
305. Maslow, A. a. L., A. E. Price, et al. "Fitness and Adiposity as Predictors of Functional Limitation in Adults." *Journal of Physical Activity & Health* **8**(1): 18-26. **No dose-response relationship investigated.**
306. May, A. M., E. Van Weert, et al. (2008) "Improved physical fitness of cancer survivors: a randomised controlled trial comparing physical training with physical and cognitive-behavioural training." *Acta oncologica (Stockholm, Sweden)*, 825-834. **No population of interest.**
307. McAuley, E., S. E. Doerksen, et al. (2008). "Pathways from physical activity to quality of life in older women." *Annals of Behavioral Medicine* **36**(1): 13-20. **No outcome of Interest.**
308. McAuley, E., K. S. Morris, et al. (2007). "Effects of change in physical activity on physical function limitations in older women: mediating roles of physical function performance and self-efficacy." *Journal of the American Geriatrics Society* **55**(12): 1967-1973. **No dose-response relationship investigated.**
309. McBride, J. M., G. O. McCaulley, et al. (2009) "Comparison of methods to quantify volume during resistance exercise." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 106-110. **No dose-response relationship investigated.**
310. McCann, M. R. and S. P. Flanagan (2010) "The effects of exercise selection and rest interval on postactivation potentiation of vertical jump performance." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 1285-1291. **No outcome of Interest.**
311. McCaulley, G. O., J. M. McBride, et al. (2009) "Acute hormonal and neuromuscular responses to hypertrophy, strength and power type resistance exercise." *European Journal of Applied Physiology*, 695-704. **No outcome of Interest.**
312. McCrate, M. E. and B. K. Kaspar (2008). "Physical activity and neuroprotection in amyotrophic lateral sclerosis." *NeuroMolecular Medicine* **10**(2): 108-117. **No dose-response relationship investigated.**

313. McKay, W., P. Chilibeck, et al. (2007). "Resting mechanomyography before and after resistance exercise." *European Journal of Applied Physiology* **102**(1): 107-117. **No dose-response relationship investigated.**
314. McLeod, H. J., S. Jaques, et al. (2009). "Base rates of physical activity in Australians with schizophrenia." *Psychiatric Rehabilitation Journal* **32**(4): 269-275. **No dose-response relationship investigated.**
315. McNamara, J. M. and D. J. Stearne (2010) "Flexible nonlinear **periodization** in a beginner college weight training class." *Journal of strength and conditioning research / National Strength & Conditioning Association*. **No dose-response relationship investigated.**
316. Meeusen, R. "Diagnosing overtraining in athletes using the two-bout exercise protocol." *British Journal of Sports Medicine* **44**(9): 642-648. **Single dose;**
317. Mehrholz, J., C. Werner, et al. (2008). "Immediate and long-term functional impact of repetitive locomotor training as an adjunct to conventional physiotherapy for non-ambulatory patients after stroke." *Disability & Rehabilitation* **30**(11): 830-836. **Different modalities of training.**
318. Mel-h Wa, J., T. Pei-Fang, et al. (2008). "Efficacy of a Target-Matching Foot-Stepping Exercise on Proprioception and Function in Patients With Knee Osteoarthritis." *Journal of Orthopaedic & Sports Physical Therapy* **38**(1): 19-25. **No dose-response relationship investigated.**
319. Mi-Joung, L., S. L. Kilbreath, et al. "Effect of Progressive Resistance Training on Muscle Performance after Chronic Stroke." *Medicine & Science in Sports & Exercise* **42**(1): 23-34. **Duplicate (Lee).**
320. Mian, O. S., V. Baltzopoulos, et al. (2007). "The Impact of Physical Training on Locomotor Function in Older People." *Sports Medicine* **37**(8): 683-701. **Review.**
321. Michael, K. and R. F. Macko (2007). "Ambulatory activity intensity profiles, fitness, and fatigue in chronic stroke." *Topics in Stroke Rehabilitation* **14**(2): 5-12. **No dose-response relationship.**
322. Middleton, N., R. Shave, et al. (2007). "Impact of Repeated Prolonged Exercise Bouts on Cardiac Function and Biomarkers." *Medicine & Science in Sports & Exercise* **39**(1): 83-90. **No outcome of Interest.**
323. Mileva, K. N., M. Kadr, et al. (2010) "Acute effects of Flexi-bar vs. Sham-bar exercise on muscle electromyography activity and performance." *Journal of strength and conditioning research / National Strength & Conditioning Association*. **Different modalities of training.**
324. Milne, H. M., K. E. Wallman, et al. (2008) "Effects of a combined aerobic and resistance exercise program in breast cancer survivors: a randomized controlled trial." *Breast cancer research and treatment*, 279-288. **Different modalities of training; No population of interest.**
325. Milot, M. H., L. Marchal-Crespo, et al. (2010) "Comparison of error-amplification and haptic-guidance training techniques for learning of a timing-based motor task by healthy individuals." *Experimental brain research. Experimentelle Hirnforschung. Expérimentation cérébrale*. **no meet inclusion criteria.**
326. Min, M., C. Xin, et al. (2008) "Stage-oriented comprehensive acupuncture treatment plus rehabilitation training for apoplectic hemiplegia." *Journal of Traditional Chinese Medicine*, 90-93. **no meet inclusion criteria.**
327. Minigalin, A. D., A. R. Shumakov, et al. "Acute and delayed biochemical and physiological effects of exhaustive weightlifting exercise." *Human Physiology* **37**(2): 200-205. **No outcome of Interest.**
328. Minshull, C., N. Gleeson, et al. (2007). "Effects of acute fatigue on the volitional and magnetically-evoked electromechanical delay of the knee flexors in males and females." *European Journal of Applied Physiology* **100**(4): 469-478. **No dose-response relationship.**
329. Miyakoshi, N. (2008). "[Therapeutic exercise]." *Clinical Calcium* **18**(11): 1611-1615. **No dose-response relationship**
330. Morgan, A. L., D. A. Tobar, et al. (2010) "Walking toward a new me: the impact of prescribed walking 10,000 steps/day on physical and psychological well-being." *Journal of physical activity & health*, 299-307. **No dose-response relationship investigated.**
331. Monga, U., S. L. Garber, et al. (2007). "Exercise Prevents Fatigue and Improves Quality of Life in Prostate Cancer Patients Undergoing Radiotherapy." *Archives of Physical Medicine & Rehabilitation* **88**(11): 1416-1422. **Single dose.**

332. Morris, M. G., H. Dawes, et al. "Muscle contractile characteristics: relationship to high-intensity exercise." *European Journal of Applied Physiology* **110**(2): 295-300. **No outcome of Interest.**
333. Motl, R. W., D. Dlugonski, et al. "Internet intervention for increasing physical activity in persons with multiple sclerosis." *Multiple Sclerosis* **17** (1): 116-128. **Single dose.**
334. Motl, R. W. and E. McAuley (2009). "Longitudinal analysis of physical activity and symptoms as predictors of change in functional limitations and disability in multiple sclerosis." *Rehabilitation Psychology* **54**(2): 204-210. **No outcome of Interest.**
335. Motl, R. W., E. McAuley, et al. (2008). "Does the relationship between physical activity and quality of life differ based on generic versus disease-targeted instruments?" *Annals of Behavioral Medicine* **36**(1): 93-99. **No outcome of Interest.**
336. Motl, R. W. and E. M. Snook (2008). "Physical activity, self-efficacy, and quality of life in multiple sclerosis." *Annals of Behavioral Medicine* **35**(1): 111-115. **No outcome of Interest. No dose-response relationship investigated.**
337. Mueller, M., F. A. Breil, et al. (2009). "Different response to eccentric and concentric training in older men and women." *European Journal of Applied Physiology* **107** (2): 145-153. **No dose-response relationship investigated.**
338. Mueser, K. T., S. I. Pratt, et al. (2010) "Randomized trial of social rehabilitation and integrated health care for older people with severe mental illness." *Journal of consulting and clinical psychology*, 561-573. **No dose-response relationship investigated.**
339. Muller, M. D., E. J. Ryan, et al. "The influence of interval versus continuous exercise on thermoregulation, torso hemodynamics, and finger dexterity in the cold." *European Journal of Applied Physiology* **109**(5): 857-867. **No outcome of Interest.**
340. Nakamura, Y., K. Tanaka, et al. (2008). "Effects of aerobic training and recreational activities in patients with chronic obstructive pulmonary disease." *International Journal of Rehabilitation Research* **31**(4): 275-283. **Different modalities of training;**
341. Nakao, H., T. Yoshikawa, et al. (2007). "Thresholds of physical activities necessary for living a self-supporting life in elderly women." *Osaka City Medical Journal* **53**(2): 53-61. **No outcome of Interest.**
342. Nash, M. S., I. van de Ven, et al. (2007). "Effects of circuit resistance training on fitness attributes and upper-extremity pain in middle-aged men with paraplegia." *Archives of Physical Medicine & Rehabilitation* **88**(1): 70-75. **No population of interest.**
343. Nederhof, E., K. Lemmink, et al. (2007). "The Effect of High Load Training on Psychomotor Speed." *International Journal of Sports Medicine* **28**(7): 595-601. **No outcome of Interest.**
344. Newton, R. U., D. R. Taaffe, et al. (2009). "A phase III clinical trial of exercise modalities on treatment side-effects in men receiving therapy for prostate cancer." *BMC Cancer* **9**: 210. **Different modalities of training;**
345. Nilsson, B. B., B. Hellesnes, et al. (2008). "Group-based Aerobic Interval Training in Patients With Chronic Heart Failure: Norwegian Ullevaal Model." *Physical Therapy* **88**(4): 523-535. **No dose-response relationship investigated.**
346. Nilsson, B. B., A. Westheim, et al. (2008). "Long-term effects of a group-based high-intensity aerobic interval-training program in patients with chronic heart failure." *American Journal of Cardiology* **102**(9): 1220-1224. **Different modalities of training.**
347. Nishijima, H., K. Satake, et al. (2007). "Effects of Exercise in Overweight Japanese with Multiple Cardiovascular Risk Factors." *Medicine & Science in Sports & Exercise* **39**(6): 926-933. **Single dose.;**
348. Nonoyama, M. L., D. Brooks, et al. "Exercise program to enhance physical performance and quality of life of older hemodialysis patients: a feasibility study." *International Urology & Nephrology* **42**(4): 1125-1130. **Single dose.;**
349. Nuzzo, J. L., J. M. McBride, et al. (2010) "Testing of the maximal dynamic output hypothesis in trained and untrained subjects." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 1269-1276. **No dose-response relationship investigated.**
350. Nyquist-Battie, C., G. F. Fletcher, et al. (2007). "Upper-extremity exercise training in heart failure." *Journal of Cardiopulmonary Rehabilitation & Prevention* **27**(1): 42-45. **Single dose.**
351. O'Shea, S. D., N. F. Taylor, et al. (2007) "A predominantly home-based progressive resistance exercise program increases knee extensor strength in the short-term in people with

- chronic obstructive pulmonary disease: a randomised controlled trial." *The Australian journal of physiotherapy*, 229-237. **Single dose.**
352. Oates, B. R., E. I. Glover, et al. (2010) "Low-volume resistance exercise attenuates the decline in strength and muscle mass associated with immobilization." *Muscle & nerve*. **No dose-response relationship investigated.**
353. Obert, P., S. Nottin, et al. (2009). "Two months of endurance training does not alter diastolic function evaluated by TDI in 9-11-year-old boys and girls." *British Journal of Sports Medicine* **47**(2): 132-135. **No dose-response relationship investigated.**
354. Ohta, M., T. Mizoue, et al. (2007). "Effect of the physical activities in leisure time and commuting to work on mental health." *Journal of Occupational Health* **49**(1): 46-52. **No outcome of Interest.**
355. Oliveira, A. S. and M. Gonçalves (2008) "Neuromuscular recovery of the biceps brachii muscle after resistance exercise." *Research in sports medicine (Print)*, 244-256. **No outcome of Interest. No dose-response relationship investigated.**
356. Oliveira, A. S., C. C. Greco, et al. (2009). "Physiological and neuromuscular profile during a body pump session: acute responses during a high-resistance training session." *Journal of Strength & Conditioning Research* **23**(2): 579-586. **No outcome of Interest. No dose-response relationship investigated.**
357. Oliveira, N. C., L. M. dos Santos Sabbag, et al. (2009). "Aerobic Exercise is Safe and Effective in Systemic Sclerosis." *International Journal of Sports Medicine* **30**(10): 728-732. **Single dose.**
358. Osteras, H., T. A. Torstensen, et al. (2009). "Dose-response effects of graded therapeutic exercises in patients with long-standing subacromial pain." *Advances in Physiotherapy* **11** (4): 199-209. **No population of interest.**
359. Osteras H, T. T. A. (2010) "The dose-response effect of medical exercise therapy on impairment in patients with unilateral longstanding subacromial pain." *The open orthopaedics journal*, 1-6. **No population of interest.**
360. Otterman, N. M., C. H. M. Van Schie, et al. "An exercise programme for patients with diabetic complications: A study on feasibility and preliminary effectiveness." *Diabetic Medicine* **28** (2): 212-217. **No dose-response relationship investigated.**
361. Ouzouni, S., E. Kouidi, et al. (2009). "Effects of intradialytic exercise training on health-related quality of life indices in haemodialysis patients." *Clinical Rehabilitation* **23**(1): 53-63. **No population of interest.**
362. Paalanne, N. P., R. I. Korpelainen, et al. (2009). "Muscular fitness in relation to physical activity and television viewing among young adults." *Medicine & Science in Sports & Exercise* **41**(11): 1997-2002. **No outcome of Interest.**
363. Page, S. J., P. Levine, et al. (2008). "Modified constraint-induced therapy in chronic stroke: results of a single-blinded randomized controlled trial." *Physical Therapy* **88**(3): 333-340. **Different modalities of training. same dose**
364. Palmer, T. G. and T. L. Uhl "Interday Reliability of Peak Muscular Power Outputs on an Isotonic Dynamometer and Assessment of Active Trunk Control Using the Chop and Lift Tests." *Journal of Athletic Training* **46**(2): 150-159. **no met criteria for inclusion.**
365. Pansarasa, O., C. Rinaldi, et al. (2009). "Resistance training of long duration modulates force and unloaded shortening velocity of single muscle fibres of young women." *Journal of Electromyography & Kinesiology* **19**(5): e290-e300. **No outcome of Interest.**
366. Paraschiv-Ionescu, A., E. Buchser, et al. (2008). "Nonlinear analysis of human physical activity patterns in health and disease." *Physical Review. E Statistical, Nonlinear, & Soft Matter Physics*. **77**(2 Pt 1): 021913. **Review.**
367. Parcell, A. C., M. T. Woolstenhulme, et al. (2009). "Structural protein alterations to resistance and endurance cycling exercise training." *Journal of Strength & Conditioning Research* **23**(2): 359-365. **no met criteria for inclusion**
368. Park, H., S. Park, et al. "Yearlong physical activity and sarcopenia in older adults: the Nakanajo Study." *European Journal of Applied Physiology* **109**(5): 953-961. **no met criteria for inclusion.**
369. Parkka, J., M. Ermes, et al. (2007). "Estimating intensity of physical activity: a comparison of wearable accelerometer and gyro sensors and 3 sensor locations." *Conference Proceedings: ... Annual International Conference of the IEEE Engineering in Medicine & Biology Society* **2007**: 1511-1514. **No dose-response relationship investigated.**

370. Parr, J. J., J. F. Yarrow, et al. (2009). "Symptomatic and functional responses to concentric-eccentric isokinetic versus eccentric-only isotonic exercise." *Journal of Athletic Training* **44**(5): 462-468. **Different modalities of training.**
371. Paterson, D. H., G. R. Jones, et al. (2007). "Ageing and physical activity: evidence to develop exercise recommendations for older adults." *Applied Physiology, Nutrition & Metabolism* **32**: S69-S108. **No dose-response relationship investigated.**
372. Peate, W. F., G. Bates, et al. (2007) "Core strength: a new model for injury prediction and prevention." *J Occup Med Toxicol.* **No outcome of Interest.**
373. Pedersen, M. T., M. B. Randers, et al. (2009) "Recreational soccer can improve the reflex response to sudden trunk loading among untrained women." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 2621-2626. **No outcome of Interest.**
374. Pereira, M. I. R., P. S. C. Gomes, et al. (2009). "Acute effects of sustained isometric knee extension on cerebral and muscle oxygenation responses." *Clinical Physiology & Functional Imaging* **29**(4): 300-308. **No outcome of Interest.**
375. Peri, K., N. Kerse, et al. (2008) "Does functionally based activity make a difference to health status and mobility? A randomised controlled trial in residential care facilities (The Promoting Independent Living Study; PILS)." *Age and ageing*, 57-63. **No dose-response relationship investigated.**
376. Pensch, L. N., C. Ugrinowitsch, et al. (2009). "Strength training improves fall-related gait kinematics in the elderly: a randomized controlled trial." *Clinical Biomechanics* **24**(10): 819-825. **Single dose.**
377. Peurala, S. H., O. Airaksinen, et al. (2007). "Effects of intensive gait-oriented physiotherapy during early acute phase of stroke." *Journal of Rehabilitation Research & Development* **44**(5): 637-648. **Single dose.**
378. Pilat, E., R. Mlynarski, et al. (2008) "Influence of DDD rate response pacing with integrated double sensors on physical efficiency and quality of life." *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*, 1189-1194. **no met criteria for inclusion.**
379. Pilutti, L. A., D. A. Lelli, et al. "Effects of 12 weeks of supported treadmill training on functional ability and quality of life in progressive multiple sclerosis: a pilot study." *Archives of Physical Medicine & Rehabilitation* **92**(1): 31-36. **Single dose.**
380. Pines, A. and E. M. Berry (2007). "Exercise in the menopause - an update." *Climacteric* **10 Suppl 2**: 42-46. **Review.**
381. Piva, S. R., G. K. Fitzgerald, et al. (2009). "Associates of physical function and pain in patients with patellofemoral pain syndrome." *Archives of Physical Medicine & Rehabilitation* **90**(2): 285-295. **No dose-response relationship investigated.**
382. Plasqui, G. (2008). "The role of physical activity in rheumatoid arthritis." *Physiology & Behavior* **94**(2): 270-275. **Review.**
383. Platz, T., S. van Kaick, et al. (2009). "Best conventional therapy versus modular impairment-oriented training for arm paresis after stroke: a single-blind, multicenter randomized controlled trial." *Neurorehabilitation & Neural Repair* **23**(7): 706-716. **Different modalities of training.**
384. Popadic Gacesa, J. Z., D. B. Kozic, et al. (2009). "Changes of functional status and volume of triceps brachii measured by magnetic resonance imaging after maximal resistance training." *Journal of Magnetic Resonance Imaging* **29**(3): 671-676. **Single dose.**
385. Portegijs, E., M. Kallinen, et al. (2008). "Effects of resistance training on lower-extremity impairments in older people with hip fracture." *Archives of Physical Medicine & Rehabilitation* **89**(9): 1667-1674. **Single dose.**
386. Prescott, E., R. Hjardem-Hansen, et al. (2009) "Effects of a 14-month low-cost maintenance training program in patients with chronic systolic heart failure: a randomized study." *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*, 430-437. **Single dose.**
387. Protas, E. J. and S. Tissier (2009). "Strength and speed training for elders with mobility disability." *Journal of Aging & Physical Activity* **17**(3): 257-271. **Single dose.**

388. Puhan, M. A., H. J. Schunemann, et al. (2008). "COPD patients' ability to follow exercise influences short-term outcomes of rehabilitation." *European Respiratory Journal* **31**(2): 304-310. **No dose-response relationship investigated.**
389. Quantrill, S. J., R. White, et al. (2007) "Short burst oxygen therapy after activities of daily living in the home in chronic obstructive pulmonary disease." *Thorax*, 702-705. **No dose-response relationship investigated.**
390. Queiroz, A. C. C., H. Kanegusuku, et al. "Effects of resistance training on blood pressure in the elderly. [Portuguese, English]." *Arquivos Brasileiros de Cardiologia* **95** (1): 135-140. **No outcome of Interest. No dose-response relationship investigated.**
391. Racinais, S. "Different effects of heat exposure upon exercise performance in the morning and afternoon." *Scandinavian Journal of Medicine & Science in Sports* **20 Suppl 3**: 80-89. **No outcome of Interest.**
392. Radziszewski, K. R. (2007). "Physical exercise in treatment of patients with lumbar discopathy." *Ortopedia Traumatologia Rehabilitacja* **9**(1): 98-106. **No population of interest.**
393. Raggi, A. and M. Leonardi (2009). "Assessing activity limitations in patients with neuromuscular diseases: is the ACTIVLIM questionnaire linked to ICF and ICF-CY?" *International Journal of Rehabilitation Research* **32**(2): 148-153. **No dose-response relationship investigated.**
394. Rahimi, R., S. S. Boroujerd, et al. (2009). "The effects of different rest intervals between sets on the training volume of female athletes." *International Journal of Fitness* **5**(1): 61-67. **No outcome of Interest. (Athlete Squat Volume).**
395. Rainoldi, A., M. Gazzoni, et al. (2008). "Mechanical and EMG responses of the vastus lateralis and changes in biochemical variables to isokinetic exercise in endurance and power athletes." *Journal of Sports Sciences* **26**(3): 311-319. **No outcome of Interest.**
396. Raj, I. S., S. R. Bird, et al. "Aging and the force-velocity relationship of muscles." *Experimental Gerontology* **45**(2): 81-90. **No outcome of Interest.**
397. Ram Felix, S. F., R. Wellington Sheree, et al. (2003) "Inspiratory muscle training for asthma." *Cochrane Database of Systematic Review.s*. **Reviews.**
398. Raso, V., G. Benard, et al. (2007). "Effect of resistance training on immunological parameters of healthy elderly women." *Medicine and Science in Sports and Exercise* **39** (12): 2152-2159. **No outcome of Interest.**
399. Ratel, S. "High-intensity and resistance training and elite young athletes." *Medicine & Sport Science* **56**: 84-96. **No population of interest.**
400. Reyes, G. F. and D. Dolny (2009). "Acute effects of various weighted bat warm-up protocols on bat velocity." *Journal of Strength & Conditioning Research* **23**(7): 2114-2118. **No outcome of Interest.**
401. Rhea, M. R., J. G. Kenn, et al. (2009) "Alterations in speed of squat movement and the use of accommodated resistance among college athletes training for power." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 2645-2650. **No outcome of Interest.**
402. Riedl, I., M. Yoshioka, et al. "Regulation of skeletal muscle transcriptome in elderly men after 6weeks of endurance training at lactate threshold intensity." *Experimental Gerontology* **45** (11): 896-903. **No dose-response relationship investigated.**
403. Rinne, M., M. Pasanen, et al. "Is generic physical activity or specific exercise associated with motor abilities?" *Medicine & Science in Sports & Exercise* **42**(9): 1760-1768. **No outcome of Interest.**
404. Rinne, M. B., S. I. Miilunpalo, et al. (2007). "Evaluation of required motor abilities in commonly practiced exercise modes and potential training effects among adults." *Journal of Physical Activity & Health* **4**(2): 203-214. **No dose-response relationship investigated.**
405. Ritti-Dias, R. M., N. Wolosker, et al. (2010) "Strength training increases walking tolerance in intermittent claudication patients: randomized trial." *Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter*, 89-95. **No dose-response relationship investigated.**
406. Robbins, D. W., T. L. Goodale, et al. (2010) "The effects of load and training pattern on acute neuromuscular responses in the upper body." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 2996-3007. **No outcome of Interest.**

407. Robbins, D. W., W. B. Young, et al. (2009) "Effects of agonist-antagonist complex resistance training on upper body strength and power development." *Journal of Sports Sciences*, 1617-1625. **No dose-response relationship investigated.**
408. Robbins, D. W., W. B. Young, et al. (2010) "The effect of a complex agonist and antagonist resistance training protocol on volume load, power output, electromyographic responses, and efficiency." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 1782-1789. **No dose-response relationship investigated.**
409. Robbins, D. W., W. B. Young, et al. (2010) "Physical performance and electromyographic responses to an acute bout of paired set strength training versus traditional strength training." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 1237-1245. **No outcome of Interest.**
410. Ronnestad, B. R., N. H. Kvamme, et al. (2008) "Short-term effects of strength and plyometric training on sprint and jump performance in professional soccer players." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 773-780. **No outcome of Interest.**
411. Rosano, C., V. K. Venkatraman, et al. (2010) "Psychomotor speed and functional brain MRI 2 years after completing a physical activity treatment." *The journals of gerontology. Series A, Biological sciences and medical sciences*, 639-647. **No dose-response relationship investigated.**
412. Rosendahl, E., Y. Gustafson, et al. (2008). "A randomized controlled trial of fall prevention by a high-intensity functional exercise program for older people living in residential care facilities." *Aging-Clinical & Experimental Research* **20**(1): 67-75. **Different modalities of training.**
413. Rosie, J. and D. Taylor (2007) "Sit-to-stand as home exercise for mobility-limited adults over 80 years of age--GrandStand System may keep you standing?" *Age and ageing*, 555-562. **Different modalities of training.**
414. Ross, E., N. Middleton, et al. (2008). "Changes in respiratory muscle and lung function following marathon running in man." *Journal of Sports Sciences* **26**(12): 1295-1301. **No outcome of Interest.**
415. Ross, R. E., N. A. Ratamess, et al. (2009) "The effects of treadmill sprint training and resistance training on maximal running velocity and power." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 385-394. **No outcome of Interest.**
416. Russell, S. D., M. A. Saval, et al. (2009) "New York Heart Association functional class predicts exercise parameters in the current era." *American Heart Journal*, S24-30. **no met inclusion criteria.**
417. Sakamoto, A., T. Maruyama, et al. "ACUTE EFFECTS OF HIGH-INTENSITY DUMBBELL EXERCISE AFTER ISOKINETIC ECCENTRIC DAMAGE: INTERACTION BETWEEN ALTERED PAIN PERCEPTION AND FATIGUE ON STATIC AND DYNAMIC MUSCLE PERFORMANCE." *Journal of Strength & Conditioning Research (Lippincott Williams & Wilkins)* **24**(8): 2042-2049. **No dose-response relationship investigated.**
418. Sakamoto, A., T. Maruyama, et al. (2009) "Effects of exhaustive dumbbell exercise after isokinetic eccentric damage: recovery of static and dynamic muscle performance." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 2467-2476. **No dose-response relationship investigated.**
419. Sallinen, J., M. Fogelholm, et al. (2007). "Effects of strength training and reduced training on functional performance and metabolic health indicators in middle-aged men." *International Journal of Sports Medicine* **28** (10): 815-822. **Different modalities of training.**
420. Salminen, M., T. Vahlberg, et al. (2008) "Effects of risk-based multifactorial fall prevention program on maximal isometric muscle strength in community-dwelling aged: a randomized controlled trial." *Aging clinical and experimental research*, 487-493. **Single dose.**
421. Salvetti, X. M., J. A. O. Filho, et al. (2008). "How much do the benefits cost? Effects of a home-based training programme on cardiovascular fitness, quality of life, programme cost and adherence for patients with coronary disease." *Clinical Rehabilitation* **22**(10-11): 987-996. **No outcome of Interest.**
422. Samogin Lopes, F. A., E. M. Menegon, et al. "Is acute static stretching able to reduce the time to exhaustion at power output corresponding to maximal oxygen uptake?" *Journal of Strength & Conditioning Research* **24**(6): 1650-1656. **no met inclusion criteria.**

423. Santos, E. J. and M. A. Janeira (2008) "Effects of complex training on explosive strength in adolescent male basketball players." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 903-909. **No population of interest.**
424. Sanudo, C. B., O. D. Galiano, et al. "Autonomous nervous system response and quality of life on women with fibromyalgia after a long-term intervention with physical exercise." *Rehabilitacion* **44**(3): 244-249. **no met inclusion criteria.**
425. Sato, D., K. Kaneda, et al. (2007). "The water exercise improves health-related quality of life of frail elderly people at day service facility." *Quality of Life Research* **16**(10): 1577-1585. **Single dose.**
426. Sato, D., K. Kaneda, et al. (2009). "Comparison two-year effects of once-weekly and twice-weekly water exercise on health-related quality of life of community-dwelling frail elderly people at a day-service facility." *Disability & Rehabilitation* **31**(2): 84-93. **Duplicate.**
427. Sawatzky, R., T. Liu-Ambrose, et al. (2007). "Physical activity as a mediator of the impact of chronic conditions on quality of life in older adults." *Health & Quality of Life Outcomes* **5**: 68. **No outcome of Interest.**
428. Sawicki, G. S., D. E. Sellers, et al. (2009). "High treatment burden in adults with cystic fibrosis: Challenges to disease self-management." *Journal of Cystic Fibrosis* **8** (2): 91-96. **No population of interest.**
429. Sayers, S. P. (2007). "High-speed power training: a novel approach to resistance training in older men and women. A brief Review. and pilot study." *Journal of Strength & Conditioning Research* **21**(2): 518-526. **Review.**
430. Sayers, S. P. (2008). "High velocity power training in older adults." *Current Aging Science* **1**(1): 62-67. **Review.**
431. Schjerve, I. E., G. A. Tyldum, et al. (2008) "Both aerobic endurance and strength training programmes improve cardiovascular health in obese adults." *Clinical science (London, England : 1979)*, 283-293. **Different modalities of training.**
432. Schneider, J. K., J. H. Cook, Jr., et al. (2008). "Cognitive-behavioral therapy, exercise, and older adults' quality of life." *Western Journal of Nursing Research* **30**(6): 704-723. **No dose-response relationship investigated.**
433. Schneiders, A. G., S. J. Sullivan, et al. (2008). "The effect of exercise on motor performance tasks used in the neurological assessment of sports-related concussion." *British Journal of Sports Medicine* **42**(12): 1011-1013. **No dose-response relationship investigated.**
434. Schwartz, A. L. and K. Winters-Stone (2009). "Effects of a 12-month randomized controlled trial of aerobic or resistance exercise during and following cancer treatment in women." *Physician & Sportsmedicine* **37**(3): 62-67. **Different modalities of training.**
435. Schwenk, M., T. Zieschang, et al. "Dual-task performances can be improved in patients with dementia: a randomized controlled trial." *Neurology* **74**(24): 1961-1968. **No dose-response relationship investigated.**
436. Scianni, A., L. F. Teixeira-Salmela, et al. (2010) "Effect of strengthening exercise in addition to task-specific gait training after stroke: a randomised trial." *International journal of stroke : official journal of the International Stroke Society*. **Different modalities of training.**
437. Sedliak, M., T. Finni, et al. (2009) "Effect of time-of-day-specific strength training on muscular hypertrophy in men." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 2451-2457. **Same dose.**
438. Sedliak, M., T. Finni, et al. (2008) "Effect of time-of-day-specific strength training on maximum strength and EMG activity of the leg extensors in men." *Journal of Sports Sciences*, 1005-1014. **Same dose.**
439. Segura-Orti, E., E. Kouidi, et al. (2009). "Effect of resistance exercise during hemodialysis on physical function and quality of life: randomized controlled trial." *Clinical Nephrology* **71**(5): 527-537. **Single dose.**
440. Sherrington, C., P. I. Pamphlett, et al. (2008). "Group exercise can improve participants' mobility in an outpatient rehabilitation setting: a randomized controlled trial." *Clinical Rehabilitation* **22**(6): 493-502. **Single dose.**
441. Shields, N., N. F. Taylor, et al. (2008). "Effects of a community-based progressive resistance training program on muscle performance and physical function in adults with Down syndrome: a randomized controlled trial." *Archives of Physical Medicine & Rehabilitation* **89**(7): 1215-1220. **Single dose.**

442. Shields, N., N. F. Taylor, et al. "A study protocol of a randomised controlled trial to investigate if a community based strength training programme improves work task performance in young adults with Down syndrome." *BMC Pediatrics* **10**: 17. **No population of interest. (Protocol).**
443. Shirasawa, H., H. Kanehisa, et al. (2009). "Differences among lower leg muscles in long-term activity during ambulatory condition without any moderate to high intensity exercise." *Journal of Electromyography & Kinesiology* **19**(2): e50-56. **No outcome of Interest.**
444. Silva Kelson, N. G., A. Mizusaki Imoto, et al. (2010) "Balance training (proprioceptive training) for patients with rheumatoid arthritis." *Cochrane Database of Systematic Review.s.*
445. Silveira, J. M., A. C. Gastaldi, et al. "Inspiratory muscle training in quadriplegic patients." *Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia E Tisiologia* **36**(3): 313-319. **Review.s**
446. Sjösten, N. M., M. Salonoja, et al. (2007) "A multifactorial fall prevention programme in the community-dwelling aged: predictors of adherence." *European journal of public health*, 464-470. **No outcome of Interest.**
447. Smeets, R. J. E. M. (2009). "Do lumbar stabilising exercises reduce pain and disability in patients with recurrent low back pain?" *Australian Journal of Physiotherapy* **55**(2): 138-138. **Different modalities of training.**
448. Sotiropoulos, K., I. Smilios, et al. "Effects of warm-up on vertical jump performance and muscle electrical activity using half-squats at low and moderate intensity." *Journal of Sports Science & Medicine* **9**(2): 326-331. **No outcome of Interest.**
449. Spencer, M., B. Dawson, et al. (2008). "Performance and metabolism in repeated sprint exercise: effect of recovery intensity." *European Journal of Applied Physiology* **103**(5): 545-552. **No outcome of Interest.**
450. Spine CL (2008). The effects of strength and power training on functional abilities in older adults. ProQuest Dissertations and Theses, Retrieved from **No dose-response relationship investigated.** <http://search.proquest.com/docview/304502048?accountid=10637>.
451. Spinetti, J., B. F. A. F. de Salles, et al. (2010) "Influence of exercise order on maximum strength and muscle volume in nonlinear periodized resistance training." *Journal of strength and conditioning research / National Strength & Conditioning Association.* **Same dose diff order.**
452. Stamatakis, E., U. Ekelund, et al. (2007). "Temporal trends in physical activity in England: the Health Survey for England 1991 to 2004." *Preventive Medicine* **45**(6): 416-423. **No dose-response relationship investigated.**
453. Standage, M., S. J. Sebire, et al. (2008). "Does Exercise Motivation Predict Engagement in Objectively Assessed Bouts of Moderate-Intensity Exercise?: A Self-Determination Theory Perspective." *Journal of Sport & Exercise Psychology* **30**(4): 337-352. **No outcome of Interest.**
454. States Rebecca, A., E. Pappas, et al. (2009) "Overground physical therapy gait training for chronic stroke patients with mobility deficits." *Cochrane Database of Systematic Review.s.*
455. Steffen, K., G. Myklebust, et al. (2008) "Preventing injuries in female youth football—a cluster-randomized controlled trial." *Scandinavian Journal of Medicine & Science in Sports*, 605-614. **No dose-response relationship investigated.**
456. Stessman, J., R. Hammerman-Rozenberg, et al. (2009). "Physical activity, function, and longevity among the very old." *Archives of Internal Medicine* **169**(16): 1476-1483. **No dose-response relationship investigated.**
457. Stevenson, M. W., J. M. Warpeha, et al. (2010) "Acute effects of elastic bands during the free-weight barbell back squat exercise on velocity, power, and force production." *Journal of strength and conditioning research / National Strength & Conditioning Association.* **No outcome of Interest.**
458. Stewart, I. and R. Pickering (2007). "Effect of prolonged exercise on arterial oxygen saturation in athletes susceptible to exercise-induced hypoxemia." *Scandinavian Journal of Medicine and Science in Sports* **17**(4): 445-451. **No outcome of Interest.**
459. Stibrant Sunnerhagen, K. (2007). "Circuit training in community-living "younger" men after stroke." *Journal of Stroke & Cerebrovascular Diseases* **16**(3): 122-129. **Single dose.**
460. Strand, V., P. Mease, et al. (2009) "Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1

- randomized controlled trial." *Arthritis research & therapy*, R170. **No dose-response relationship investigated.**
461. Strasser, B., M. Keinrad, et al. (2009). "Efficacy of systematic endurance and resistance training on muscle strength and endurance performance in elderly adults--a randomized controlled trial." *Wiener Klinische Wochenschrift* **121**(23-24): 757-764. **Different modalities of training.**
462. Sullivan, D. H., P. K. Roberson, et al. (2007). "Effects of muscle strength training and megestrol acetate on strength, muscle mass, and function in frail older people." *Journal of the American Geriatrics Society* **55**(1): 20-28. **no met inclusion criteria.**
463. Sullivan, K. J., D. A. Brown, et al. (2007) "Effects of task-specific locomotor and strength training in adults who were ambulatory after stroke: results of the STEPS randomized clinical trial." *Physical Therapy*, 1580-1602. **Different modalities of training.**
464. Sumide, T., K. Sakuraba, et al. (2009). "Effect of resistance exercise training combined with relatively low vascular occlusion." *Journal of Science & Medicine in Sport* **12**(1): 107-112. **No dose-response relationship investigated.**
465. Sutbeyaz, S. T., F. Koseoglu, et al. (2010) "Respiratory muscle training improves cardiopulmonary function and exercise tolerance in subjects with subacute stroke: a randomized controlled trial." *Clinical Rehabilitation*, 240-250. **No dose-response relationship investigated.**
466. Suzuki, T. and S. Murase "Influence of outdoor activity and indoor activity on cognition decline: use of an infrared sensor to measure activity." *Telemedicine Journal & E-Health* **16**(6): 686-690. **Different modalities of training.**
467. Sverrisdottir, Y. B., L. M. Jansson, et al. "Muscle sympathetic nerve activity is related to a surrogate marker of endothelial function in healthy individuals." *PLoS ONE [Electronic Resource]* **5**(2): e9257. **no met inclusion criteria**
468. Swank, A. M., D. C. Funk, et al. "Effect of resistance training and aerobic conditioning on muscular strength and submaximal fitness for individuals with chronic heart failure: influence of age and gender." *Journal of Strength & Conditioning Research* **24**(5): 1298-1305. **No dose-response relationship investigated.**
469. Tabet, J.-Y., P. Meurin, et al. (2009). "Benefits of exercise training in chronic heart failure." *Archives of cardiovascular diseases* **102**(10): 721-730. **Review.**
470. Tajima, F., K. Nakamura, et al. (2007). "Benefits of sports activities in persons with spinal cord injuries." *Japanese Journal of Clinical Sports Medicine* **15**(3): 9-9. **no population of interest.**
471. Takahashi, T., Y. Arai, et al. (2008). "[Effects of resistance training on physical fitness, muscle strength, and natural killer cell activity in female university students]." *Nippon Eiseigaku Zasshi - Japanese Journal of Hygiene* **63**(3): 642-650. **Language Japanese**
472. Tal-Akabi, A., U. Steiger, et al. (2007) "Neuromuscular adaptation to early post-operative, high-intensity, short resistance training of non-operated lower extremity in elderly patients: a randomized controlled trial." *Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine*, 724-729. **no met inclusion criteria.**
473. Tamari, K. (2009). "Diabetes predicts decreased quality of life among community-dwelling seniors undertaking progressive resistance exercise: an observational study." *Australian Journal of Physiotherapy* **55**(3): 201-205. **no met inclusion criteria**
474. Teixeira, L. E. P. P., K. N. G. Silva, et al. "Progressive load training for the quadriceps muscle associated with proprioception exercises for the prevention of falls in postmenopausal women with osteoporosis: a randomized controlled trial." *Osteoporosis International* **21**(4): 589-596. **Single dose.**
475. Tentori, F., S. J. Elder, et al. "Physical exercise among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS): correlates and associated outcomes." *Nephrology Dialysis Transplantation* **25**(9): 3050-3062. **No dose-response relationship investigated.**
476. Tessier, S., A. Vuillemin, et al. (2007). "Association between leisure-time physical activity and health-related quality of life changes over time." *Preventive Medicine* **44** (3): 202-208. **Different modalities of training. & self-reported.**
477. Tharenos, C. L. and D. Santorino (2009). "Photographing ugandan physical activity: perspectives from Mbararan youth." *Progress in Community Health Partnerships* **3**(2): 123-132. **no met inclusion criteria.**

478. Thiel, A., U. Gomolinsky, et al. (2009). "[Stereotypes of ageing and sporting activity in the over-50s]." *Zeitschrift fur Gerontologie und Geriatrie* **42**(2): 145-154. **no met inclusion criteria.**
479. Thomas, K., D. French, et al. (2009) "The effect of two plyometric training techniques on muscular power and agility in youth soccer players." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 332-335. **No outcome of Interest.**
480. Tian, Y., L. Shi, et al. (2007) "Effects of active and passive training apparatus combined with rehabilitation training on lower limb function of stroke patients during recovery period." *Neural Regeneration Research*, 636-640. **no met inclusion criteria.**
481. Tokmakidis, S. P., V. I. Kalapotharakos, et al. (2009). "Effects of detraining on muscle strength and mass after high or moderate intensity of resistance training in older adults." *Clinical Physiology & Functional Imaging* **29**(4): 316-319. **no met inclusion criteria (Detrain).**
482. Tolomio, S., A. Ermolao, et al. (2008). "Short-term adapted physical activity program improves bone quality in osteopenic/osteoporotic postmenopausal women." *Journal of Physical Activity & Health* **5**(6): 844-853. **No outcome of Interest.**
483. Tomas-Carus, P., A. Hakkinen, et al. (2007). "Aquatic training and detraining on fitness and quality of life in fibromyalgia." *Medicine & Science in Sports & Exercise* **39**(7): 1044-1050. **Different modalities of training.**
484. Topp, R., A. M. Swank, et al. (2009) "The effect of prehabilitation exercise on strength and functioning after total knee arthroplasty." *PM & R : the journal of injury, function, and rehabilitation*, 729-735. **no population of interest.**
485. Trappe, S., D. Costill, et al. (2009). "Exercise in **space**: human skeletal muscle after 6 months aboard the International Space Station." *Journal of Applied Physiology* **106**(4): 1159-1168. **no met inclusion criteria**
486. Trojian, T. H., K. Mody, et al. (2007). "Exercise and Colon Cancer: Primary and Secondary Prevention." *Current Sports Medicine Reports* **6**(2): 120-124. **No dose-response relationship investigated.**
487. Troosters, T., F. Sciurba, et al. "Physical inactivity in patients with COPD, a controlled multi-center pilot-study." *Respiratory Medicine* **104**(7): 1005-1011. **No dose-response relationship investigated.**
488. Trzaskoma, L., J. Tihanyi, et al. (2010) "The effect of a short-term combined conditioning training for the development of leg strength and power." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 2498-2505. **Different modalities of training.**
489. Tudor-Locke, C., W. D. Johnson, et al. "Frequently reported activities by intensity for U.S. adults: the American Time Use Survey." *American Journal of Preventive Medicine* **39**(4): e13-20. **No dose-response relationship investigated.**
490. Tudor-Locke, C. and L. Lutes (2009). "Why do pedometers work?: A reflection upon the factors related to successfully increasing physical activity." *Sports Medicine (Auckland)* **39**(12): 981-993. **no met inclusion criteria.**
491. Tung, F. L., Y. R. Yang, et al. "Balance outcomes after additional sit-to-stand training in subjects with stroke: a randomized controlled trial." *Clinical Rehabilitation* **24** (6): 533-542. **Different modalities of training.**
492. Turk, Z., D. Lonzaric, et al. "The benefits of regular kinesiotherapy once a week for postmenopausal women: an aged-matched study." *Collegium Antropologicum* **34**(3): 995-999. **Single dose.**
493. Turner, A. P., D. R. Kivlahan, et al. (2009). "Exercise and quality of life among people with multiple sclerosis: looking beyond physical functioning to mental health and participation in life." *Archives of Physical Medicine & Rehabilitation* **90**(3): 420-428. **no population of interest.**
494. Twiss, J. J., N. L. Waltman, et al. (2009). "An exercise intervention for breast cancer survivors with bone loss." *Journal of Nursing Scholarship* **41**(1): 20-27. **no population of interest.**
495. Twist, C. and R. G. Eston (2007). "THE EFFECT OF MUSCLE-DAMAGING EXERCISE ON MAXIMAL INTENSITY CYCLING AND DROP JUMP PERFORMANCE." *Journal of Exercise Science & Fitness* **5**(2): 79-87. **No outcome of Interest.**
496. Unlu, E., E. Eksioğlu, et al. (2007). "The effect of exercise on hip muscle strength, gait speed and cadence in patients with total hip arthroplasty: A randomized controlled study." *Clinical Rehabilitation* **21** (8): 706-711. **no population of interest.**

497. Urinary Incontinence Treatment, N. (2007) "Design of the Behavior Enhances Drug Reduction of Incontinence (BE-DRI) study." *Contemporary clinical trials*, 48-58. **no met inclusion criteria.**
498. Utsunomiya, M., K. Nitta, et al. "Changes in Blood Flow, Temperature and Muscle Endurance in Association with Cryotherapy." *Journal of Physical Therapy Science* **22**(1): 43-49. **no met inclusion criteria.**
499. Utter, A., D. Nieman, et al. (2007). "Ratings of Perceived Exertion During Intermittent and Continuous Exercise." *Perceptual and Motor Skills* **104**(3 Pt 2): 1079-1087. **no met inclusion criteria.**
500. Valenti, M., G. Porzio, et al. (2008). "Physical exercise and quality of life in breast cancer survivors." *International Journal of Medical Sciences* **5**(1): 24-28. **no population of interest.**
501. Valkeinen, H., M. Alen, et al. (2008). "Effects of concurrent strength and endurance training on physical fitness and symptoms in postmenopausal women with fibromyalgia: a randomized controlled trial." *Archives of Physical Medicine and Rehabilitation* **89**(9): 1660-1666. **Single dose.**
502. Valtonen, A., T. Pääyhänen, et al. "Effects of Aquatic Resistance Training on Mobility Limitation and Lower-Limb Impairments After Knee Replacement." *Archives of Physical Medicine & Rehabilitation* **91**(6): 833-839. **Single dose.**
503. van den Berg-Emons, R. J., J. B. Bussmann, et al. (2008). "A prospective study on physical activity levels after spinal cord injury during inpatient rehabilitation and the year after discharge." *Archives of Physical Medicine & Rehabilitation* **89**(11): 2094-2101. **no population of interest.**
504. van der Kooij, S. M., J. K. de Vries-Bouwstra, et al. (2009) "Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis." *Arthritis and rheumatism*, 4-12. **No dose-response relationship investigated.**
505. van der Slot, W. M. A., M. E. Roebroek, et al. (2007). "Everyday physical activity and community participation of adults with hemiplegic Cerebral Palsy." *Disability & Rehabilitation* **29**(3): 179-189. **No dose-response relationship investigated.**
506. van Helvoort, H. A., R. C. de Boer, et al. "Exercises commonly used in rehabilitation of patients with chronic obstructive pulmonary disease: cardiopulmonary responses and effect over time." *Archives of Physical Medicine & Rehabilitation* **92**(1): 111-117. **No dose-response relationship investigated.**
507. van Uffelen, J. G. Z., M. J. M. Chinapaw, et al. (2009). "Feasibility and Effectiveness of a Walking Program for Community-Dwelling Older Adults With Mild Cognitive Impairment." *Journal of Aging & Physical Activity* **17**(4): 398-415. **No dose-response relationship investigated.**
508. van Weering, M. G. H., M. M. R. Vollenbroek-Hutten, et al. (2009). "Daily physical activities in chronic lower back pain patients assessed with accelerometry." *European Journal of Pain: Ejp* **13**(6): 649-654. **no population of interest.**
509. Vance, D. (2010) "Improving speed of processing and everyday functioning in adults with HIV by using cognitive remediation therapy." *European journal of neurology*. **no population of interest.**
510. Vanderthommen, M., S. Makrof, et al. "Comparison of active and electrostimulated recovery strategies after fatiguing exercise." *Journal of Sports Science & Medicine* **9**(2): 164-169. **no met inclusion criteria**
511. Vanner, E. A., P. Block, et al. (2008). "Pilot study exploring quality of life and barriers to leisure-time physical activity in persons with moderate to severe multiple sclerosis." *Disability and Health Journal* **1** (1): 58-65. **No dose-response relationship investigated.**
512. Vila-Chã, C., D. Falla, et al. (2010) "Motor unit behavior during submaximal contractions following six weeks of either endurance or strength training." *Journal of applied physiology* (Bethesda, Md. : 1985). **No outcome of Interest.**
513. Vissing, K., M. Brink, et al. (2008). "Muscle adaptations to plyometric vs. resistance training in untrained young men." *Journal of Strength & Conditioning Research* **22**(6): 1799-1810. **Different modalities of training.**
514. Vliet Vlieland Thea, P. M., M. Munneke, et al. (2008) "Dynamic exercise therapy for treating rheumatoid arthritis." *Cochrane Database of Systematic Reviews*.
515. Vogler, C. M., C. Sherrington, et al. (2009). "Reducing risk of falling in older people discharged from hospital: a randomized controlled trial comparing seated exercises, weight-

- bearing exercises, and social visits." *Archives of Physical Medicine & Rehabilitation* **90**(8): 1317-1324. **Different modalities of training.**
516. Voigt-Radloff, S., M. Graff, et al. (2009) "WHEDA study: effectiveness of occupational therapy at home for older people with dementia and their caregivers--the design of a pragmatic randomised controlled trial evaluating a Dutch programme in seven German centres." *BMC Geriatrics*, **44**. **No dose-response relationship investigated.**
517. Volaklis, K. A., A. T. Spassis, et al. (2007). "Land versus water exercise in patients with coronary artery disease: effects on body composition, blood lipids, and physical fitness." *American Heart Journal* **154**(3): 560.e561-566. **Different modalities of training.**
518. Von Stengel, S., W. Kemmler, et al. (2007) "Differential effects of strength versus power training on bone mineral density in postmenopausal women: A 2-year longitudinal study." *British Journal of Sports Medicine*, 649-655. **No outcome of Interest.**
519. Wagenmakers, R., M. Stevens, et al. (2008). "Habitual physical activity behavior of patients after primary total hip arthroplasty." *Physical Therapy* **88**(9): 1039-1048. **no population of interest.**
520. Walker, P. P., A. Burnett, et al. (2008). "Lower limb activity and its determinants in COPD." *Thorax* **63**(8): 683-689. **Single dose.**
521. Wallace, A. C., P. Talelli, et al. "Standardizing the intensity of upper limb treatment in rehabilitation medicine." *Clinical Rehabilitation* **24**(5): 471-478. **No dose-response relationship investigated.**
522. Warburton, D. E., S. S. Bredin, et al. (2007) "The health benefits of interactive video game exercise." *Applied physiology, nutrition, and metabolism = Physiologie appliquée, nutrition et métabolisme*, 655-663. **No dose-response relationship investigated.**
523. Warburton, D. E. R., A. Taylor, et al. (2007). "Central haemodynamics and peripheral muscle function during exercise in patients with chronic heart failure." *Applied Physiology, Nutrition & Metabolism* **32**(2): 318-331. **No outcome of Interest.**
524. Watanabe, H., K. Urabe, et al. (2007). "Relationship between physical activity and quality of life in osteoarthritis of the knee." *Japanese Journal of Clinical Sports Medicine* **15**(2): 7-7. **No outcome of Interest.**
525. Webber, S. C. and M. M. Porter (2010) "Effects of ankle power training on movement time in mobility-impaired older women." *Medicine and science in sports and exercise*. **Different modalities of training.**
526. Weikert, M., R. W. Motl, et al. "Accelerometry in persons with multiple sclerosis: measurement of physical activity or walking mobility?" *Journal of the Neurological Sciences* **290**(1-2): 6-11. **No outcome of Interest.**
527. Weisgerber, M., K. Webber, et al. (2008). "Moderate and vigorous exercise programs in children with asthma: safety, parental satisfaction, and asthma outcomes." *Pediatric Pulmonology* **43**(12): 1175-1182. **no population of interest.**
528. Wells, G. D., D. L. Wilkes, et al. (2008). "Reliability and validity of the habitual activity estimation scale (HAES) in patients with cystic fibrosis." *Pediatric Pulmonology* **43**(4): 345-353. **No dose-response relationship investigated.**
529. Wen-Ching, C., Y. Yea-Ru, et al. (2008). "Balance improvement in patients with benign paroxysmal positional vertigo." *Clinical Rehabilitation* **22**(4): 338-347. **Single dose.**
530. Wernbom, M., J. Augustsson, et al. (2008). "Ischemic strength training: a low-load alternative to heavy resistance exercise?" *Scandinavian Journal of Medicine & Science in Sports* **18**(4): 401-416. **no met inclusion criteria**
531. Wieser, M. and P. Haber (2007). "The Effects of Systematic Resistance Training in the Elderly." *International Journal of Sports Medicine* **28**(1): 59-65. **Single dose.**
532. Wiggins, M. S. and E. S. Simonavice (2008). "Quality of Life Benefits: A 12 Month Exercise & Cancer Recovery Case Study." *Kentucky Newsletter for Health, Physical Education, Recreation & Dance* **44**(2): 16-19. **No dose-response relationship investigated.**
533. Winchester, J. B., J. M. McBride, et al. (2008) "Eight weeks of ballistic exercise improves power independently of changes in strength and muscle fiber type expression." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 1728-1734. **No outcome of Interest.**

534. Wisløff, U., A. Støylen, et al. (2007) "Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study." *Circulation*, 3086-3094. **No outcome of Interest.**
535. Wittmann, M., S. Spohn, et al. (2007). "[Patient education in COPD during inpatient rehabilitation improves quality of life and morbidity]." *Pneumologie* **61**(10): 636-642. **No dose-response relationship investigated.**
536. Wong, P. L., A. Chaouachi, et al. "Effect of preseason concurrent muscular strength and high-intensity interval training in professional soccer players." *Journal of Strength and Conditioning Research* **24** (3): 653-660. **No dose-response relationship investigated.**
537. Woo, J., A. Hong, et al. (2007). "A randomised controlled trial of Tai Chi and resistance exercise on bone health, muscle strength and balance in community-living elderly people." *Age & Ageing* **36**(3): 262-268. **No dose-response relationship investigated.**
538. Xiaolin, Y., R. Telama, et al. (2008). "The Longitudinal Effects of Physical Activity History on Metabolic Syndrome." *Medicine & Science in Sports & Exercise* **40**(8): 1424-1431. **No dose-response relationship investigated.**
539. Yamauchi, J., S. Nakayama, et al. (2009). "Effects of bodyweight-based exercise training on muscle functions of leg multi-joint movement in elderly individuals." *Geriatrics & gerontology international* **9**(3): 262-269. **No dose-response relationship investigated.**
540. Yang, A.-L., S.-D. Lee, et al. (2007). "Effects of exercise intervention on patients with stroke with prior coronary artery disease: aerobic capacity, functional ability, and lipid profile: a pilot study." *Journal of Rehabilitation Medicine* **39**(1): 88-90. **Single dose.**
541. Yang, P., B. C. Frier, et al. (2007) "Respiratory muscle training and the performance of a simulated anti-G straining maneuver." *Aviation, space, and environmental medicine*, 1035-1041. **No outcome of Interest.**
542. Yasuda, T., S. Fujita, et al. (2010) "Effects of low-intensity bench press training with restricted arm muscle blood flow on chest muscle hypertrophy: a pilot study." *Clinical physiology and functional imaging*. **Single dose.**
543. Yeo, W. K., C. D. Paton, et al. (2008). "Skeletal muscle adaptation and performance responses to once a day versus twice every second day endurance training regimens." *Journal of Applied Physiology* **105**(5): 1462-1470. **No outcome of Interest.**
544. Yip, Y. B., J. W. H. Sit, et al. (2007). "Effects of a self-management arthritis programme with an added exercise component for osteoarthritic knee: randomized controlled trial." *Journal of Advanced Nursing* **59**(1): 20-28. **Single dose.**
545. Yong Tai, W., R. Bernard, et al. (2008). "Fundamental Locomotive Activity Time Efficiency With Differently Positioning Drive-Axis Wheelchairs Among Elders." *Adapted Physical Activity Quarterly* **25**(4): 322-334. **No dose-response relationship investigated.**
546. Yoshizawa, M., S. Maeda, et al. (2009). "Effect of 12 weeks of moderate-intensity resistance training on arterial stiffness: a randomised controlled trial in women aged 32-59 years." *British Journal of Sports Medicine* **43**(8): 615-618. **Single dose. No outcome of Interest.**
547. Young, W., R. Gulli, et al. "Acute effect of exercise on kicking accuracy in elite Australian football players." *Journal of Science & Medicine in Sport* **13**(1): 85-89. **No outcome of Interest.**
548. Yousefi, B., V. Tadibi, et al. (2009) "Exercise therapy, quality of life, and activities of daily living in patients with Parkinson disease: a small scale quasi-randomised trial." *Trials*, 67. **Single dose.**
549. Zheng, A., R. Sakari, et al. (2009) "Effects of a low-frequency sound wave therapy programme on functional capacity, blood circulation and bone metabolism in frail old men and women." *Clinical Rehabilitation*, 897-908. **no met inclusion criteria**
550. Zwick, R. H., O. C. Burghuber, et al. (2009). "[The effect of one year outpatient pulmonary rehabilitation on patients with COPD]." *Wiener Klinische Wochenschrift* **121**(5-6): 189-195. **Single dose.**

ARTICLES EXCLUDED BY ABSTRACT BECAUSE PRESENT IN THE CORE REVIEWS:

1. Candow, D. G. and D. G. Burke (2007) "Effect of short-term equal-volume resistance training with different workout frequency on muscle mass and strength in untrained men

- and women." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 204-207.
2. de Vos NJ, Singh NA, et al. (2008). "Effect of power-training intensity on the contribution of force and velocity to peak power in older adults." *J Aging Phys Act* **16**(4): 393-407.
 3. Humburg, H., H. Baars, et al. (2007) "1-Set vs. 3-set resistance training: a crossover study." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 578-582.
 4. Nakamura, Y., K. Tanaka, et al. (2007). "Effects of exercise frequency on functional fitness in older adult women." *Archives of Gerontology & Geriatrics* **44**(2): 163-173.
 5. Rønnestad, B. R., W. Egeland, et al. (2007) "Dissimilar effects of one- and three-set strength training on strength and muscle mass gains in upper and lower body in untrained subjects." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 157-163.
 6. Bottaro, M., S. N. Machado, et al. (2007). "Effect of high versus low-velocity resistance training on muscular fitness and functional performance in older men." *European Journal of Applied Physiology* **99**(3): 257-264.

STUDIES EXCLUDED VIA FULL-TEXT:

1. Alcaraz, P. E., J. Sánchez-Lorente, et al. (2008) "Physical performance and cardiovascular responses to an acute bout of heavy resistance circuit training versus traditional strength training." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 667-671. **Different modalities of training.**
2. *Arnardottir, R., G. Boman, et al. (2007). "Interval training compared with continuous training in patients with COPD." *Respiratory Medicine* **101**(6): 1196-1204. No population of interest. (not healthy adult mixed age 43-80y.*
3. *Askim T, Morkved S, et al. (2010). "Effects of a community-based intensive motor training program combined with early supported discharge after treatment in a comprehensive stroke unit: a randomized, controlled trial." *Stroke* **41**(8): 1697-1703. Different training modalities.*
4. Behm DG, Reardon G, Fitzgerald J, Drinkwater E. (2002) "The effect of 5, 10, and 20 repetition maximums on the recovery of voluntary and evoked contractile properties". *J Strength Cond Res*. 2002 May;16(2):209-18. **No dose optimization trial.**
5. Bemben, D. A. and M. G. Bemben "Dose-response effect of 40 weeks of resistance training on bone mineral density in older adults." *Osteoporosis International* **22** (1): 179-186. **No outcome of Interest. Single dose.**
6. *Byl NN, Pitsch EA, et al. (2008). "Functional Outcomes Can Vary by Dose: Learning-Based Sensorimotor Training for Patients Stable Poststroke." *Neurorehabilitation and Neural Repair* **22**(5): 494-504. No ExBT.*
7. *Buford, T. W., S. J. Rossi, et al. (2007) "A comparison of periodization models during nine weeks with equated volume and intensity for strength." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 1245-1250. Different training modalities.*
8. Cheema, B., H. Abas, et al. (2007). "Randomized controlled trial of intradialytic resistance training to target muscle wasting in ESRD: the Progressive Exercise for Anabolism in Kidney Disease (PEAK) study." *American Journal of Kidney Diseases* **50**(4): 574-584. **no meet inclusion criteria.**
9. Combs, S. A., M. D. Diehl, et al. "Boxing training for patients with Parkinson disease: a case series." *Physical Therapy* **91**(1): 132-142. **Single dose.**
10. *Cooke EV, Tallis RC, et al. (2010). "Efficacy of functional strength training on restoration of lower-limb motor function early after stroke: phase I randomized controlled trial." *Neurorehabilitation & Neural Repair* **24**(1): 88-96 Different training modalities*
11. Dromerick, A. W., C. E. Lang, et al. (2009). "Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS): A single-center RCT." *Neurology* **73**(3): 195-201. **Different modalities of training, same dose.**

12. Delecluse C, Coppennolle HV, Willems E, Leemputte MV, Diels R, Goris M. Influence of high-resistance and high-velocity training on sprint performance. *Medicine & Science in Sports & Exercise*. 1995;27(8):1203-9. **Different therapies.**
13. Dolezal BA, Potteiger JA. Concurrent resistance and endurance training influence basal metabolic rate in nondieting individuals. *Journal of Applied Physiology*. 1998 August 1, 1998;85(2):695-700. **Different therapies.**
14. DONNELLY JE, JACOBSEN DJ, HEELAN SNYDER KS, al. E. The effects of 18 months of intermittent vs continuous exercise on aerobic capacity, body weight and composition, and metabolic fitness in previously sedentary, moderately obese females. *Int J Obesity Relat Metab Disord*. 2000;24:566-72. **Different therapies.**
15. Ebben WP, Kindler AG, Chirdon KA, et al (2004). "The effect of highload vs. high-repetition training on endurance performance". *Journal of Strength and Conditioning Research*, 2004, 18(3), 513–517 **Different training modalities**
16. Farthing J, Chilibeck P (2003). "The effects of eccentric and concentric training at different velocities on muscle hypertrophy". *European Journal of Applied Physiology*. 89(6):578-86. **Different Therapies.**
17. Fry AC, Kraemer WJ, Weseman CA, et al. (1991). The effects of an off-season strength and conditioning program on starters and non-starters in women's intercollegiate volleyball. *J Appl Sport Sci Res* 5:174-81. **Single dose.**
18. Hoffman JR, Ratamess NA, Cooper JJ, Kang JIE, Chilakos ART, Faigenbaum AD. (2005). Comparison of Loaded and Unloaded Jump Squat Training on Strength/Power Performance in College Football Players. *The Journal of Strength & Conditioning Research*. 19(4):810-5. **Different therapies.**
19. Kang, J., E. Chaloupka, et al. (2009). "Regulating intensity using perceived exertion: effect of exercise duration." *European Journal of Applied Physiology* **105**(3): 445-451. **No dose-response relationship.**
20. *Katula, J. A., W. J. Jack, et al.* (2008). "Enhancing quality of life in older adults: A comparison of muscular strength and power training." *Health and Quality of Life Outcomes* **6**(45). **Trials included in a larger pilot study (Marsh,2009).**
21. Kawamori N, Crum AJ, Blumert PA, Kulik JR, Childers JT, Wood JA, et al. (2005) Influence of Different Relative Intensities on Power Output During the Hang Power Clean: Identification of the Optimal Load. *The Journal of Strength & Conditioning Research*. 19(3):698-708. **No dose investigated.**
22. *Kimura, A.* (2008). "Cut-off Point of Physical Activity for Elderly Hemiplegics with Deconditioning." *Rigakuryoho Kagaku* **23**(3): 375-382. **Language restriction on full text.**
23. Kraemer WJ, Ratamess N, Fry AC, et al. (2000) Influence of resistance training volume and periodization on physiological and performance adaptations in college women tennis players. *Am J Sports Med*. 28:626-33. **Different therapies.**
24. Landin, D. and A. G. Nelson (2007) "Early phase strength development: a four-week training comparison of different programs." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 1113-1116. **Same dose Diff order.**
25. Langhammer, B., B. Lindmark, et al. (2007) "Stroke patients and long-term training: is it worthwhile? A randomized comparison of two different training strategies after rehabilitation." *Clinical Rehabilitation*, 495-510. **Different modalities of training.**
26. Langhammer, B., J. K. Stanghelle, et al. (2008) "Exercise and health-related quality of life during the first year following acute stroke. A randomized controlled trial." *Brain injury : [BI]*, 135-145. **Different modalities of training.**
27. LaRoche, D. P., C. A. Knight, et al. (2007). "Explosive force and fractionated reaction time in elderly low- and high-active women." *Medicine and Science in Sports and Exercise* **39** (9): 1659-1665. **Same Dose applied**
28. *Marsh, A. P., M. E. Miller, et al.* (2009). "Lower extremity muscle function after strength or power training in older adults." *Journal of Aging & Physical Activity* **17**(4): 416-443. **Different modalities of training. same dose (speed of movement).**

29. *Martin, C. K., T. S. Church, et al.* (2009). "Exercise dose and quality of life: a randomized controlled trial." *Archives of Internal Medicine* **169**(3): 269-278. **No outcome of Interest.**
30. *Marx JO, Ratamess NA, Nindl BC, et al* (2001). Low-volume circuit versus high-volume periodized resistance training in women. *MEDICINE & SCIENCE IN SPORTS & EXERCISE* **4**:635-643 **Different modalities of training.**
31. *Mazzetti S, Douglass M, Yocum A, Harber M.* (2007) Effect of Explosive versus Slow Contractions and Exercise Intensity on Energy Expenditure. *Medicine & Science in Sports & Exercise.* **39**(8):1291-301 **No outcome of Interest.**
32. *McBride JM, Triplett-McBride T, Davie A, Newton RU* (2002). "The effect of heavy- vs light-load jump squats on the development of strength, power, and speed". *Journal of Strength and Conditioning Research*, 2002, **16**(1), 75–82 **No population of interest. (Athlete).**
33. *Monteiro, A. G., M. S. Aoki, et al.* (2009) "Nonlinear periodization maximizes strength gains in split resistance training routines." *Journal of strength and conditioning research / National Strength & Conditioning Association*, 1321-1326. . **Different training modalities.**
34. *Mookerjee S, Ratamess N.* (1999) Comparison of Strength Differences and Joint Action Durations Between Full and Partial Range-of-Motion Bench Press Exercise. *The Journal of Strength & Conditioning Research.* **13**(1):76-81 **Different training.**
35. *Neils CM, Uderman BE, Brice GA, Winchester JB, McGuigan MR* (2005). Influence of contraction velocity in untrained individuals over the initial early phase of resistance training. *J Strength Cond Res*;19(4):883-7 **Different modalities of training.**
36. *Orr R, DeVos NJ, Singh NA, et al* (2006). Power training improves balance in healthy older adults. *J Gerontol A Biol Sci Med Sci.* **61**(1):78-85. **Duplicate.**
37. *Ostrowski KJ, Wilson GJ, Weatherby R, Murphy PW, Lyttle AD* (1997). "The effect of weight training volume on hormonal output and muscular size and function". *Journal of strength and conditioning research* **11**(1):148-154. **No outcome of Interest.**
38. *Reid, K. F., D. M. Callahan, et al.* (2008). "Lower extremity power training in elderly subjects with mobility limitations: A randomized controlled trial." *Aging - Clinical and Experimental Research* **20** (4): 337-343. **Different modalities of training. same dose (speed of movement).**
39. *Rhea MR, Phillips WT, Burkett LN, Ball SD, al. e.* (2002) A comparison of linear and daily undulating periodized programs with equated volume and intensity for strength. *J Strength Cond Res.* **16**(2):250-5 **Same dose.**
40. *Sforzo GA, Touey PR.* (1996) Manipulating Exercise Order Affects Muscular Performance During a Resistance Exercise Training Session. *The Journal of Strength & Conditioning Research.* **10**(1):20-4. **Same dose.**
41. *Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB.* (2002) Exercise Type and Intensity in Relation to Coronary Heart Disease in Men. *JAMA: The Journal of the American Medical Association*, **288**(16):1994-2000. **Vague dose.**
42. *Tanimoto M, Sanada K, et al.* (2008). "Effects of whole-body low-intensity resistance training with slow movement and tonic force generation on muscular size and strength in young men." *J Strength Cond Res.* **22**(6): 1926-1938. **Single dose.**
43. *Tanimoto, M., H. Arakawa, et al.* (2009). "Changes in Muscle Activation and Force Generation Patterns During Cycling Movements Because of Low-Intensity Squat Training With Slow Movement and Tonic Force Generation." *Journal of Strength & Conditioning Research* **23**(8): 2367-2376. **No outcome of Interest.**
44. *Tanimoto, M., H. Kawano, et al.* (2009) "Low-intensity resistance training with slow movement and tonic force generation increases basal limb blood flow." *Clinical physiology and functional imaging*, 128-135. **Single dose.**
45. *Thomas GA, Kraemer WJ, Spiering BA, Volek JS, Anderson JM, Maresh CM.* (2007) Maximal Power At Different Percentages of One Repetition Maximum: Influence of Resistance and Gender. *The Journal of Strength & Conditioning Research.* **21**(2):336-42. **Not controlling for dose.**
46. *Tran QT, Docherty D, Behm D* (2006). The effects of varying time under tension and volume load on acute neuromuscular responses. *Eur J Appl Physiol.* **98**(4):402-10. **Different training modalities.**

47. Willardson JM and B. LN (2008). "The effect of different rest intervals between sets on volume components and strength gains." J Strength Cond Res. 22(1): 146-152. **No population of interest.** (Athlete)
48. Willardson, J. M., J. Emmett, et al. (2008) "Effect of short-term failure versus nonfailure training on lower body muscular endurance." International journal of sports physiology and performance, 279-293. **No outcome of Interest.**
49. Gillam GM. (1981). "Effects of frequency of weight training on muscle strength enhancement". The Journal of sports medicine and physical fitness 21(4):432-6. **NO Full-txt available.**
50. Sipe, C. L. (2008) "The effects of strength and power training on functional abilities in older adults." **(Dissertation project).**
51. Stone MH, Johnson RL, Carter DR (1979). "A short term comparison of two different methods of resistance training on leg strength and power". Journal of strength and conditioning research **NO Full-txt available.**
52. Stone MH, Potteiger JA, Pierce KC, et al (2000). "Comparison of the effects of three different weight-training programs on the one repetition maximum squat". Journal of strength and conditioning research 14(3) **NO Full-txt available.**
53. Paoli A, Pacelli F, et al. (2010). "Effects of three distinct protocols of fitness training on body composition, strength and blood lactate." J Sports Med Phys Fitness` **50: 43-51.NO Full-txt available.**

Appendix D : Narrative systematic review on dose optimization approaches in pharmaceutical clinical research

REFERENCE LIST OF EXCLUDED ARTICLES AT FULL-TEXT REVIEW STAGE

1. Wong, S. F. (2009). "New dosing schedules of Dasatinib for CML and adverse event management." Journal of Hematology and Oncology **2**(10). *NOT DOSE OPTIMIZATION STUDY*
2. Mulhall, J. P., S. Bukofzer, et al. (2001). "An open-label, uncontrolled dose-optimization study of sublingual apomorphine in erectile dysfunction." Clinical Therapeutics **23 (8)**: 1260-1271. *NOT DOSE OPTIMIZATION STUDY*
3. Murphy, W. K., F. V. Fossella, et al. (1993). "Phase II study of taxol in patients with untreated advanced non-small-cell lung cancer." Journal of the National Cancer Institute **85**(5): 384-388. *NOT DOSE OPTIMIZATION STUDY*
4. Plaxe, S. C., J. A. Blessing, et al. (2002). "Phase II trial of pyrazoloacridine in patients with persistent or recurrent endometrial carcinoma: A Gynecologic Oncology Group study." Gynecologic Oncology **84 (2)**: 241-244. *NOT DOSE OPTIMIZATION STUDY*
5. Pavlu, J. and D. Marin (2009). "Dasatinib and chronic myeloid leukemia: Two-year follow-up in eight clinical trials." Clinical Lymphoma and Myeloma **9 (6)**: 417-424. *NOT DOSE OPTIMIZATION STUDY*
6. Porsteinsson, A., R. Sperling, et al. (2011). "Imaging and cerebrospinal fluid biomarker results of a phase II dose-ranging study of ELND005 (Scyllo-inositol) in mild-to-moderate Alzheimer's disease." Alzheimer's and Dementia Conference: Alzheimer's Association International Conference, AAIC 11 Paris France. Conference Start: 20110716 Conference End: 20110721. Conference Publication: (var.pagings). 7 (4 SUPPL. 1): S695. *NOT DOSE OPTIMIZATION STUDY*

7. Reuben, D. B., S. H. Hirsch, et al. (2005). "The effects of megestrol acetate suspension for elderly patients with reduced appetite after hospitalization: A phase II randomized clinical trial." Journal of the American Geriatrics Society **53 (6)**: 970-975. *NOT DOSE OPTIMIZATION STUDY*
8. Rhee, P., J. Morris, et al. (2000). "Recombinant humanized monoclonal antibody against CD18 (rhuMAb CD18) in traumatic hemorrhagic shock: Results of a phase II clinical trial." Journal of Trauma - Injury, Infection and Critical Care **49 (4)**: 611-620. *NOT DOSE OPTIMIZATION STUDY*
9. Shanafelt, T. D., T. G. Call, et al. (2009). "Phase I trial of daily oral polyphenon E in patients with asymptomatic Rai stage 0 to II chronic lymphocytic leukemia." Journal of Clinical Oncology **27 (23)**: 3808-3814. *NO INCLUSION CRITERIA*
10. Thall, P. F., H. G. Sung, et al. (2001). "Dose-finding based on feasibility and toxicity in T-cell infusion trials." Biometrics **57 (3)**: 914-921. *NOT DOSE OPTIMIZATION STUDY*
11. Sinnige, H. A. M., J. Buter, et al. (1993). "Phase I-II study of the addition of alpha-2a interferon to 5-fluorouracil/leucovorin. Pharmacokinetic interaction of alpha-2a interferon and leucovorin." European Journal of Cancer Part A: General Topics **29 (12)**: 1715-1720. *NOT DOSE OPTIMIZATION STUDY*
12. Smith, A. M., T. Justin, et al. (2000). "Phase I/II study of G17-DT, an anti-gastrin immunogen, in advanced colorectal cancer." Clinical Cancer Research **6 (12)**: 4719-4724. *NOT DOSE OPTIMIZATION STUDY*
13. Shuin, T., Y. Kubota, et al. (1994). "A phase II study of prophylactic intravesical chemotherapy with 4'-epirubicin in recurrent superficial bladder cancer: comparison of 4'-epirubicin and adriamycin." Cancer Chemotherapy & Pharmacology **35 Suppl**: S52-56. *NOT DOSE OPTIMIZATION STUDY*
14. Trachtman, H., F. C. Fervenza, et al. (2011). "A phase 1, single-dose study of fresolimumab, an anti-TGF-B antibody, in treatment-resistant primary

- focal segmental glomerulosclerosis." Kidney International **79 (11)**: 1236-1243. . *NOT DOSE OPTIMIZATION STUDY*
15. Tsukiyama, I., S. Katano, et al. (2001). "Multi-institutional phase I and II trial of simultaneous intracavitary hyperthermia and brachytherapy for advanced esophageal cancer." Journal of Brachytherapy International **17 (4)**: 299-308. *NOT DOSE OPTIMIZATION STUDY*
 16. Kendra, K., R. Plummer, et al. (2011). "Phase I dose-finding study for pazopanib (P) and paclitaxel (T) in combination in the first-line setting in patients (pts) with advanced solid tumours." European Journal of Cancer Conference: 2011 European Multidisciplinary Cancer Congress Stockholm Sweden. Conference Start: 20110923 Conference End: 20110927. Conference Publication: (var.pagings). **47**: S146. Not full-text available
 17. Murphy, J. R. and D. L. Hall (1997). "A logistic dose-ranging method for phase I clinical investigations trials." Journal of Biopharmaceutical Statistics **7 (4)**: 635-647. Not full-text available
 18. Pena-Rossi, C., S. Schreiber, et al. (2008). "Clinical trial: A multicentre, randomized, double-blind, placebo-controlled, dose-finding, phase II study of subcutaneous interferon-beta-1a in moderately active ulcerative colitis." Alimentary Pharmacology and Therapeutics **28 (6)**: 758-767. Not full-text available
 19. Perera, P. M. S., S. F. Jayamanna, et al. (2009). "A phase II clinical trial to assess the safety of clonidine in acute organophosphorus pesticide poisoning." Trials **10 (pp 73)**(1745). Not full-text available
 20. Perez, E. A., T. Coe, et al. (1996). "Phase I study of paclitaxel with oral etoposide in advanced solid tumors." Cancer Journal **2 (5)**: 286-290. Not full-text available
 21. Planting, A. S., M. E. van der Burg, et al. (1993). "Phase I/II study of a short course of weekly cisplatin in patients with advanced solid tumours." British Journal of Cancer **68(4)**: 789-792. Not full-text available
 22. Portnow, J., S. Koehler, et al. (2010). "A phase I study of bortezomib (BTZ) and temozolomide (TMZ) in patients with advanced solid tumors." Journal of Clinical Oncology. Conference **28(15 SUPPL. 1)**. Not full-text available

23. Recchia, F., G. Saggio, et al. (2006). "Dose-finding study of docetaxel added to ifosfamide and cisplatin followed by concomitant capecitabine and radiotherapy in the treatment of locally advanced squamous cell carcinoma of the head and neck." Anticancer Research **26 (3 B)**: 2317-2324. Not full-text available
24. Reckamp, K. L., M. Koczywas, et al. (2010). "Randomized, placebo-controlled, phase II trial of EGFR and COX-2 inhibition in advanced non-small cell lung cancer." Journal of Clinical Oncology. Conference **28(15 SUPPL. 1)**. Not full-text available
25. Reddy, G. K., L. Shivakumar, et al. (2007). "Preliminary results of a phase II dose-finding study of subcutaneous Hematide in patients with cancer receiving chemotherapy." Supportive Cancer Therapy **4 (2)**: 74-75. Not full-text available
26. Reinhart, K., T. Gluck, et al. (2004). "CD14 receptor occupancy in severe sepsis: Results of a phase I clinical trial with a recombinant chimeric CD14 monoclonal antibody (IC14)." Critical Care Medicine **32 (5)**: 1100-1108. Not full-text available
27. Rhee, E. J., W. Y. Lee, et al. (2010). "A multicenter, randomized, placebo-controlled, double-blind phase II trial evaluating the optimal dose, efficacy and safety of LC 15-0444 in patients with type 2 diabetes." Diabetes, Obesity and Metabolism **12 (12)**: 1113-1119. Not full-text available
28. Richardson, P. G., R. J. Soiffer, et al. (2010). "Defibrotide for the Treatment of Severe Hepatic Veno-Occlusive Disease and Multiorgan Failure after Stem Cell Transplantation: A Multicenter, Randomized, Dose-Finding Trial." Biology of Blood and Marrow Transplantation **16 (7)**: 1005-1017. Not full-text available
29. Rixe, O., S. X. Franco, et al. (2009). "A randomized, phase II, dose-finding study of the pan-ErbB receptor tyrosine-kinase inhibitor CI-1033 in patients with pretreated metastatic breast cancer." Cancer Chemotherapy and Pharmacology **64 (6)**: 1139-1148. Not full-text available

30. Robert, F., M. P. Ezekiel, et al. (2001). "Phase I study of anti-epidermal growth factor receptor antibody cetuximab in combination with radiation therapy in patients with advanced head and neck cancer." Journal of Clinical Oncology **19 (13)**: 3234-3243. Not full-text available
31. Rocca, A., R. Maltoni, et al. (2010). "A phase IB dose-finding trial of liposomal doxorubicin in combination with capecitabine in patients with pretreated metastatic breast cancer." Cancer Chemotherapy and Pharmacology **65 (5)**: 871-876. Not full-text available
32. Rodgers, K. E., J. Oliver, et al. (2006). "Phase I/II dose escalation study of angiotensin 1-7 [A(1-7)] administered before and after chemotherapy in patients with newly diagnosed breast cancer." Cancer Chemotherapy and Pharmacology **57 (5)**: 559-568. Not full-text available
33. Roila, F., J. Rolski, et al. (2009). "Randomized, double-blind, dose-ranging trial of the oral neurokinin-1 receptor antagonist casopitant mesylate for the prevention of cisplatin-induced nausea and vomiting." Annals of Oncology **20 (11)**: 1867-1873. Not full-text available
34. Rose, P. G. (2005). "Pegylated liposomal doxorubicin: Optimizing the dosing schedule in ovarian cancer." Oncologist **10 (3)**: 205-214. Not full-text available
35. Rose, P. G., J. A. Blessing, et al. (2003). "A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: A Gynecologic Oncology Group study." Gynecologic Oncology **88 (2)**: 130-135. Not full-text available
36. Rose, P. G., B. J. Monk, et al. (2011). "An open-label, single-arm Phase II study of intravenous weekly (Days 1 and 8) topotecan in combination with carboplatin (Day 1) every 21 days as second-line therapy in patients with platinum-sensitive relapsed ovarian cancer." Gynecologic Oncology **120 (1)**: 38-42. Not full-text available
37. Rosenwasser, R. H. (2006). "Intra-arterial reteplase and intravenous abciximab in patients with acute ischemic stroke: An open-label, dose-ranging, phase I study - Commentary." Neurosurgery **59 (4)**: 796. Not full-text available

38. Rossi, C. P., S. B. Hanauer, et al. (2009). "Interferon beta-1a for the maintenance of remission in patients with Crohn's disease: Results of a phase II dose-finding study." BMC Gastroenterology **9**(22). Not full-text available
39. Rothenberg, M. L., J. G. Kuhn, et al. (2001). "Phase I dose-finding and pharmacokinetic trial of irinotecan (CPT-11) administered every two weeks." Annals of Oncology **12** (11): 1631-1641. Not full-text available
40. Rougier, P. (2007). "A phase I dose-finding study using an innovative sequential biweekly schedule of irinotecan followed 24 hours later by capecitabine." Advances in Gastrointestinal Cancers **5** (3): 14. Not full-text available
41. Saletti, P., C. Sessa, et al. (2011). "Phase i dose-finding study of vandetanib in combination with gemcitabine in locally advanced unresectable or metastatic pancreatic adenocarcinoma." Oncology **81** (1): 50-54. Not full-text available
42. Santisteban, M., J. C. Buckner, et al. (2009). "Phase II trial of two different irinotecan schedules with pharmacokinetic analysis in patients with recurrent glioma: North Central Cancer Treatment Group results." Journal of Neuro-Oncology **92**(2): 165-175. Not full-text available
43. Sastre, J., L. Paz-Ares, et al. (2005). "A phase I, dose-finding study of irinotecan (CPT-11) short i.v. infusion combined with fixed dose of 5-fluorouracil (5-FU) protracted i.v. infusion in adult patients with advanced solid tumours." Cancer Chemotherapy and Pharmacology **55** (5): 453-460. Not full-text available
44. Scagliotti, G. V., L. Crino, et al. (1996). "Preliminary results of a dose-finding study of paclitaxel and carboplatin in patients with advanced non-small cell lung cancer." Seminars in Oncology **23** (6 SUPPL. 16): 80-83. Not full-text available
45. Scagliotti, G. V., L. Crino, et al. (1999). "Phase I/II dose finding study of paclitaxel and carboplatin in advanced non-small cell lung cancer." Lung Cancer **25** (1): 39-46. Not full-text available

46. Scarffe, J. H. (1992). "A randomised vehicle controlled multicenter dose finding phase. II. Study of glycosylated rhuG-CSF in 121 patients after bone marrow transplantation." Journal of nutritional science and vitaminology **Spec No**: 365-367. Not full-text available
47. Scheinin, M., A. Kallio, et al. (1987). "Dose-finding and tolerability study of medetomidine in four healthy volunteers. An open phase-I investigation." Current Therapeutic Research - Clinical and Experimental **41 (5)**: 637-646. Not full-text available
48. Schilsky, R. L., M. E. Dolan, et al. (2000). "Phase I clinical and pharmacological study of O6-benzylguanine followed by carmustine in patients with advanced cancer." Clinical Cancer Research **6(8)**: 3025-3031. Not full-text available
49. Schimmer, A. D., S. O'Brien, et al. (2008). "A phase i study of the pan bcl-2FamilyInhibitor obatoclax mesylate in patients with advanced hematologic malignancies." Clinical Cancer Research **14 (24)**: 8295-8301. Not full-text available
50. Schmid, P., B. Flath, et al. (2005). "Gemcitabine and mitoxantrone in metastatic breast cancer: A phase-I-study." Investigational New Drugs **23 (4)**: 349-356. Not full-text available
51. Schmid, P., J. Krockner, et al. (2005). "Primary chemotherapy with gemcitabine, liposomal doxorubicin and docetaxel in patients with locally advanced breast cancer: results of a phase I trial." Anti-Cancer Drugs **16(1)**: 21-29. Not full-text available
52. Schoemaker, N. E., R. A. A. Mathot, et al. (2002). "Development of an optimal pharmacokinetic sampling schedule for rubitecan administered orally in a daily times five schedule." Cancer Chemotherapy and Pharmacology **50 (6)**: 514-517. Not full-text available
53. Schoffski, P., T. Hagedorn, et al. (2000). "Repeated administration of short infusions of bendamustine: A phase I study in patients with advanced progressive solid tumours." Journal of Cancer Research and Clinical Oncology **126 (1)**: 41-47. Not full-text available

54. Schoffski, P., P. Reichardt, et al. (2010). "A phase I-II study of everolimus (RAD001) in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors." Annals of Oncology **21 (10)**: 1990-1998. Not full-text available
55. Schooley, R. T., N. Clumeck, et al. (2001). "A dose-ranging study to evaluate the antiretroviral activity and safety of amprenavir alone and in combination with abacavir in HIV-infected adults with limited antiretroviral experience." Antiviral Therapy **6 (2)**: 89-96. Not full-text available
56. Schulman, G., R. Agarwal, et al. (2006). "A multicenter, randomized, double-blind, placebo-controlled, dose-ranging study of AST-120 (Kremezin) in patients with moderate to severe CKD." American Journal of Kidney Diseases **47 (4)**: 565-577. Not full-text available
57. Schultze-Seemann, W., K. Mross, et al. (1994). "Intravesical idarubicin - A phase-I study." Urological Research **22 (2)**: 99-104. Not full-text available
58. Schwartz, S., M. Etropolski, et al. (2011). "Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: Results of a randomized-withdrawal, placebo-controlled trial." Current Medical Research and Opinion **27 (1)**: 151-162. Not full-text available
59. Schwartzberg, L. S., S. L. Sankar, et al. (2009). "An open-label, dose-escalating study of Maxy-G34, a novel potent, long-acting Pegylated G-CSF, compared with pegfilgrastim (PF) for the treatment of chemotherapy induced neutropenia (CIN)." Journal of Clinical Oncology **Conference: 2009 Annual Meeting of the American Society of Clinical Oncology, ASCO Orlando, FL United States. Conference Start: 20090529 Conference End: 20090602. Conference Publication: (var.pagings). 27 (15 SUPPL. 1)**: e14500. Not full-text available
60. Seegers, V., S. Chevret, et al. (2011). "Dose-finding design driven by efficacy in onco-hematology phase I/II trials." Statistics in Medicine **30 (13)**: 1574-1583. Not full-text available
61. Segal, B. M., C. S. Constantinescu, et al. (2008). "Repeated subcutaneous injections of IL12/23 p40 neutralising antibody, ustekinumab, in patients

- with relapsing-remitting multiple sclerosis: a phase II, double-blind, placebo-controlled, randomised, dose-ranging study." The Lancet Neurology **7 (9)**: 796-804. Not full-text available
62. Segawa, Y., K. Aogi, et al. (2009). "A phase II dose-ranging study of palonosetron in Japanese patients receiving moderately emetogenic chemotherapy, including anthracycline and cyclophosphamide-based chemotherapy." Annals of Oncology **20(11)**: 1874-1880. Not full-text available
63. Sehouli, J., D. Stengel, et al. (2008). "Weekly paclitaxel and carboplatin (PC-W) for patients with primary advanced ovarian cancer: Results of a multicenter phase-II study of the NOGGO." Cancer Chemotherapy and Pharmacology **61 (2)**: 243-250. Not full-text available
64. Seiffert, D., B. E. Thomas, et al. (2003). "Effects of the glycoprotein IIb/IIIa antagonist Roxifiban on P-selectin expression, fibrinogen binding, and microaggregate formation in a phase I dose-finding study: no evidence for platelet activation during treatment with a glycoprotein IIb/IIIa antagonist." Platelets **14(3)**: 179-187. Not full-text available
65. Seiwert, T. Y., P. P. Connell, et al. (2007). "A phase I study of pemetrexed, carboplatin, and concurrent radiotherapy in patients with locally advanced or metastatic non-small cell lung or esophageal cancer." Clinical Cancer Research **13 (2 I)**: 515-522. Not full-text available
66. Selim, M., J. Goldstein, et al. (2011). "Safety and tolerability of deferoxamine in acute cerebral hemorrhage: DFO in ICH study." Stroke Conference: 2011 International Stroke Conference Los Angeles, CA United States. Conference Start: 20110209 Conference End: 20110211. Conference Publication: (var.pagings). **42 (3)**: e60-e61. Not full-text available
67. Sessa, C., S. Cresta, et al. (2009). "Phase I clinical and pharmacokinetic study of trabectedin and cisplatin in solid tumours." European Journal of Cancer **45(12)**: 2116-2122. Not full-text available
68. Sessa, C., C. Cuvier, et al. (2002). "Phase I clinical and pharmacokinetic studies of the taxoid derivative RPR 109881A administered as a 1-hour or

- a 3-hour infusion in patients with advanced solid tumors." Annals of Oncology **13 (7)**: 1140-1150. Not full-text available
69. Seto, T., K. Yoh, et al. (2002). "A phase I study of combination chemotherapy with gemcitabine and oral UFT for advanced non-small cell lung cancer." British Journal of Cancer **86 (11)**: 1701-1704. Not full-text available
70. Shimada, M., J. Kigawa, et al. (2007). "Phase I trial of paclitaxel, doxorubicin, and carboplatin (TAC) for the treatment of endometrial cancer." International Journal of Gynecological Cancer **17 (1)**: 210-214. Not full-text available
71. Shiraki, M., M. Fukunaga, et al. (2003). "A double-blind dose-ranging study of risedronate in Japanese patients with osteoporosis (a study by the Risedronate Late Phase II Research Group)." Osteoporosis International **14 (3)**: 225-234. Not full-text available
72. Silverman, L., A. Verma, et al. (2009). "Phase I trial of the combination of the epigenetic modulators vorinostat and azacitidine (azaC) in patients with the Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML). An update from the NY Cancer Consortium." Leukemia Research Conference: 10th International Symposium on Myelodysplastic Syndromes Patras Greece. Conference Start: 20090506 Conference End: 20090509 Sponsor: The Myelodysplastic Syndromes Foundation. Conference Publication: (var.pagings). **33**: S135-S136. Not full-text available
73. Smith, I. (2004). "Phase II studies of pemetrexed in metastatic breast and gynecologic cancers." Oncology (Williston Park, N.Y.) **18 (13 Suppl 8)**: 63-65. Not full-text available
74. Traina, T. A., M. Theodoulou, et al. (2009). "A novel capecitabine dosing schedule combined with bevacizumab is safe and active in patients with metastatic breast cancer: A phase II study." Cancer Research. Conference: 31st Annual San Antonio Breast Cancer Symposium San Antonio, TX United States. Conference Start **69(2 Suppl. S)**. Not full-text available

75. Trump, D. L., H. Payne, et al. (2010). "Phase I study of the specific endothelin A receptor antagonist zibotentan (ZD4054) combined with docetaxel in patients with metastatic castration-resistant prostate cancer: Assessment of efficacy, pain, and safety." Journal of Clinical Oncology. Conference **28**(15 SUPPL. 1). Not full-text available
76. Tsuda, H., M. Tanaka, et al. (2001). "Phase I-II study of neoadjuvant chemoradiotherapy followed by radical surgery in locally advanced cervical cancer." Anti-Cancer Drugs **12 (10)**: 853-858. Not full-text available

Appendix E : PIS, IC, and GP letter

University of East Anglia, version 2.1, 28/01/2014



Participant Information sheet

Study Title:

Establishing a feasible optimal therapeutic dose using a new methodology for stroke rehabilitation

You are being invited to take part in a research study. Before you decide whether you would like to take part you need to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information, [contact numbers on page 10 of this information pack](#).

Take time to decide whether or not you wish to take part.

What is the purpose of this study?

Literature suggests that an adequate dose of specific functional tasks training is needed to produce brain reorganisation and improve motor recovery after stroke. Identifying the most beneficial dose or optimal therapeutic dose of exercise-based therapies is important to maximally exploit the benefits of the rehabilitative intervention. However, we still do not know how much therapy is needed to maximise motor-recovery after stroke.

To investigate whether it is possible to identify the dose of intervention able to drive the greatest benefit we have designed a research study delivering an upper-limb intervention which could address some of the difficulties encountered by stroke survivors.

1

This clinical study is part of the research project undertaken by Elisabetta Colucci for a Post-graduate degree supported by the University of East Anglia.

Why have I been asked to take part?

The intervention we are using is most likely to benefit people who are discharged from in-patient rehabilitation wards that have moderate weakness after stroke. In detail we are looking for:

- adults aged 18+ years;
- presence of moderate upper limb weakness/impairment due to stroke;
- participants able to imitate action with the non-paretic upper limb and to participate in physiotherapy;
- participants should not be receiving other therapy to improve upper limb motor function.

Do I have to take part?

No. It is up to you to decide. Taking part in the research study is entirely voluntary. If you want to you can speak to a member of the research team before you decide.

You are free to withdraw from the study at any time and you do not have to give a reason. A decision to withdraw at any time, or a decision not to take part, will **not affect** the standard of care you receive or will receive in the future

What will happen if I decide to take part?

Your interest in participating in this study will be recorded on the day of the presentation of the study to the Stroke Group meeting. 24-hours later a telephone

call will be made to you by the researcher to check your continued interest in taking part. If you are still happy to participate in the study, one of the research team will see you during the next Stroke Group meeting or at home to assess if you are suitable to participate in the study.

We cannot guarantee that all people who express an interest in participating will be invited to take part in the study. This does not depend on you but on the characteristic of the study design. If this will be the case you will be informed and thanked for your interest.

In order to be enrolled in this trial you should be: able to open and close your most affected hand at least six times in one minute but not more than 25 times in one minute.

If you are **not suitable** to participate in the study, you will be told by a member of the research team and no further action will be required.

If you are **suitable** for this trial you will be asked to **sign a consent form** you have previously received to show you **agree to take part**.

If you still wish to take part in the study you will be asked to:

- attend the Movement Laboratory at the University of East Anglia three times:
 - first day of each training week (2 weeks). During these two visits some measurements will be taken and you will exercise with 2 other participants. On the first session you will be taught the training task and all information will be provided to enable you to perform the training session on your own home;

- and at the end of the study to collect the measurements as the first session.

These sessions at the Movement Laboratory will last for approximately 3 hours and will be supervised by 2 persons of the research team. Breaks and refreshments will be provided during the sessions. You are more than welcome to ask for additional breaks if you want to.

You are welcome to bring someone with you to the Movement Laboratory sessions; however, to respect the privacy of everyone else, they will have to wait in a waiting area near the laboratory during the session.

- exercise at the assigned dose (number of repetition tasks) in the same manner on your own at home 4 days a week, for 2 weeks ;
- you will be asked to complete a *Dose monitoring sheet* recording the number of repetitions and the time you spent exercising.

The intervention consists of movements of the fingers and thumb of the paretic (more affected) hand against a tailored resistance applied by a resistance-graded rubber band. The rubber band is arranged on a 3-point frame. You should insert fingers and thumb into the frame and then open your hand to take off the rubber band and then place it on a second 3-point frame. Each removal and placing of a band counts as one repetition.

This intervention is designed to increase ability to produce muscle force in your weakest hand and secondarily in the forearm. A frame and elastic bands will be given to you to exercise at home. All elastic bands are latex-free; if you are concerned about any possible allergy please feel free to speak with any member the research team about it.

Measurements

You will be assessed at two points during this trial: at the beginning of the trial and after the 2 weeks of training.

A member of the research team will look at:

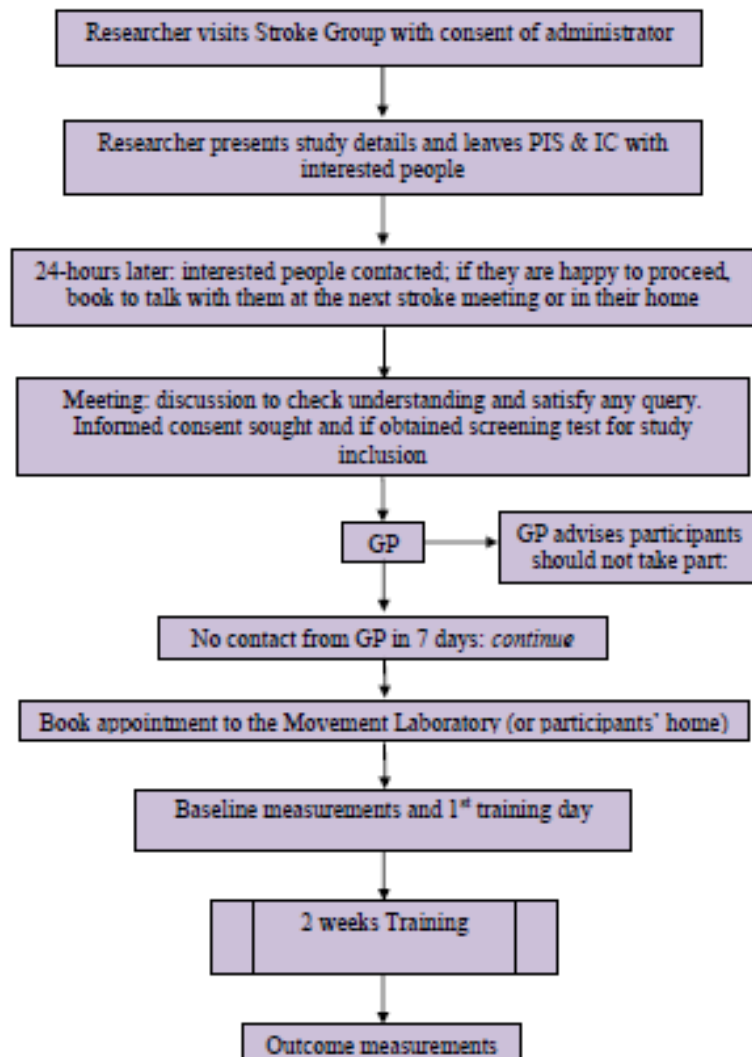
- your hand and arm strength;
- your ability to use your more affected arm in everyday activities. For example, lift different sized objects from the table onto a box in front of you;
- your brain activity in response to the intervention using Transcranial magnetic stimulation. This measurement is safe and painless and involves the use of surface electrodes placed on your skin which has been "cleaned" with an exfoliating gel beforehand. The electrodes will be placed on the skin over specific muscles of the forearm and hand. A magnetic stimulus will be given to locate the active spot over the scalp where the best connection to the specific muscles can be obtained and the strength of this connection will be investigated.

With your consent the Research Team will tell your GP that you are taking part in the study and check that there are no medical reasons why you can't take part.

You will be identified by a number. None of your personal details are given.

When you agree to take part in this study you agree to not participate in any other upper-limb rehabilitative intervention during the 2 weeks of the trial but you should continue with your usual daily activities.

Diagram to show the procedure for the study



Expenses and payments

We cannot pay you for participating in the research but will arrange and pay for any taxi journeys you may need to reach the Movement Laboratory at UEA or other travel expenses if you decide to use your own car. Taking part in the research will not cost you money.

Are there any possible risks with this study?

Although unlikely, there is a **small risk** that you may experience some pain or discomfort if you overwork your hand or arm. This will be **closely monitored**. **Therapy can be stopped at any time**. If you want to withdraw from the study simply tell us.

If there are any **questions** during the study that you **do not want to answer**, you **do not have to answer them**.

What are the possible benefits of taking part in the study?

Previous studies have shown that functional repetitive tasks **improved motor ability** of people after stroke. However we do not know the exact amount of therapy needed to reach the greatest possible benefit.

Will anyone else know that I am in this study?

With your consent we will inform your GP that you are taking part in the study. If we are concerned at any time about your health during your participation in this study we will **report these concerns** to your **GP** or the appropriate **health care professional**.

What if there is a problem?

If you have any **complaints** about the way you have been dealt with or any harm is caused during the study this will be addressed. An independent person is available for you to contact if you would like to speak with someone not involved in this study. **All contact details are available on page 10.**

What happens when the study stops?

This is the first dose-finding study of motor intervention after stroke. The results of this study will tell us whether it is possible to apply this design to investigate the Optimal Therapeutic Dose of other motor interventions.

Will my taking part in the study be kept confidential?

Yes, all the information about you and your participation in the study will be kept strictly confidential. We will follow ethical and legal practice guidelines and all information about you will be handled in confidence. The research team will only have access to information about you that is relevant to the study.

All information will be kept strictly confidential.

Information may include details such as your date of birth and the date and diagnosis of your stroke. Personal information such as your address will also be required to allow us to visit you at home.

You will be given a trial number for the purpose of collecting and analysing data.

This means you will remain anonymous.

The data will only be accessed by authorised persons within the Research Teams.

How will my information be stored?

Data will be stored securely in the research office during the study and for 5 years after the study.

All procedures for handling, processing, storage and destruction of data are compliant with the Data Protection Act 1998.

What will happen to the results of the research study?

The results of the trial will be analysed and used to justify whether dose-finding studies are applicable in motor interventions after stroke.

The results will be published in an academic journal but individual participants will not be identifiable. Part of this study will contribute to a PhD for Elisabetta Colucci (Research Physiotherapist).

Who has reviewed the study?

The NRES Ethic Committee East of England has approved the study.

Thank you for taking the time to read this information. If you choose to participate, you will keep a copy of this participant information sheet and the signed consent form.

Contact details

You can contact:

Lead research

Elisabetta Colucci

email e.colucci@uea.ac.uk

Tel: 01603593320 (please leave a message, only
Elisabetta can access it and it will be checked on a daily
basis)

Post: School of Rehabilitation Science, Postgraduate Box
1.23, Queen's Building, University of East Anglia, Norwich
Research Park, Norwich, NR4 7TJ

Academic Supervisor

Prof. Valerie Pomeroy

email: V.Pomeroy@uea.ac.uk

Tel: 1603 591438

Fax: 1603 593166

Independent contact

Andrew Walker

email: andrew.walker@uea.ac.uk

Research office Tel: 01603 591923

CONSENT FORM

Dose-finding Trial

Establishing a feasible optimal therapeutic dose using a new
methodology for stroke rehabilitation

Name of Researcher: _____

Name of Participant: _____

NB. If the potential participant is unable to write, please find an independent witness who may complete this form as verbal consent is given by the potential participant. The independent witness should read each of the 5 items to the potential participant and if the participant agrees, the independent witness should initial each of the boxes with his/her own initials.

The purpose of the independent witness is to physically complete this consent form on the instruction of a participant in the instance that the participant cannot do so for him or herself due to a physical inability to hold and or use a pen, or in the instance in which attempting to do so would or appears to cause distress to the participant. The independent witness cannot provide consent on behalf of a participant.

An independent witness must:

- *Not be part of the research team*
- *Not be managed by a member of the research team*

2 copies of this form must be completed (No photocopies):

- *1 copy for participant*
- *1 copy for researcher site file*



Acquired Brain Injury Rehabilitation Alliance (ABIRA)
School of Rehabilitation Science
Queen's Building
University of East Anglia
Norwich Research Park
Norwich
NR4 7TJ
UK

Date:

Dear Dr

I am writing to inform you that your patient (DOB.....) has consented to take part in a trial that is currently underway at the University of East Anglia. This trial is called "*Establishing a feasible optimal therapeutic dose using a new methodology for stroke rehabilitation*" and has been funded by the University of East Anglia. We are aiming to recruit participants who have been discharged from an in-patient rehabilitation ward and have been left with moderate upper-limb paresis after stroke. Please find a one page copy of the protocol.

If you have any concerns about the patient participating in the study please contact me within 10 working days of the date of this letter.

If you require any further information about the study then please contact either myself (Elisabetta Colucci) the Chief Investigator, or my supervisor Prof. Valerie Pomeroy.

Research Physiotherapist
Elisabetta Colucci
e.colucci@uea.ac.uk
Tel: 01603 593320

Prof. Valerie Pomeroy
V.Pomeroy@uea.ac.uk
Tel: 1603 591438
Fax: 1603 593166

Yours sincerely
Elisabetta Colucci

Ethics reference:
Version 1.0, 08/10/2013

Establishing a feasible optimal therapeutic dose using a new methodology for stroke rehabilitation

Description of Intervention:

The training task delivered in this research trial involves a synergistic extension and abduction movements of the fingers and thumb of the paretic hand against a tailored resistance applied by resistance-graded rubber bands. The rubber bands are arranged on a three point frame (see Fig 1). This intervention is designed to increase ability to produce and modulate voluntary force in antagonistic muscle groups in contra-lesional hand (more affected) and secondarily in the forearm. Participants should insert fingers and thumb into the frame and then open their hand (extend and abduct fingers and thumb) to take off a rubber band and then, place it on a second, identical, frame (see Fig 2). Each removal and placing of a band counts as one repetition. Participants should move the band from one three-point frame to the other and back again for the number of repetitions assigned. On the first session of training the research therapist will demonstrate the task; participant will then perform five practice repetitions of the task with the ipsi-lesional hand before starting the training with the contra-lesional hand. Participants will be asked to train 5 days per week for 2 consecutive weeks at the assigned training dose (number of repetitions).

Fig 1. Three-point frame device with rubber band



Fig 2. Training task sequence



Primary objectives of this research study are to:

- assess participants' acceptability of this dose-finding trial design;
- verify feasibility of the delivering intervention and capability of identifying the optimal therapeutic dose (OTD).

Inclusion criteria:

People who were discharged from in-patient rehabilitation wards which have moderate paresis after stroke. In detail:

- adults aged 18+ years;
- presence of moderate upper limb paresis/impairment defined as participants able to open and close their paretic hand six times in one minute but unable to do this 25 times in one minute, with an extra, light resistance band placed around fingers and thumb;
- able to imitate action with the non-paretic upper limb ;
- participants should be discharged from stroke rehabilitation services and thus not be receiving therapy to improve upper limb motor function.

Research Physiotherapist: Colucci Elisabetta
Contact details: e.colucci@uea.ac.uk
01603 593320
Ethics reference:

Dose-Finding Study

Protocol version 3: 08 October 2013
Version 1 Date 11/11/2013

Participant Screening Form

Date / /
Researcher ID:
Stroke Group

Forename
Surname

Inclusion Criteria

Potential Participant able to able to open and close your most affected hand six times in one minute with an extra-extra-light resistance band

Y N

Potential Participant unable to do this 25 times in one minute with an extra-extra-light resistance band

Y N

Potential Participant able to able to imitate with the less affected arm:

Attempts 1 2 3 4 5 = TOT result

0= action NOT reproduced

1= INCORRECTLY reproduced action

2= CORRECTLY reproduced action

Participant is included if scoring 8/10 or above

Satisfactory Inclusion Criteria: Y N

Appendix F : NRES final ethic Approval



Health Research Authority

NRES Committee East of England - Norfolk
Nottingham REC Centre
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839368

07 February 2014

Mrs Elisabetta Colucci
Post-graduate research student
University of East Anglia
School of Rehabilitation Sciences, Queen's Building
Norwich Research Park
Norwich
NR4 7TJ

Dear Mrs Colucci

Study title:	Establishing a feasible optimal therapeutic dose using a new methodology for stroke rehabilitation
REC reference:	14/EE/0005
Protocol number:	n/a
IRAS project ID:	102281

Thank you for your letter of 29 January 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Lead Reviewer.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Ms Tracy Leavesley, NRESCommittee.EastofEngland-Norfolk@nhs.net

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

I am pleased to confirm that the favourable opinion applies to the following research site(s), subject to site management permission being obtained prior to the start of the study at the site (see under 'Conditions of the favourable opinion below').

Research Site	Principal Investigator / Local Collaborator
Movement Laboratory	Professor Valerie Pomeroy

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.r4forum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Covering Letter	Letter from Elisabetta Colucci	28 November 2013
Evidence of Insurance or Indemnity	University of East Anglia	28 November 2013
Evidence of Insurance or Indemnity	Zurich Municipal Public Liability Insurance	22 May 2013
Evidence of Insurance or Indemnity	Zurich Municipal Professional Negligence Insurance	22 May 2013
GP/Consultant Information Sheets	1.0	08 October 2013
Investigator CV	Elisabetta Colucci	21 November 2013
Investigator CV	Valerie M Pomeroy	14 March 2013
Other: Dose monitoring sheet	2.0	08 October 2013
Participant Consent Form: Dose-Finding Trial	2.0	08 October 2013
Participant Information Sheet	2.1	28 January 2014
Protocol	3.0	08 October 2013
REC application	102281/533068/1/245	26 November 2013
REC application	IRAS SSA form 102281/533061/7/403/204728/28 6454	26 November 2013
Response to Request for Further Information	Email from Elisabetta Colucci	29 January 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document 'After ethical review – guidance for researchers' gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

14/EE/0005	Please quote this number on all correspondence
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We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

With the Committee's best wishes for the success of this project.

Yours sincerely



Dr Michael Sheldon
Chair

Email: NRESCommittee.EastofEngland-Norfolk@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Mrs Susan Steel

Appendix G Dose-finding monitoring sheet

P. ID |D|F|-|_|_|_|_|_| Date |_|_|-|_|_|-|_|_|_|_|_| (DD-MM-YYYY) Version 2.0 08/10/2013

Dose monitoring sheet DAY 1 week1 (Lab session)

Number of repetition ASSIGNED:

Number of repetitions ACHIEVED today:

If you **NOT** complete the assigned number of task repetitions **Why?** Choose from the following:

- | | |
|---|--|
| <input type="checkbox"/> NO TIME/ too Busy | <input type="checkbox"/> PAIN or discomfort on my affected hand or arm |
| <input type="checkbox"/> I was BORED | <input type="checkbox"/> The numbers of repetitions were TOO MUCH |
| <input type="checkbox"/> I was TIRED | <input type="checkbox"/> I CANNOT DO it/ I am not able to do it |
| <input type="checkbox"/> I was SICK or not well | |

Other: (please specify)

How long did you exercise today (total duration in minutes):

How did you find the training? (Chose one or more from the following options):

- | | | |
|--|--|---|
| <input type="checkbox"/> Too Difficult | <input type="checkbox"/> Barely Doable | <input type="checkbox"/> Feasible |
| <input type="checkbox"/> Annoying | <input type="checkbox"/> Stimulating | <input type="checkbox"/> TOO MUCH intense |

Other: (please specify)

Did you notice any pain or discomfort due to the training? YES NO

If YES please specify:.....

Did you notice any improvement in the paretic hand/arm? YES NO

If YES please specify:.....

Any more comments:.....

.....

Appendix H : Dose finding Outcome W1

Dose-Finding Study

Visit 1, Week 1 Baseline Page 1

Protocol version 3: 08 October 2013
CRF Version 1 Date 11/11/2013

Participant Number	Initials	Date of Visit
D _F_ / _ _ _ _ _ _	_ _ _	_ _ _ _ _ _ _ _ _ D D M M Y Y

Machine code: |_|_|

Visit 1, Week 1 Baseline measurements:

Assessor ID
|_|_|_|

AGE: |_|_|_|

GENDER: |_|

TIME SINCE STROKE: |_|_| YEARS |_|_| MONTHS

SIDE OF STROKE: Left / Right (delete as appropriate)

DOMINANTE SIDE AFFECTED: Y / N

HAND BREADTH: (taken from the less affected hand)

|_|_|_| CM from the top of the 3rd finger to the base of the wrist with fingers extended and adducted

|_|_|_| CM from the top of the 1st finger to the top of the little finger with fingers extended and completely abducted

Dose-Finding Study

Visit 1, Week 1 Baseline Page 2

Protocol version 3: 08 October 2013
CRF Version 1 Date 11/11/2013

Participant Number _D_ _F_ / _ _ _ _ _	Initials _ _ _	Date of Visit _ _ _ _ _ _ _ _ D D M M Y Y
--	--------------------	---

Assessor ID
|_|_|_|

1. CANDO DIGIT-EXTEND

I. Was the Cando Digit-Extend Test conducted? Yes No

If NO, gives reason

Participant did not attend

Participant refused

Participant unable/unwell

II. Number of times a participant can open and close their hand with a beige band in one minute

|_|_|_|

III. Highest level of resistance against which two reps are possible in one minute:

Band colour	COMPLETED	UNABLE	number completed if unable
beige	<input type="checkbox"/>	<input type="checkbox"/>	_
yellow	<input type="checkbox"/>	<input type="checkbox"/>	_
red	<input type="checkbox"/>	<input type="checkbox"/>	_
green	<input type="checkbox"/>	<input type="checkbox"/>	_
blue	<input type="checkbox"/>	<input type="checkbox"/>	_

Dose-Finding Study

Visit 1, Week 1 Baseline Page 3

Protocol version 3: 08 October 2013
CRF Version 1 Date 11/11/2013

Participant Number _D_ _F_ _ / _ _ _ _	Initials _ _ _	Date of Visit _ _ _ _ _ _ _ _ D D M M Y Y
--	--------------------	---

Assessor ID
|_|_|_|

2. UPPER LIMB STRENGTH

Grp Force and Pinch Force paretic upper limb

I. Did the participant attend the strength test? Yes No

I. Hand Grp Force

a. Trial 1 |_|_|_|_| kg

OR Not attempted

If not attempted, reason why:

Participant unable to understand instructions

Participant refused

Other

If Other, specify

b. Trial 2 |_|_|_|_| Kg

OR Not attempted

If not attempted, reason why:

Participant unable to understand instructions

Participant refused

Other

If Other, specify

c. Trial 3 |_|_|_|_| kg

OR Not attempted

If not attempted, reason why:

Participant unable to understand instructions

Participant refused

Other

If Other, specify

Dose-Finding Study

Protocol version 3: 08 October 2013
CRF Version 1 Date 11/11/2013

Participant Number	Initials	Date of Visit
_ _ _ _ _ _ _ _ _ _ _ _ _ _ _	_ _ _ _ _	_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ D D M M Y Y

UPPER LIMB STRENGTH (continue)

ii. Pinch Grp Force

a. Trial 1 |_|_|_|_|_|_|_|_|_| kg

OR Not attempted

If not attempted, reason why:

Participant unable to understand instructions

Participant refused

Other

If Other, specify

b. Trial 2 |_|_|_|_|_|_|_|_|_| kg OR

Not attempted

If not attempted, reason why:

Participant unable to understand instructions

Participant refused

Other

If Other, specify

c. Trial 3 |_|_|_|_|_|_|_|_|_| kg

OR Not attempted

If not attempted, reason why:

Participant unable to understand instructions

Participant refused

Other

If Other, specify

Dose-Finding Study

Visit 1, Week 1 Baseline Page 5

Protocol version 3: 08 October 2013
CRF Version 1 Date 11/11/2013

Participant Number _D_ _F_ _ _ _ _ _ _	Initials _ _ _ _	Date of Visit _ _ _ _ _ _ _ _ _ _ _ _ <small>D D M M Y Y</small>
--	----------------------	--

Assessor ID
|_|_|_|_|

3. Modified Box and Bloes test (mBBT)

I. Was the mBBT conducted? Yes No

If NO, gives reason

Participant did not attend

Participant refused

Participant unable/unwell

a. Trial 1 (tennis ball) number of tasks in 1 minute _____ OR Not attempted

If not attempted, reason why:

Participant unable to understand instructions

Participant refused

Other

If Other, specify

b. Trial 2 (2,5 cm cubes) number of tasks in 1 minute _____ OR Not attempted

If not attempted, reason why:

Participant unable to understand instructions

Participant refused

Other

If Other, specify

c. Trial 2 (5 cm cubes) number of tasks in 1 minute _____ OR Not attempted

If not attempted, reason why:

Participant unable to understand instructions

Participant refused

Other

If Other, specify

Dose-Finding Study

Visit 1, Week 1 Baseline Page 6

Protocol version 3: 08 October 2013
CRF Version 1 Date 11/11/2013

Participant Number	Initials	Date of Visit
_ _ _ _ _ _ _ _ _ _ _ _ _	_ _ _	_ _ _ _ _ _ _ _ _ _ _
		D D M M Y Y

Visit 1, Week 1 Baseline: Transcranial Magnetic Stimulation TMS

_____	_____	_____
Name (PRINT)	Signature (Person completing the form)	D D M M Y Y Y Y

Dose-Finding Study

Visit 1, Week 1 Baseline Page 7

Protocol version 3: 08 October 2013
CRF Version 1 Date 11/11/2013

Participant Number _D_ _F_ / _ _ _ _ _ _ _ _	Initials _ _ _ _	Date of Visit _ _ _ _ _ _ _ _ _ _ _ _ D D M M Y Y
--	----------------------	---

Assessor ID
|_|_|_|_|

A. Transcranial Magnetic Stimulation (TMS)

1. Did participant attend? YES NO
- If no, specific Reason:
- Participant declined
- Participant unable to attend
- Other
- If other please specify _____
- If Yes, time of day |_|_|:|_|_| hrs (24 hour clock)

B. Rest Biceps (non-paretic arm)

With the arm supported and palm facing upwards ask the participant to raise their forearm away from the support (i.e. flexing elbow) and to hold forearm there (assessor to demonstrate).

1. Was at rest threshold found? YES NO
- If Yes, stimulator output at threshold |_|_|_| %
- If No, go to section C

	Percentage of Rest threshold	Frame Number	Stimulator Output Intensity (%)
(I)	a) 100%	_ _ _	_ _ _ %
	b) 100%	_ _ _	_ _ _ %
	c) 100%	_ _ _	_ _ _ %
	d) 100%	_ _ _	_ _ _ %
	e) 100%	_ _ _	_ _ _ %

Dose-Finding Study

Visit 1, Week 1 Baseline Page 8

Protocol version 3: 08 October 2013
CRF Version 1 Date: 11/11/2013

Participant Number _ _ _ _ _F_ _ _ _ _ _ _ _ _ _	Initials _ _ _ _ _	Date of Visit _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ D D M M Y Y
--	------------------------	---

(II)	a) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	b) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	c) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	d) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	e) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
(III)	a) 120%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	b) 120%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	c) 120%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	d) 120%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	e) 120%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
(IV)	a) 130%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	b) 130%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	c) 130%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	d) 130%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	e) 130%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %

C. Rest Wrist Extension (non-paretic arm)

With the arm supported and palm facing downwards as the participant to raise their palm away from the support (i.e. extending wrist) and to hold the hand there (assessor to demonstrate)

Visual feedback will be given to maintain 10% of MVC (maximum voluntary contraction).

1. Was the at rest threshold found? YES NO
 If Yes, stimulator output at threshold |_|_|_|_| %
 If No, go to section D

Dose-Finding Study

Visit 1, Week 1 Baseline Page 9

Protocol version 3: 08 October 2013
CRF Version 1 Date 11/11/2013

Participant Number _P_ _F_ / _ _ _ _ _	Initials _ _ _	Date of Visit _ _ _ _ _ _ _ _ D M M Y Y
--	--------------------	---

	Percentage of Rest threshold	Frame Number	Stimulator Output Intensity (%)
(I)	a) 100%	_ _ _	_ _ _ %
	b) 100%	_ _ _	_ _ _ %
	c) 100%	_ _ _	_ _ _ %
	d) 100%	_ _ _	_ _ _ %
	e) 100%	_ _ _	_ _ _ %
(II)	a) 110%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	b) 110%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	c) 110%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	d) 110%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	e) 110%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
(III)	a) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	b) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	c) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	d) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	e) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
(IV)	a) 130%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	b) 130%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	c) 130%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %

Dose-Finding Study

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Protocol version 3: 08 October 2013

CRF Version 1 Date 11/11/2013

Participant Number _D_ _F_ / _ _ _ _ _ _ _ _	Initials _ _ _ _ _	Date of Visit _ _ _ _ _ _ _ _ _ _ _ _ _ _ D D M M Y Y
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d) 130%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
e) 130%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %

D. Rest Biceps (paretic arm)

With the arm supported and palm facing upwards ask the participant to raise their forearm away from the support (i.e. flexing elbow) and to hold forearm there (assessor to demonstrate).

1. Was at rest threshold found? YES NO
 If Yes, stimulator output at threshold |_|_|_|_| %
 If No, go to section E

	Percentage of Rest threshold	Frame Number	Stimulator Output Intensity (%)
(I)	a) 100%	_ _ _ _	_ _ _ _ %
	b) 100%	_ _ _ _	_ _ _ _ %
	c) 100%	_ _ _ _	_ _ _ _ %
	d) 100%	_ _ _ _	_ _ _ _ %
	e) 100%	_ _ _ _	_ _ _ _ %
(II)	a) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	b) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	c) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	d) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	e) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %

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Participant Number _P_ _F_ / _ _ _ _ _ _	Initials _ _ _ _	Date of Visit _ _ _ _ _ _ _ _ _ _ _ _ D D M M Y Y
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	d) 100%	_ _ _	_ _ _ %
	e) 100%	_ _ _	_ _ _ %
(II)	a) 110%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	b) 110%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	c) 110%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	d) 110%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	e) 110%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
(III)	a) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	b) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	c) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	d) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	e) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
(IV)	a) 130%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	b) 130%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	c) 130%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	d) 130%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	e) 130%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %

F. Rest Thumb Abduction (non-paretic hand)

With the arm and hand supported palm facing up as the participant to move their thumb away from their hand (thumb abduction) and to hold that position (assessor to demonstrate).

Dose-Finding Study

Protocol version 3: 08 October 2013
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Participant Number _ _ _ _ _F_ _ _ _ _ _ _ _ _ _	Initials _ _ _ _ _	Date of Visit _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ D D M M Y Y
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1. Was at rest threshold found? Yes No
 If Yes, stimulator output at threshold _____ %
 If No, go to section G

	Percentage of Rest threshold	Frame Number	Stimulator Output Intensity (%)
(I)	a) 100%	_ _ _ _	_ _ _ _ %
	b) 100%	_ _ _ _	_ _ _ _ %
	c) 100%	_ _ _ _	_ _ _ _ %
	d) 100%	_ _ _ _	_ _ _ _ %
	e) 100%	_ _ _ _	_ _ _ _ %
(II)	a) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	b) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	c) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	d) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	e) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
(III)	a) 120%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	b) 120%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	c) 120%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	d) 120%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	e) 120%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %

Dose-Finding Study

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Participant Number _ _ _ _ _F_ _ _ _ _ _ _ _ _ _	Initials _ _ _ _ _	Date of Visit _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ D D M M Y Y
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(iv)	a) 130%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	b) 130%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	c) 130%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	d) 130%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	e) 130%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %

F. Rest Thumb Abduction (paretic hand)

With the arm and hand supported palm facing up as the participant to move their thumb away from their hand (thumb abduction) and to hold that position (assessor to demonstrate).

1. Was at rest threshold found? Yes No
 If Yes, stimulator output at threshold |_|_|_|_| %
 If No, go to question I

	Percentage of Rest threshold	Frame Number	Stimulator Output Intensity (%)
(i)	a) 100%	_ _ _ _	_ _ _ _ %
	b) 100%	_ _ _ _	_ _ _ _ %
	c) 100%	_ _ _ _	_ _ _ _ %
	d) 100%	_ _ _ _	_ _ _ _ %
	e) 100%	_ _ _ _	_ _ _ _ %
	a) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %
	b) 110%	_ _ _ _ <input type="checkbox"/> Not applicable	_ _ _ _ %

Dose-Finding Study

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Participant Number _P_ _F_ / _ _ _ _ _ _	Initials _ _ _ _	Date of Visit _ _ _ _ _ _ _ _ _ _ D D M M Y Y
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(II)	c) 110%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	d) 110%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	e) 110%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
(III)	a) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	b) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	c) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	d) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	e) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
(IV)	a) 130%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	b) 130%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	c) 130%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	d) 130%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	e) 130%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %

G. Stimulate the non-stroke hemisphere, record Ipsilateral activation of paretic biceps

With arm supported and palm facing upwards ask the participant to raise their forearm away from the support (i.e. flexing elbow) and to hold forearm there (assessor to demonstrate).

Please use at rest threshold found in section B "Active Biceps Movement (non-paretic arm)" as the 100% level to calculate the below thresholds.

Percentage of Rest threshold	Frame Number	Stimulator Output Intensity (%)
a) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %

Dose-Finding Study

Visit 1, Week 1 Baseline Page 16

Protocol version 3: 08 October 2013
 CRF Version 1 Date 11/11/2013

Participant Number _D_ _F_ / _ _ _ _ _ _ _ _	Initials _ _ _ _	Date of Visit _ _ _ _ _ _ _ _ D D M M Y Y
--	----------------------	---

(I)	b) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	c) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	d) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	e) 120%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
(II)	a) 140%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	b) 140%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	c) 140%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	d) 140%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	e) 140%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
(III)	a) 160%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	b) 160%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	c) 160%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	d) 160%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %
	e) 160%	_ _ _ <input type="checkbox"/> Not applicable	_ _ _ %

Appendix I : Dose finding Outcome W3

Dose-Finding Study

Visit 3, Outcome measurements Page 1

Protocol version 3: 08 October 2013
CRF Version 1 Date 11/11/2013

Participant Number _D_ _F_ / _ _ _ _ _ _ _ _	Initials _ _ _ _	Date of Visit _ _ _ _ _ _ _ _ D D M M Y Y
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Machine code: |_|_|

Visit 3

Outcome measurements:

Assessor ID
|_|_|_|

1. CANDO DIGIT-EXTEND

- i. Was the Cando Digit-Extend Test conducted? Yes No

If NO, gives reason

Participant did not attend

Participant refused

Participant unable/unwell

- ii. Number of times a participant can open and close their hand with a beige band in one minute

|_|_|_|

- iii. Highest level of resistance against which two reps are possible in one minute:

Band colour	COMPLETED	UNABLE	number completed if unable
beige	<input type="checkbox"/>	<input type="checkbox"/>	_
yellow	<input type="checkbox"/>	<input type="checkbox"/>	_
red	<input type="checkbox"/>	<input type="checkbox"/>	_
green	<input type="checkbox"/>	<input type="checkbox"/>	_
blue	<input type="checkbox"/>	<input type="checkbox"/>	_

Appendix J : Medical screening

Participant Number	Initials	Date of Visit
_ _ _	_ _ _	_ _ _ _ _ _ _
		D D M M Y Y Y Y



Medical Screening Questionnaire

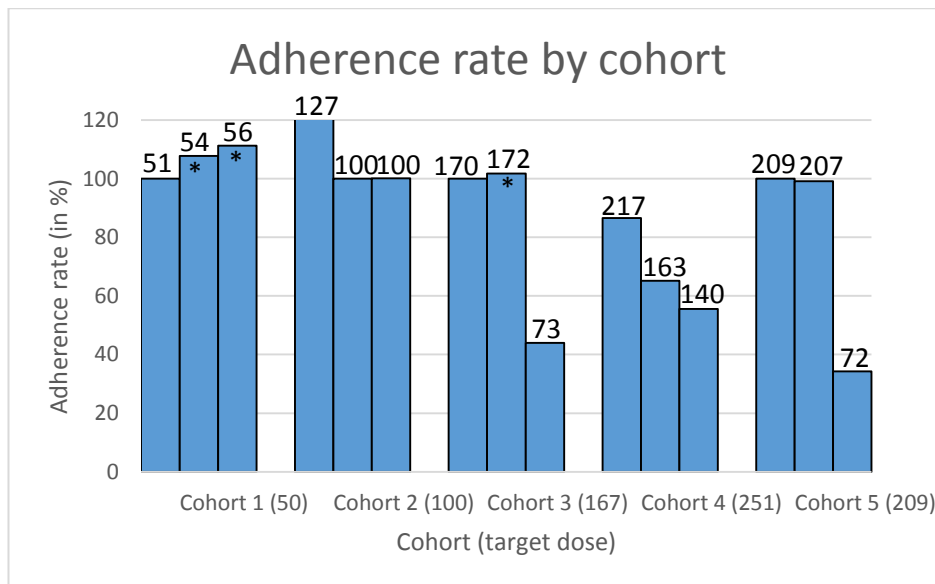
Please answer the following questions. When you are finished the researcher will go over the answers with you.

Thank you.

Question	Yes	No
1. Do you have a heart pacemaker, artificial heart valves, pacing wires or defibrillator?		
2. Do you have any implanted devices (e.g. programmable hydrocephalus shunt; nerve stimulator; cochlear implant; aneurysm clip; insulin, drug or infusion pump)?		
3. Have you had any surgery to your head (including ears/eyes/brain), neck or spine?		
4. Have you ever sustained any injuries involving metal to the eyes or any other part of the body?		
5. Have you ever had a fit or blackout, or do you have epilepsy?		
6. Have you ever had an MRI?		

Appendix K : Participants' adherence rates

Figure 7-1: Participants' adherence rates (in %) by cohort and participants' mean number of daily repetitions



Notes: the vertical bars reports adherence rate; the x bar reports cohort of study and numbers of assigned repetitions (in parenthesis). Figures above the bars shown average number of daily repetitions achieved in the training period.

(*) Participants who were considered adherent but did not fully comply with the target dose for reasons not related to the trial or the dose.

Appendix L : TMS results

Change on MEP amplitude

Following the data on MEP amplitude in response to a 100% of the motor threshold are reported at pre and post intervention points for all the three assessed muscle for all participants on affected and unaffected side. Acknowledging the relationship between MEP amplitude and stimulus intensity, the changes in MEP amplitude in response to a 110%, 120% and 130% of the recruitment curve (RC) are reported.

Biceps brachii

Table 7-1 shows MEP amplitude at 100% of the RC at pre and post intervention on BB muscle for all participants on affected and unaffected side. Changes of amplitude from pre to post intervention are reported in the table as well as in Figure 7.18.

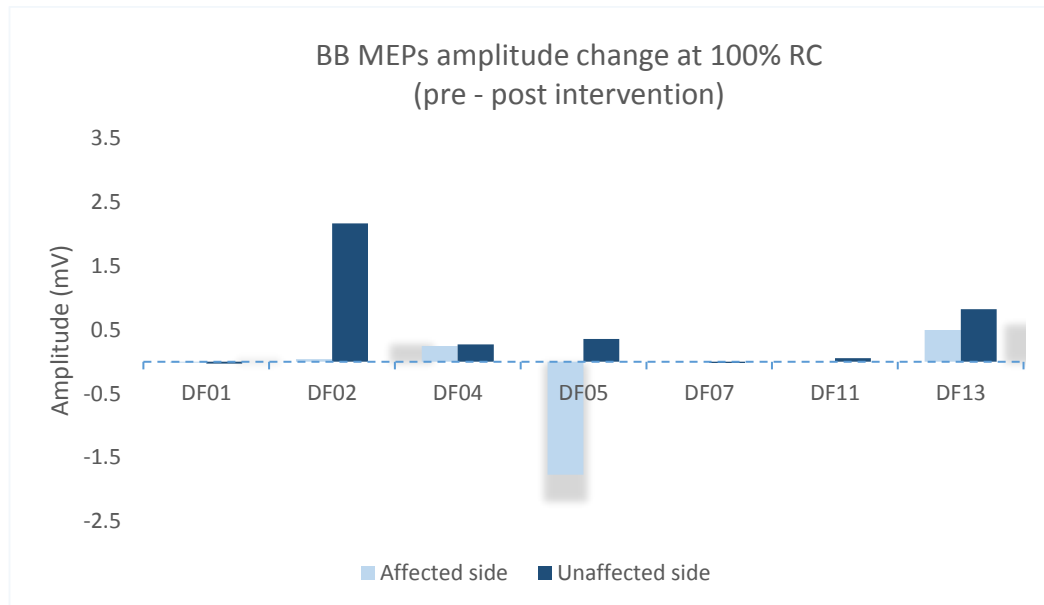
Table 7-1: MEP amplitude at 100% of the recruitment curve (RC) on biceps brachii muscle (BB) at baseline (pre intervention) and outcome (post intervention) for all participants on affected and unaffected side.

BB 100% RC							
Cohort (dose)	Participant	Affected side			Unaffected side		
		Baseline ^a	Outcome ^a	Change ^a	Baseline ^a	Outcome ^a	Change ^a
1(50)	DF01	0.3730	0.3613	-0.0117	0.2275	0.1968	-0.0308
1(50)	DF02	0.1764	0.2197	0.0433	1.0918	3.2598	2.1680
2(100)	DF04	0.4263	0.6714	0.2451	0.2046	0.4761	0.2715
2(100)	DF05	1.9540	0.7539	-1.7690	0.1914	0.5503	0.3589
3(167)	DF07	.	0.3657	.	0.1606	0.1421	-0.0186
4(251)	DF11	.	0.2183	.	0.0781	0.1367	0.0586
5(209)	DF13	0.0757	0.5752	0.4995	0.1333	0.9575	0.8242

Notes: (a)= MEP amplitude in mVolts. The dots represent when a resting motor threshold could not be obtained.

As expected, from this table I can see that there is individual heterogeneity in excitability and MEP amplitude between brain sides as well as between participants. More consistent responses are found in the unaffected side.

Figure 7-2: Changes in MEP amplitude from pre to post intervention on biceps brachii muscle (BB) at 100% of the RC for all participants on affected and unaffected side.



Notes: the bars represents the difference in excitability identified by changes in MEP amplitude for each participants from pre to post intervention for affected (light blue bars) and unaffected (dark blue bars) side.

Consistently with Table 7-1, Figure 9-2 shows that some participants increased and some decreased in the affected side (light blue bars). Whereas, more consistency was found in the unaffected side (dark blue bars).

Table 7-2 shows changes in MEP amplitude at 110% 120% and 130% of the RC from pre to post intervention on BB muscle for all participants on affected and unaffected side.

Table 7-2: Changes in MEPs amplitude at 110%, 120% and 130% of the RC at baseline (pre intervention) and outcome (post intervention) on biceps brachii muscle (BB) for all participants on affected and unaffected side.

BB		Affected side			Unaffected side		
Cohort (dose)	Participant	Change at 110% RC ^a	Change at 120% RC ^a	Change at 130% RC ^a	Change at 110% RC ^a	Change at 120% RC ^a	Change at 130% RC ^a
1(50)	DF01	.	.	.	-0.192	-0.015	.
1(50)	DF02	.	.	.	-0.687	0.229	-1.34326
2(100)	DF04	0.331	0.139	.	1.356	1.278	1.256836
2(100)	DF05	-0.415	0.354	4.970703	0.412	0.635	.
3(167)	DF07	.	.	.	-0.082	-0.308	-0.6084
4(251)	DF11	.	.	.	0.073	.	.
5(209)	DF13	0.754	.	.	0.795	1.491	.

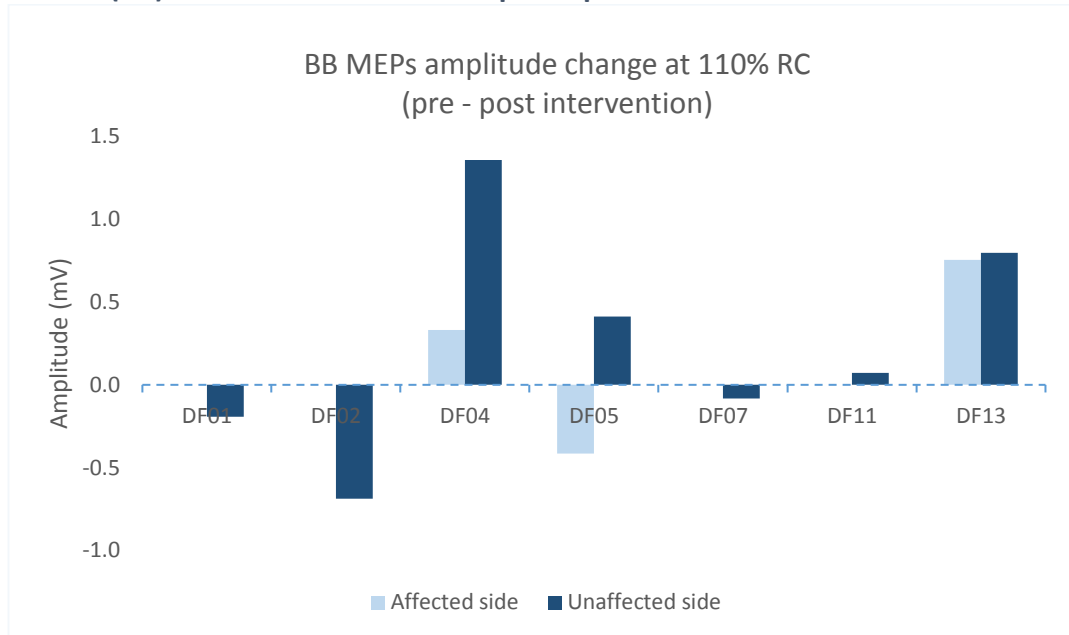
Notes: (a)= MEP amplitude in mVolts. The dots represent when a resting motor threshold could not be obtained.

From this table it can be seen that there are individual differences in excitability and MEP amplitude between brain sides as well as between participants. More consistent responses are found in the unaffected side.

Figure 7-3, Figure 7-4 and Figure 7-5 show the changes in the BB muscle at 110%, 120% and 130% of the RC for all participants respectively.

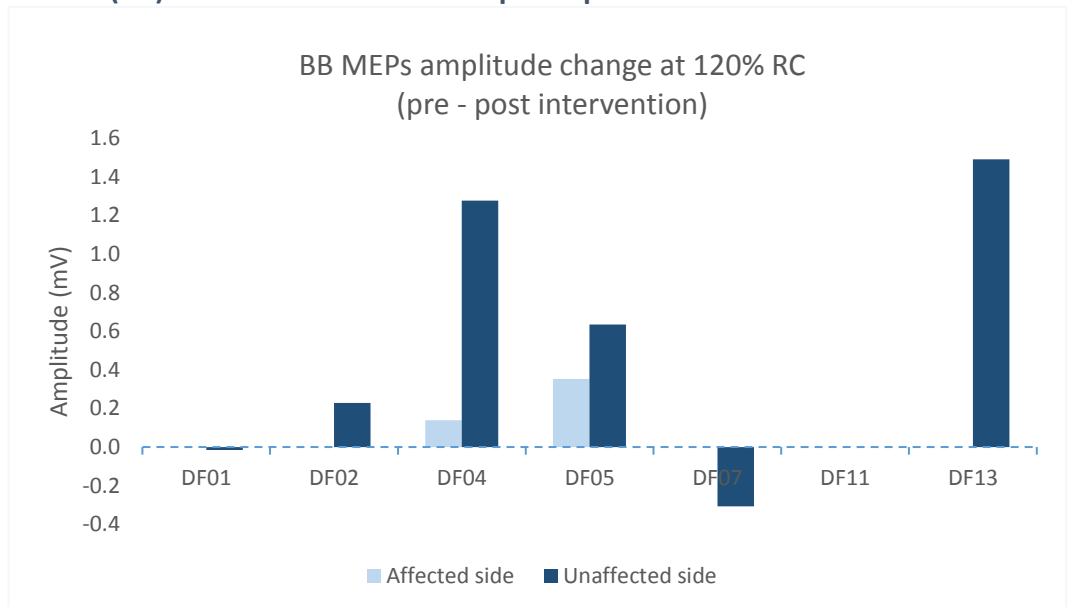
As with Table 7-2, Figure 7-3 to Figure 7-5 show that in both sides some participants increased and some decreased. More consistent responses are found in the unaffected side. As expected, as the stimulus (%RMT) increases less muscle responses are seen in the affected side. This is because the motor threshold had to be higher.

Figure 7-3: Changes in MEPs amplitude from pre to post intervention on biceps brachii muscle (BB) at 110% of the RC for all participants on affected and unaffected side.



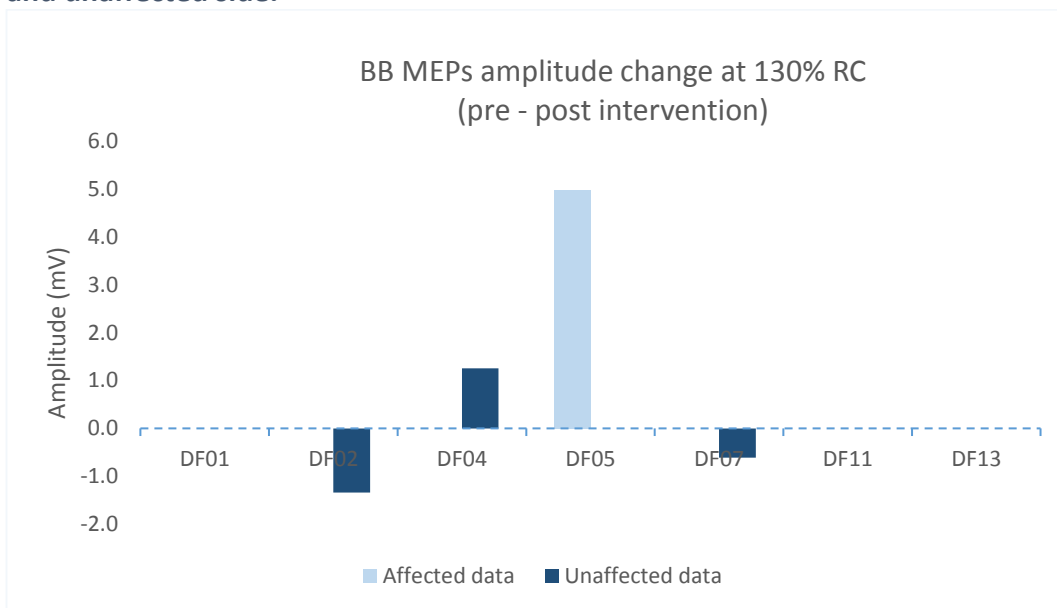
Notes: the bars represents the difference in excitability identified by changes in MEP amplitude for each participants from pre to post intervention for affected (light blue bars) and unaffected (dark blue bars) side.

Figure 7-4: Changes in MEPs amplitude from pre to post intervention on biceps brachii muscle (BB) at 120% of the RC for all participants on affected and unaffected side.



Notes: the bars represents the difference in excitability identified by changes in MEP amplitude for each participants from pre to post intervention for affected (light blue bars) and unaffected (dark blue bars) side.

Figure 7-5: Changes in MEPs amplitude from pre to post intervention on biceps brachii muscle (BB) at 130% of the RC for all participants on affected and unaffected side.



Notes: the bars represents the difference in excitability identified by changes in MEP amplitude for each participants from pre to post intervention for affected (light blue bars) and unaffected (dark blue bars) side.

Extensor carpi radialis

Table 7-3 shows MEPs amplitude at 100% of the RC from pre to post intervention on ECR muscle for all participants on affected and unaffected side. Changes of amplitude from pre to post intervention are reported in the table and in Figure 7-6.

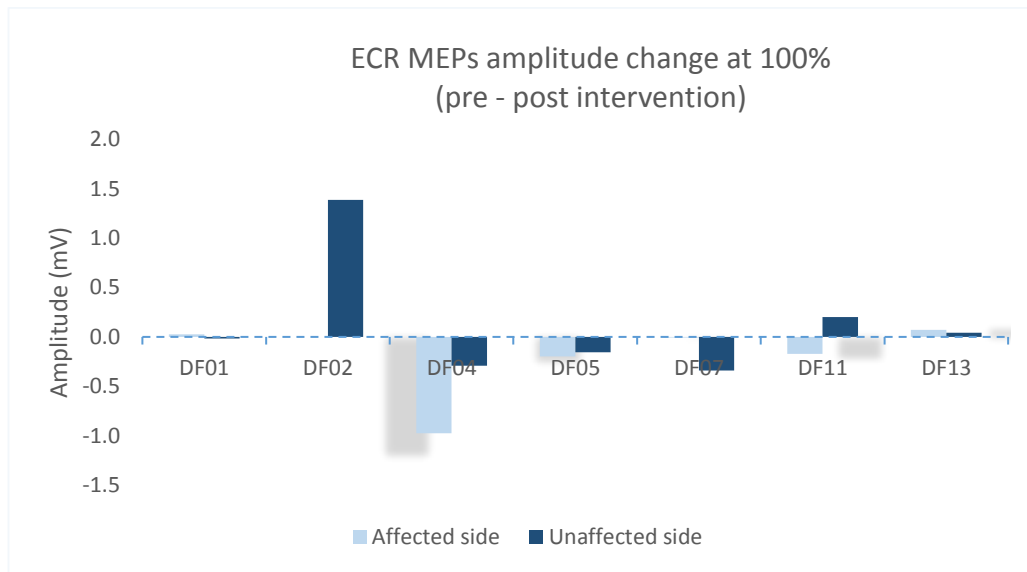
Table 7-3: MEPs amplitude at 100% of the recruitment curve (RC) at baseline (pre intervention) and outcome (post intervention) on extensor carpi radialis muscle (ECR) for all participants on affected and unaffected side.

ECR 100% RC							
		Affected side			Unaffected side		
Cohort (dose)	Participant	Baseline ^a	Outcome ^a	Change ^a	Baseline ^a	Outcome ^a	Change ^a
1(50)	DF01	0.712	0.738	0.026	0.190	0.172	-0.018
1(50)	DF02	0.863			1.098	2.487	1.389
2(100)	DF04	1.213	0.237	-0.976	1.016	0.724	-0.292
2(100)	DF05	1.040	0.842	-0.198	0.448	0.293	-0.155
3(167)	DF07	0.230	0.224	-0.007	0.620	0.280	-0.339
4(251)	DF11	1.009	0.838	-0.171	0.200	0.401	0.201
5(209)	DF13	0.329	0.398	0.070	0.584	0.626	0.042

Notes: (a)= MEP amplitude in mVolts. The dots represent when a resting motor threshold could not be obtained.

As expected, from this table it can be seen that there were more responses and more consistency on ECR muscle than on BB muscle. However, some heterogeneity in the changes on excitability between participants are reported.

Figure 7-6: Changes in MEPs amplitude from pre to post intervention on extensor carpi radialis muscle (ECR) at 100% of the recruitment curve (RC) for all participants on affected and unaffected side.



Notes: the bars represents the difference in excitability identified by changes in MEP amplitude for each participants from pre to post intervention for affected (light blue bars) and unaffected (dark blue bars) side.

Table 7-3 and Figure 7-6 shows that again, some participants increased and some decreased brain excitability. More consistency in the responses between hemisphere sides is found in ECR muscle than BB muscle.

Table 7-4 shows changes in MEP amplitude at 110% 120% and 130% of the RC from pre to post intervention on ECR muscle for all participants on affected and unaffected side.

Table 7-4: Changes in MEPs amplitude at 110%, 120% and 130% of the RC at baseline (pre intervention) and outcome (post intervention) on extensor carpi radialis muscle (ECR) for all participants on affected and unaffected side.

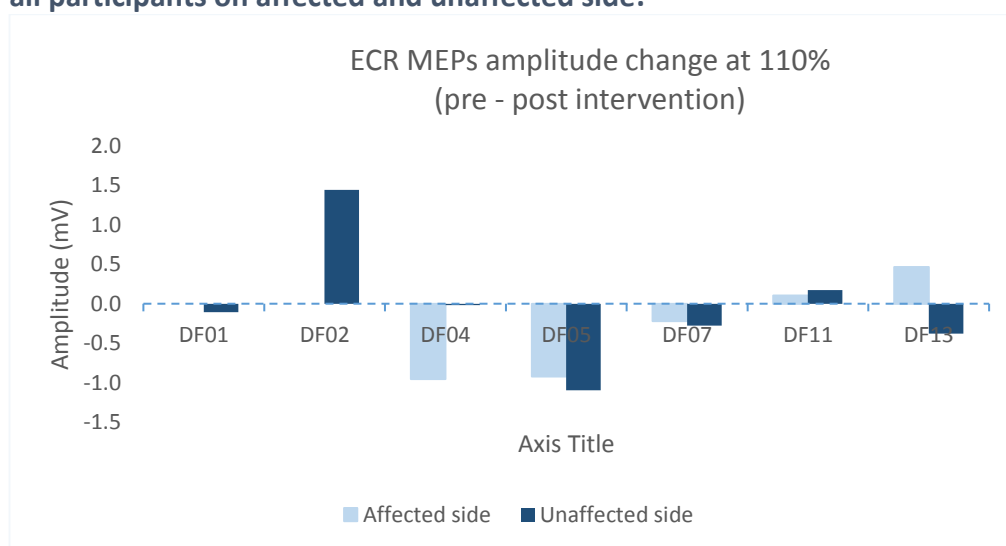
ECR		Affected side			Unaffected side		
Cohort (dose)	Participant	Change at 110% RC ^a	Change at 120% RC ^a	Change at 130% RC ^a	Change at 110% RC ^a	Change at 120% RC ^a	Change at 130% RC ^a
1(50)	DF01	.	.	.	-0.107	-0.157	.
1(50)	DF02	.	.	.	1.439	-0.036	0.355
2(100)	DF04	-0.955	0.237	0.804	-0.016	-0.08	0.533
2(100)	DF05	-0.923	-0.769	-1.063	-1.097	-1.333	-1.821
3(167)	DF07	-0.222	-0.375	0.036	-0.278	0.023	-0.03
4(251)	DF11	0.104	-0.405	-0.054	0.172	0.278	0.07
5(209)	DF13	0.462	0.744	-1.172	-0.379	0.201	0.012

Notes: (a)= MEP amplitude in mVolts. The dots represent when a resting motor threshold could not be obtained.

From this table, as before, it can be seen that there are individual differences in excitability and MEP amplitude between brain sides as well as between participants. More consistent responses are found in the unaffected side.

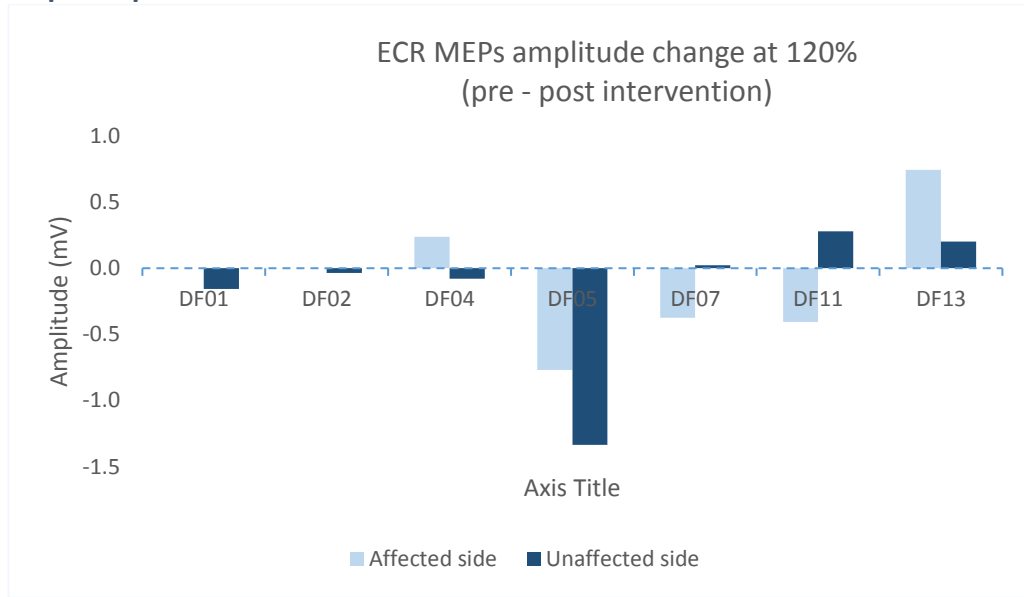
Figure 7-7, Figure 7-8, and Figure 7-9 show the changes in the ECR muscle at 110%, 120% and 130% of the RC for all participants respectively.

Figure 7-7: Changes in MEPs amplitude from pre to post intervention on extensor carpi radialis muscle (ECR) at 110% of the recruitment curve (RC) for all participants on affected and unaffected side.



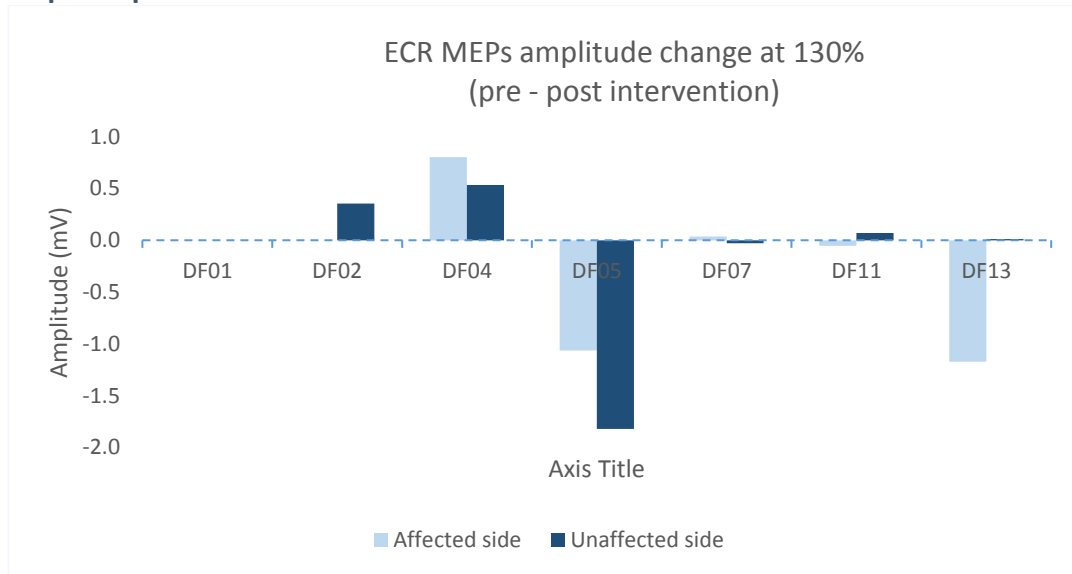
Notes: the bars represents the difference in excitability identified by changes in MEP amplitude for each participants from pre to post intervention for affected (light blue bars) and unaffected (dark blue bars) side.

Figure 7-8: Changes in MEPs amplitude from pre to post intervention on extensor carpi radialis muscle (ECR) at 120% of the recruitment curve (RC) for all participants on affected and unaffected side.



Notes: the bars represents the difference in excitability identified by changes in MEP amplitude for each participants from pre to post intervention for affected (light blue bars) and unaffected (dark blue bars) side

Figure 7-9: Changes in MEPs amplitude from pre to post intervention on extensor carpi radialis muscle (ECR) at 130% of the recruitment curve (RC) for all participants on affected and unaffected side.



Notes: the bars represents the difference in excitability identified by changes in MEP amplitude for each participants between baseline to outcome measures for affected (light blue bars) and unaffected (dark blue bars) side.

As with Table 7-4,

Figure 7-7 to 7-25 show that in both sides some participants increased and some decreased. Variability on the changes is found between individual's affected (light blue bar) and unaffected side (dark blue side) as well as between participants. More consistent responses are found in the unaffected side. As expected, as the stimulus (%RMT) gets bigger less muscle responses are seen in the affected side. This is because the motor threshold had to be higher.

Abductor pollicis brevis

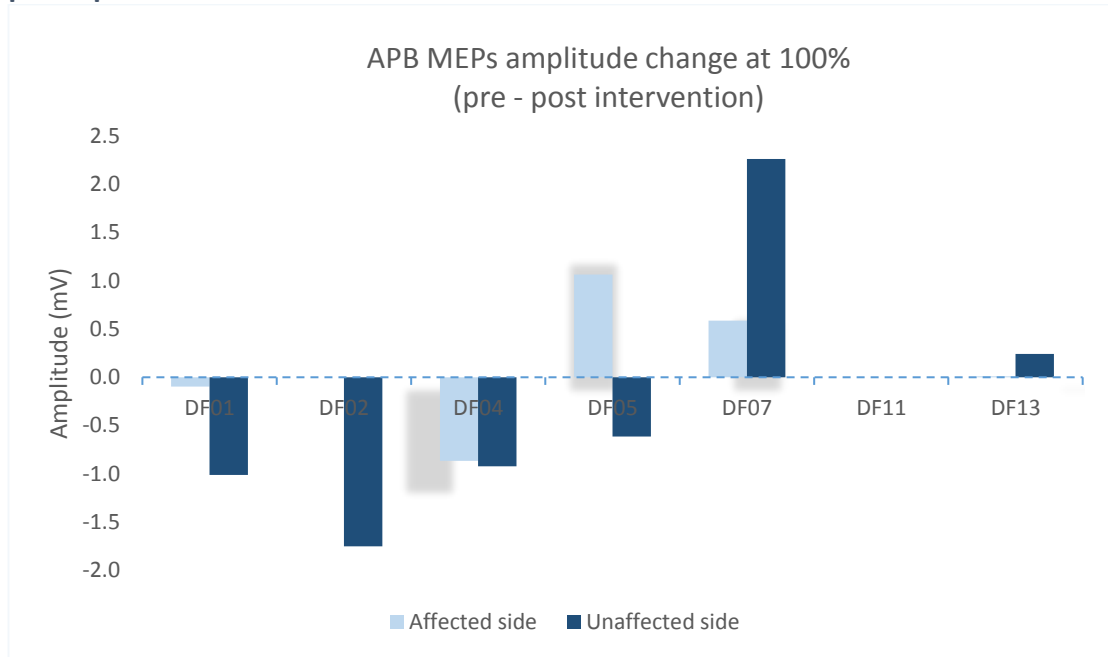
Table 7-5 shows MEPs amplitude at 100% of the RC from pre to post intervention on APB muscle for all participants on affected and unaffected side. Changes of amplitude from pre to post intervention are reported in the table as well as in Figure 7-26.

Table 7-5: MEPs amplitude at 100% of the recruitment curve (RC) at baseline (pre intervention) and outcome (post intervention) measure points on abductor pollicis brevis (APB) for all participants on affected and unaffected side.

APB 100% RC							
		Affected side			Unaffected side		
Cohort (dose)	Participant	Baseline ^a	Outcome ^a	Change ^a	Baseline ^a	Outcome ^a	Change ^a
1(50)	DF01	0.676	0.580	-0.096	1.528	0.516	-1.012
1(50)	DF02	.	0.373	.	4.265	2.513	-1.752
2(100)	DF04	3.141	2.277	-0.864	1.800	0.877	-0.922
2(100)	DF05	3.093	4.158	1.065	1.122	0.507	-0.615
3(167)	DF07	0.628	1.214	0.586	0.388	2.647	2.259
4(251)	DF11	0.549	.	.	0.308	.	.
5(209)	DF13	1.546	1.556	0.010	0.379	0.621	0.242

Notes: (a)= MEP amplitude in mVolts. The dots represent when a resting motor threshold could not be obtained.

Figure 7-10: Changes in MEPs amplitude from pre to post intervention on abductor pollicis brevis (APB) at 100% of the recruitment curve (RC) for all participants on affected and unaffected side.



Notes: the bars represents the difference in excitability identified by changes in MEP amplitude for each participants from pre to post intervention for affected (light blue bars) and unaffected (dark blue bars) side.

Consistently with the Table 7-5, Figure 7-10 shows variability on the changes on APB muscle at 100% of the RC between individual’s affected (light blue bar) and unaffected side (dark blue side) as well as between participants. More consistent responses were found in the unaffected side.

As for ECR, from this table it can be seen that there was more consistent responses on APB muscle that on BB muscle.

Table 7-6 shows changes in MEP amplitude at 110% 120% and 130%of the RC from pre to post intervention on APB muscle for all participants on affected and unaffected side.

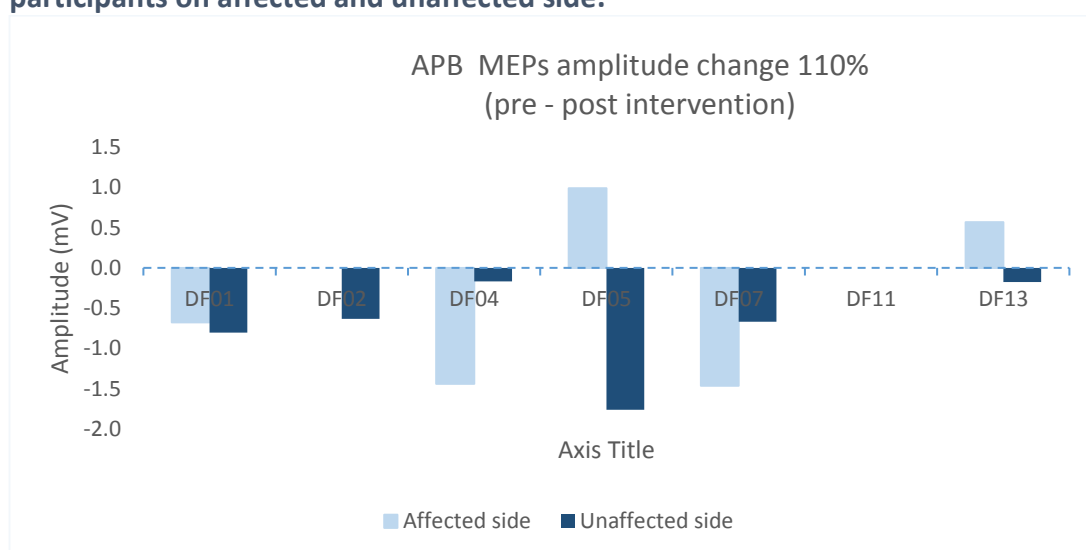
Table 7-6: Change in MEPs amplitude at 110%, 120% and 130% of RC at baseline (pre intervention) and outcome (post intervention) on abductor pollicis brevis (APB) for all participants on affected and unaffected side.

APB		Affected side			Unaffected side		
Cohort (dose)	Participant	Change at 110% RC ^a	Change at 120% RC ^a	Change at 130% RC ^a	Change at 110% RC ^a	Change at 120% RC ^a	Change at 130% RC ^a
1(50)	DF01	-0.677	.	.	-0.805	-1.756	.
1(50)	DF02	.	.	.	-0.632	-1.161	-1.79
2(100)	DF04	-1.442	-2.16	-1.412	-0.167	0.319	1.184
2(100)	DF05	0.988	0.169	1.78	-1.763	-0.96	.
3(167)	DF07	-1.466	-2.209	-2.148	-0.668	-4.374	-3.845
4(251)	DF11
5(209)	DF13	0.569	0.748	0.573	-0.177	0.027	0.537

Notes: (a)= MEP amplitude in mVolts. The dots represent when a resting motor threshold could not be obtained.

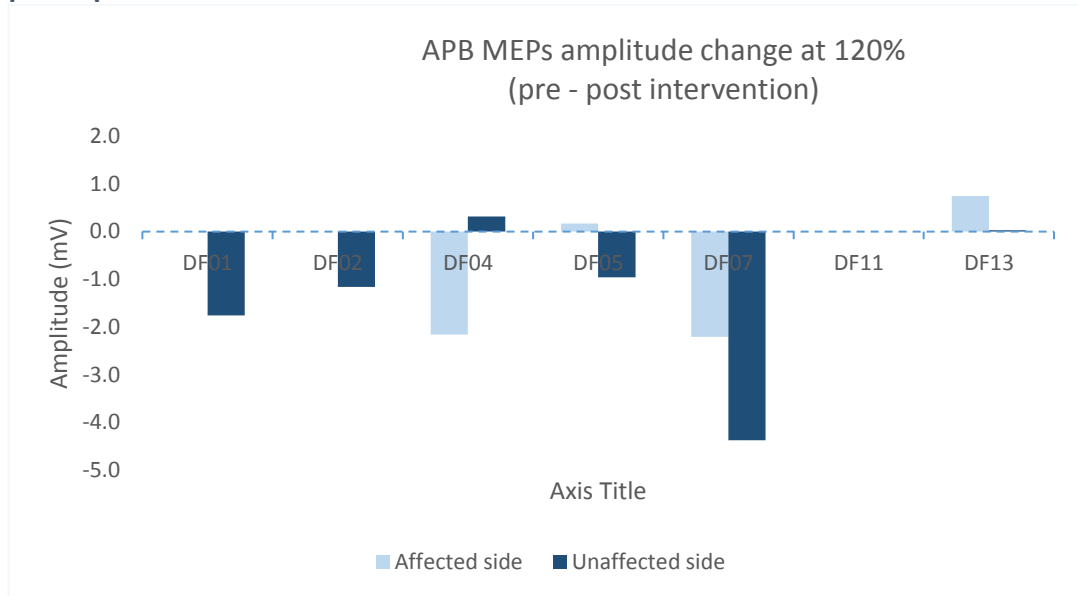
From this table, as before, it can be seen that there are individual differences in excitability and MEP amplitude between brain sides as well as between participants. More consistent responses are found in the unaffected side. Figure 7-11, Figure 7-12 and Figure 7-13 show the changes in the APB muscle at 110%, 120% and 130% of the RC for all participants respectively.

Figure 7-11: Changes in MEPs amplitude from pre to post intervention on abductor pollicis brevis (APB) at 110% of the recruitment curve (RC) for all participants on affected and unaffected side.



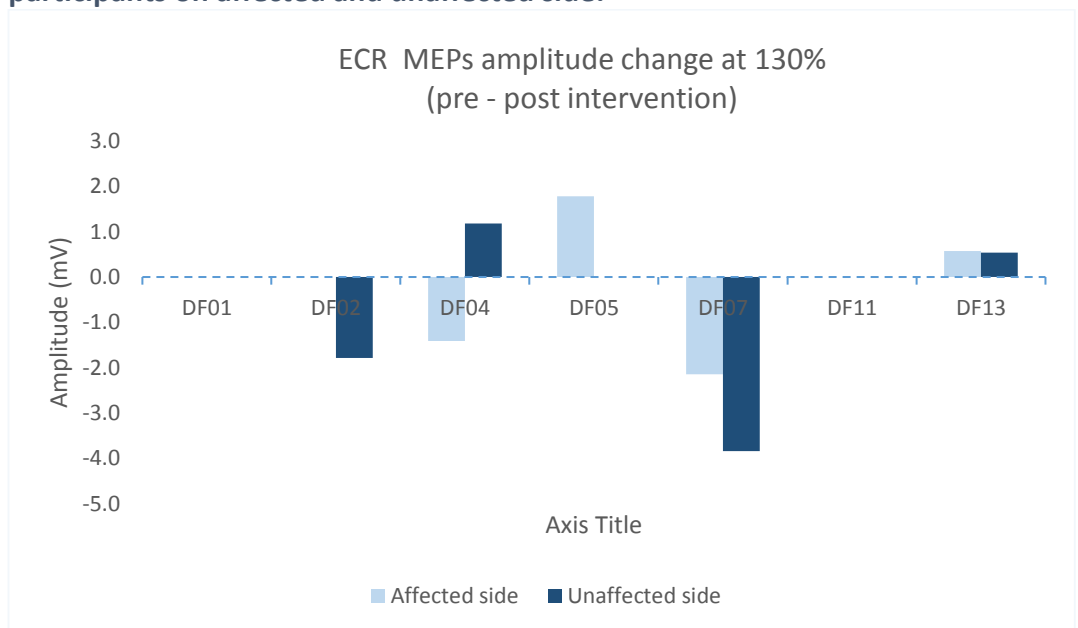
Notes: the bars represents the difference in excitability identified by changes in MEP amplitude for each participants from pre to post intervention for affected (light blue bars) and unaffected (dark blue bars) side.

Figure 7-12: Changes in MEPs amplitude from pre to post intervention on abductor pollicis brevis (APB) at 120% of the recruitment curve (RC) for all participants on affected and unaffected side.



Notes: the bars represents the difference in excitability identified by changes in MEP amplitude for each participants from pre to post intervention for affected (light blue bars) and unaffected (dark blue bars) side.

Figure 7-13: Changes in MEPs amplitude from pre to post intervention on abductor pollicis brevis (APB) at 130% of the recruitment curve (RC) for all participants on affected and unaffected side.



Notes: the bars represents the difference in excitability identified by changes in MEP amplitude for each participants from pre to post intervention for affected (light blue bars) and unaffected (dark blue bars) side.

As with Table 7-6, Figure 7-11 to Figure 7-29 show variability on the changes on APB muscle between individual's affected side (light blue bar) and unaffected side (dark blue side) as well as between participants. As before, more consistent responses are found in the unaffected side and as the stimulus (%RMT) gets bigger less muscle responses are seen. This is because the motor threshold had to be higher.

Summary of changes in MEPs amplitude

From Figure 9-2 to Figure 7-13 it can be seen that variability in the changes in MEP amplitude is found between affected and unaffected side among participants in all the three assessed muscles. This demonstrates intra-participant variability in MEP amplitude changes after the two weeks of intervention.

Inter-participants variability is also highlighted from results. Some participants had an increased amplitude MEPs and an increased resting motor threshold after the two weeks of the task training. This would suggest an increased excitability and brain plasticity among them. However, some patients experienced a decrease in excitability which cannot be fully explained. The heterogeneity on changes was found across all muscle and thus, it can be representative of the all motor system. Variability on the cortical spinal pathway excitability could be due to many factors. The variability in the technique and the diminished presence and quality of MEPs in stroke patients can explain in part these results [58,319]. Moreover, differences between people may contribute to this variability in TMS responses. Patients' characteristics such as, age and genetic factors [21,320,321,322], location, size, severity, and time since the brain injury can all influence the TMS results [56,62,286]. The trial sample was heterogenic in several characteristics such as, age and time since stroke. The difference in cortical representation between proximal and distal muscles and the difference in TMS response according to the muscle under investigation are other important factors in interpreting these results. Martin et al. (2006) found that distal upper limb muscles were more susceptible and stable in responding to repeated pulse of TMS [323]. In line with

these results, in our study ECR and APB muscles (proximal muscles) provide more consistent changes than BB muscle (distal muscle) in MEPs amplitude.

Overall, pre to post intervention individual changes in MEPs amplitude were observed in both affected and unaffected brain sides in the three muscles assessed expressing intra-participant variability. This is consistent with studies that found changes also in contralesional (unaffected) hemisphere excitability as a result of over-recruitment⁶⁸ and reduced inhibitory pathways [324,325]. Changes in the unbalanced brain excitability can contribute to improvements of motor function [326]. I speculate that the variability of inhibition and excitation I have found could be a sign that the brain is trying to reorganise the lost balance between hemispheres and some plasticity is happening as a result of the intervention.

Change on RMT

Table 7-7 shows the RMT from pre to post intervention on BB muscle for all participants for affected and unaffected side. Changes in RMT from pre to post intervention are reported in the table as well as in Figure 7-30.

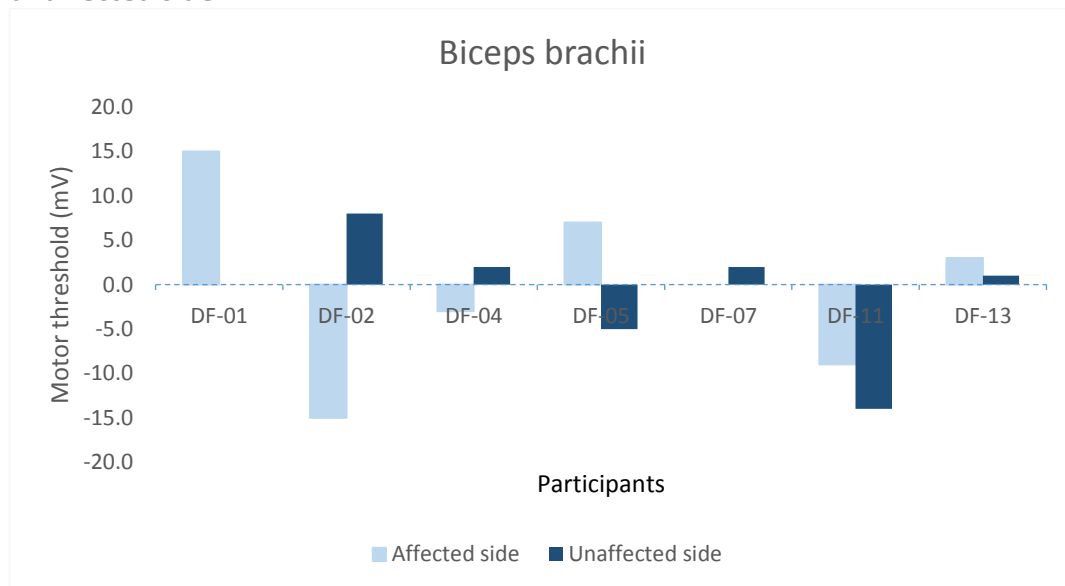
⁶⁸ I.e. recruitment of brain circuits on the unaffected side normally involved in other functions are used to supply the deficit in the affected hemisphere.

Table 7-7: Resting motor threshold (RMT) differences between the baseline (pre intervention) and outcome (post intervention) on biceps brachii muscle (BB) for all participants for affected and unaffected side.

BB								
Cohort (dose)	Participant	Affected side			Unaffected side			
		Baseline	Outcome	Change	Baseline	Outcome	Change	
1(50)	DF-01	80	95	15	79	79	0	
	DF-02	94	79	-15	60	68	8	
2(100)	DF-04	72	69	-3	61	63	2	
	DF-05	46	53	7	69	64	-5	
3(167)	DF-07	.	74	.	54	56	2	
4(251)	DF-11	94	85	-9	86	72	-14	
5(209)	DF-13	48	51	3	47	48	1	

Notes: motor threshold in mVolts. The dots represent when a resting motor threshold could not be obtained.

Figure 7-14: Changes in rest motor thresholds (RMT) from pre to post intervention on biceps brachii muscle (BB) for all participants for affected and unaffected side.



Notes: the bars represent changes in resting motor threshold from pre to post intervention in BB muscle in both affected (light blue bars) and unaffected (dark blue bars) arms.

As Table 7-7, Figure 7-14 shows variability in direction of RMT changes from pre to post intervention for BB muscle for all participants. It can be seen that there is individual variability between affected (light blue bars) and unaffected side (dark blue bars) as well as between participants. Some participants increased the motor threshold and others decreased the motor threshold in both arms providing inconsistent changes in RMT between participants

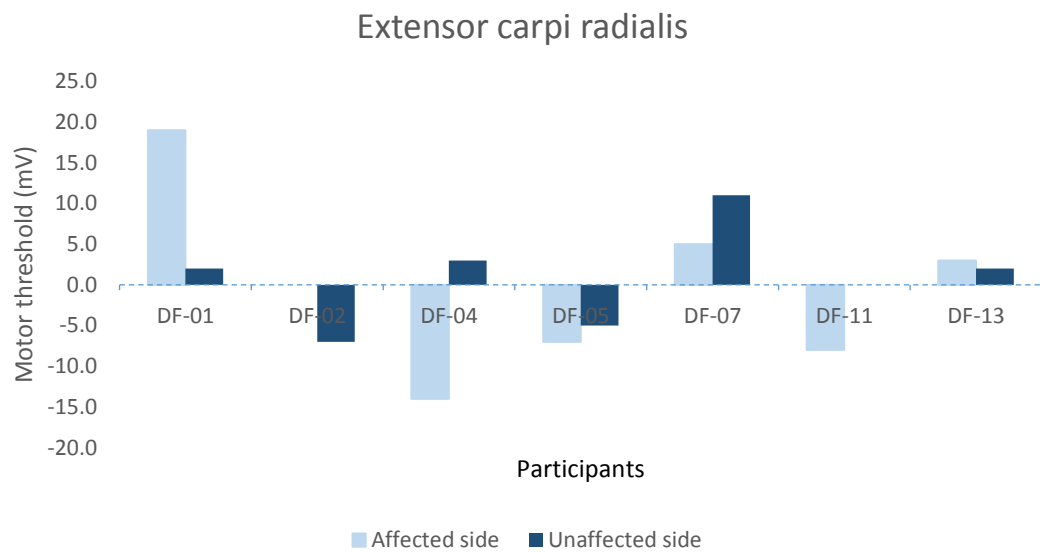
Table 7-8 shows the RMT from pre to post intervention on ECR muscle for all participants for affected and unaffected side. Changes in RMT from pre to post intervention are reported.

Table 7-8: Resting motor threshold (RMT) differences between the baseline (pre intervention) and outcome (post intervention) on extensor carpi radialis muscle (ECR) for all participants for affected and unaffected side.

ECR							
Cohort (dose)	Participant	Affected side			Unaffected side		
		Baseline	Outcome	Change	Baseline	Outcome	Change
1(50)	DF-01	78	97	19	72	74	2
	DF-02	97	.	.	57	50	-7
2(100)	DF-04	64	50	-14	52	55	3
	DF-05	48	41	-7	59	54	-5
3(167)	DF-07	52	57	5	41	52	11
4(251)	DF-11	68	60	-8	64	64	0
5(209)	DF-13	42	45	3	36	38	2

Notes: (motor threshold in mVolts. The dots represent when a resting motor threshold could not be obtained.

Figure 7-15: Changes in resting motor threshold (RMT) from pre to post intervention on extensor carpi radialis muscle (ECR) for all participants for affected and unaffected side.



Notes: the bars represent changes in resting motor threshold from pre to post intervention in BB muscle in both affected (light blue bars) and unaffected (dark blue bars) arms.

As with Table 7-8, Figure 7-15 shows variability in direction of RMT changes from pre to post intervention for ECR muscle for all participants. It can be seen that there is individual variability between affected (light blue bars) and unaffected side (dark blue bars) as well as between participants. Some participants increased the motor threshold and others decreased the motor threshold in both arms.

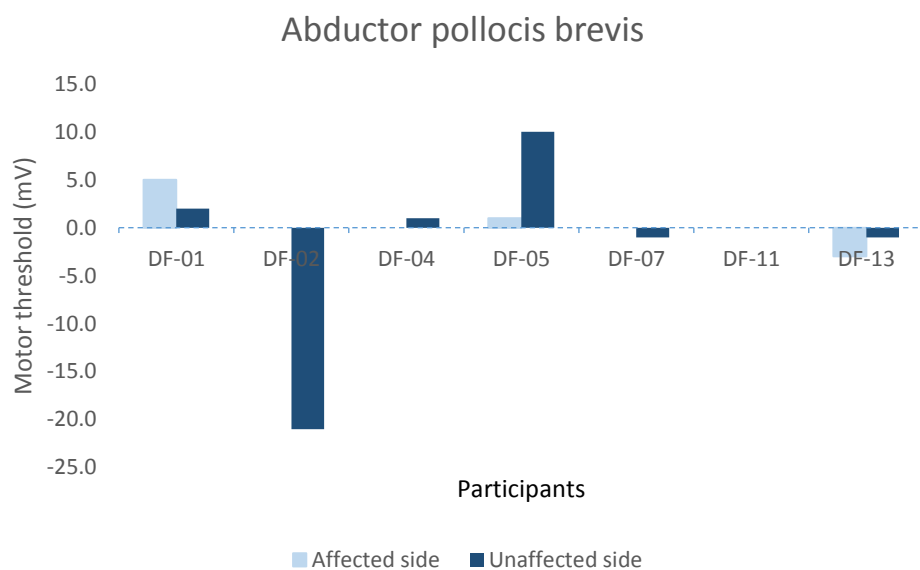
Table 7-9 shows the RMT from pre to post intervention on APB for all participants for affected and unaffected side. Changes in RMT between baseline and outcome measures are reported in the table as well as in Figure 7-32.

Table 7-9: Resting motor threshold (RMT) differences between the baseline (pre intervention) and outcome (post intervention) on abductor pollicis brevis muscle (APB) for all participants for affected and unaffected side.

Abductor Pollicis Brevis							
Cohort (dose)	Participant	Affected side			Unaffected side		
		Baseline	Outcome	Change	Baseline	Outcome	Change
1(50)	DF-01	76	81	5	75	77	2
	DF-02	.	83		68	47	-21
2(100)	DF-04	54	54	0	50	51	1
	DF-05	40	41	1	58	68	10
3(167)	DF-07	57	57	0	46	45	-1
4(251)	DF-11	80	.	.	65	.	.
5(209)	DF-13	41	38	-3	36	35	-1

Notes: motor threshold in mVolts. The dots represent when a resting motor threshold could not be obtained.

Figure 7-16: Changes in resting motor threshold (RMT) from pre to post intervention on abductor pollicis brevis muscle (APB) for all participants for affected and unaffected side.



Notes: the bars represent changes in resting motor threshold from pre to post intervention in BB muscle in both affected (light blue bars) and unaffected (dark blue bars) arms.

Figure 7-16 shows variability in direction of RMT changes from pre to post intervention for APB muscle for all participants undertaking TMS. As with

Table 7-9, it can be seen that there is individual variability between affected (light blue bars) and unaffected side (dark blue bars) as well as between participants. Some participants increased the motor threshold and others decreased the motor threshold in both arms.

Appendix M : Trial recruitment letter

Norfolk and Norwich University Hospital 
NHS Trust

Recipients address

**Norfolk and Norwich University
Hospital**
Colney Lane
Norwich
NR4 7UY

Date

Dear XXX,

I am writing to tell you about **research** being carried out in Norfolk by **Dr Jane Cross and a team of researchers at The University of East Anglia**.

Dr Cross and her team are **seeing whether a new physiotherapy treatment is effective** for people who have a stroke. They want to find out whether doing **6 weeks of a new therapy** called “Functional Strength Training” can **help people**

to **use their arm and leg better for daily activities** such as walking and getting dressed.

The Research team **are asking people who have had a stroke within the last 5 years** to take part. In all the researchers are **looking for 58 people** who have weakness in their **arm and leg** caused by their stroke. **Your details** were identified from your **in-patient stay** after having your stroke.

What would I have to do?

Taking part in the study would mean having **physiotherapy for your arm or leg for 4 days a week for 6 weeks**. Each training session will be **an hour** long. You might practise **tasks for the arm** such as **reaching for objects, unscrewing lids** and **pouring water**; or **tasks for the leg** such as **climbing stairs, standing, and walking**. We would need to **assess your arm and leg** before and after the 6 weeks of therapy.

All the therapy and assessments would be in your home with a research physiotherapist. We may also **ask questions** about how you found the therapy and whether it was what you were hoping for.

Am I the right person for this research?

Are you walking as well as you had done before the stroke?

Are you able to use your arm as well as you had done before the stroke?

If your answer is **NO** to both these questions then **you may be able to be included in this research.**

Taking part in this research is **entirely voluntary**. You **will not be out of pocket** if you decide you would like to take part.

Please return the **reply slip** in the **stamped address envelope** to show whether or not you would like to have **more information about the study.**

If you would like to talk to somebody before deciding, please contact Kath Mares on 01603 593099 or 07827 840497.

If the research team has not heard from you within 2 weeks we will send you one reminder by post.

Thank you for taking the time to consider this invitation

Yours sincerely



Dr Phy Myint

Consultant in Elderly
Medicine

Dr Kneale Metcalf

Consultant in Elderly
Medicine

Appendix N : Expression of interest



Functional Strength Training to improve walking and upper limb function in people later after stroke

EXPRESSION OF INTEREST FORM

Thank you for filling in this form and expressing an interest in being part of this research. Following receipt of this form we will contact you by telephone to arrange to come and visit you to discuss the research further.

Information about you

Name:
Address:
Tel:
Postcode:

Thank you for filling in this form. Please do not hesitate to contact me if you have any questions about the study or filling in the form.

Please return the form in the envelope provided to: Kath Mares, School of Allied Health Professions, Queen's Building, University of East Anglia, Norwich NR4 7TJ

Tel: (01603) 593099 – if no reply please leave a message and I will call back
Email: k.mares@uea.ac.uk

FeST1vAIS (ISRCTN71632550)
Ethics reference: 09/H0308/147

Appendix O : Participant Information Sheet

University of East Anglia, version 5. 1/4/2011



Participant Information sheet

Study Title:

Functional Strength Training to improve walking and upper limb function in people later after stroke: a phase II Trial (Protocol, version 4)

You are invited to take part in a **research study**. Before you decide whether you would like to take part you **need to understand why** the research is being done and **what would be involved**. Please take time to **read the following information carefully**.

Talk to others about the study if you wish. If you have **any questions** or would like **further information** there are some **contact numbers on page 10 and 11 of this information pack**.

- **Part 1** describes the **purpose of this study** and **what will happen** if you decide to take part.
- **Part 2** gives **detailed information** about **how the study will be carried out**

Part 1

What is the purpose of this study?

Weakness in the **arm and leg** is common **after stroke** and this can affect people's ability to walk and carry out daily activities.

Many people think that there is little chance of further improvement a year after stroke. Most people do not receive therapy at this time. We want to find out whether a **new therapy called Functional Strength Training (FST)** is effective for people **at least six months after their stroke**. We also want to find out what people **think about FST** and whether it is **suitable to be provided to people in their own homes**

What is Functional Strength Training (FST)?

Functional Training involves **practising activities** that you do every day such as walking and reaching for objects. Adding **'Strength' Training** means increasing the **number of times the activity is practised** or **making the activity harder bit by bit**.

FST for the leg



Activities could include:
Standing up from chairs at different heights
Climbing steps or stairs
Exercises with weights sitting down

FST for the



Activities could include:
Reaching for objects from cupboards **Lifting** objects of different weights.
Tying shoelaces, undoing buttons

2

Why have I been asked to take part?

You have been chosen because you have had a **stroke within the last 5 years**. If you decide to take part you will be one of **58 participants** in this study.

We are looking for people who;

- Have weakness in their **arm and leg** following a stroke;
- Are **not receiving physiotherapy** for their arm and leg;

Do I have to take part?

No. It is **up to you to decide**. Taking part in the research study is **entirely voluntary**. If you want to you can **speak to a member of the research team before you decide**.

You are **free to withdraw from the study at any time** and you

What will happen if I decide to take part?

Once you are happy that you **want to take part** in the study, one of the **research team will visit you at home**.

On your home visit a member of the research team will **assess your arm and leg** to see whether or not you are **suitable to participate** in the study.

3

If you are **not suitable** to participate in the study, you will be told by the Research team and you will **not be asked to take any further part** in the study.

If you are you will be asked to **sign a consent form** to show you **agree to take part**. We will leave the consent form with you for 1 week so that you can think about becoming part of the study. If you still wish to take part in the study a Researcher will come and visit you at home and will take some **more measurements** of your arm and leg. They will also help you complete a **questionnaire about your health and use of health services**

This will take approximately **30-40 minutes**.

In order to do this we will:

- Assess your ability to **stand and walk**
- Assess your ability to **use your stroke arm in every day activities**.
For example, lift different sized objects from the table onto a box in front of you

Examples of activities the researcher will use to assess your arm:



Touch your



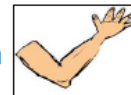
9 Hole Peg Test

With your consent the **Research Team** will tell your **GP** that you are **taking part** in the study and check that there are **no medical reasons** why you can't take part.

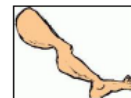
After the home visit

If you are suitable for the study you will be allocated to **group 1 or group 2 at random**

- **Group 1** will receive 6 weeks of FST training for their arm



- **Group 2** will receive 6 weeks of FST training for their leg



You will be **identified by a number**. None of your personal details are given. The research therapist giving the FST training will **tell you which group you are in**.

Can I choose which group I get allocated?

No. Participants have to be **randomly allocated** to either of the groups to allow us to find out **whether this treatment is effective or not**. The researcher who does the **assessments** at the **start and end** of the study **will not know which group you are in** and therefore will not be able to influence the findings. This is called a **'blind trial'**. You must **not tell the assessor which group you**

Outcome and follow- up assessments

After the 6 weeks of FST training the researcher will assess your arm and leg again, using the same assessments as before. This will also happen 6 weeks after the FST training has stopped so we can see if any improvements in your arm and leg have been maintained.

Weekly measures of arm and leg function

Once a week (usually the first visit each week) the therapist who is visiting you to carry out the intervention will carry out a brief assessment of your arm and leg movement. This information will be used to tell us whether 6 weeks of therapy is enough, too little or too much. This assessment should only take about 20 minutes and won't impact on the time you have for the intervention.

Interviews



A small number of participants (6 out of the 58) will be chosen to take part in two interviews as well as the FST therapy.

There will be two interviews conducted by an Independent Researcher. These will take place in your home before and after the FST therapy period.

The **purpose** of the interviews is to help us find out whether or not you find this level of training **acceptable** and whether it is suitable to be

Interview 1

Will take place **before you start the FST** Training

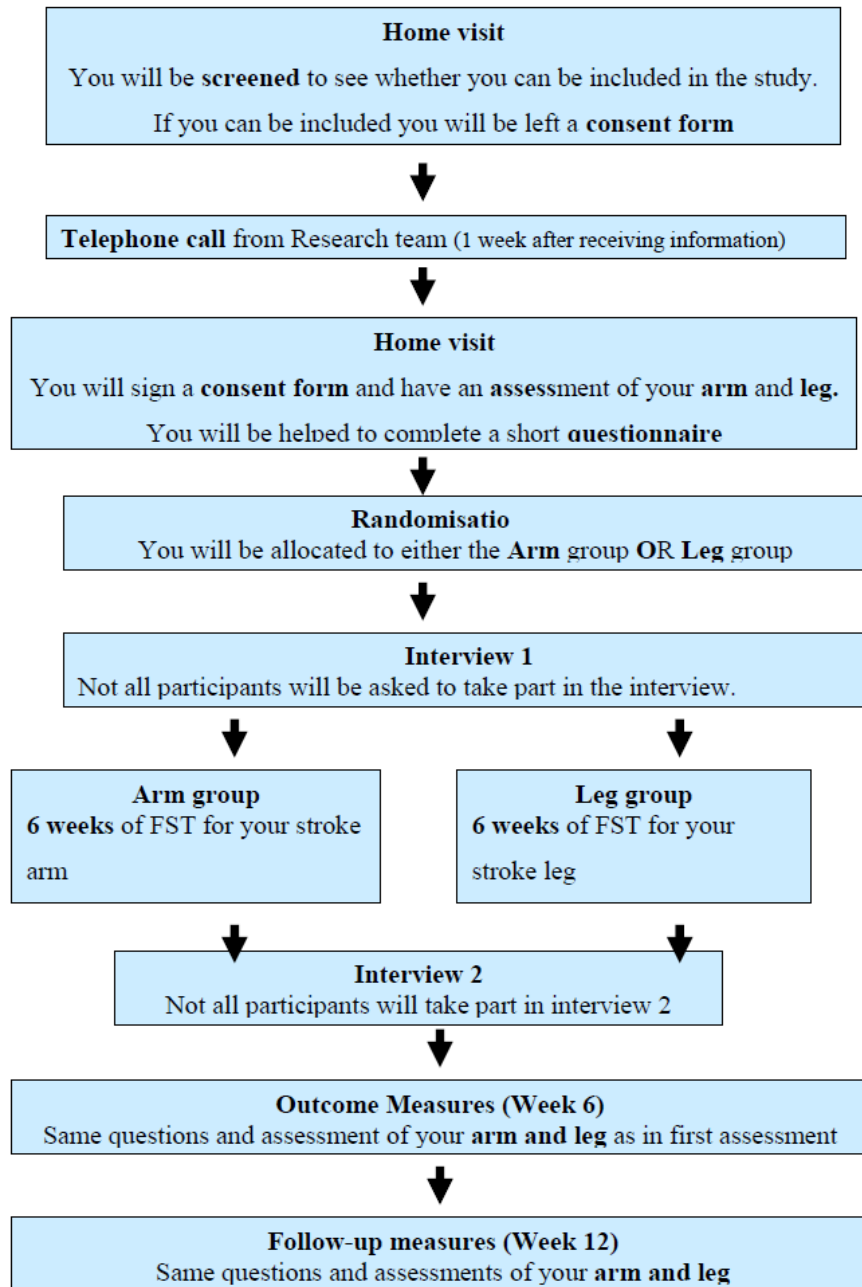
You will be asked questions about what life was like **before your stroke**. We want to find out what **difficulties you now have because of your stroke** and **what you are hoping to achieve** by participating in the FST training.

Interview 2

Will take place **after the 6 weeks of FST** Training

You will be asked for **feedback** about what you thought of the FST training. For example if it was too tiring and whether you saw any benefits.

Diagram to show the procedure for the study





Expenses

The study will take place **entirely within your own home** and therefore there will be **no travel expenses**.



Are there any possible risks with this study?

There is a **small risk** that you may experience some pain or discomfort if you overwork your arm or leg in therapy. This will be **closely monitored** and we will pace therapy to your level of ability.

Therapy can be stopped at any time. If you want to stop being involved you simply tell us.



What are the possible benefits of taking part in

Previous studies have shown that functional strength training improved recovery of people early after stroke. However we do not know if the

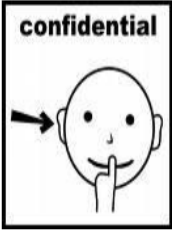
What happens when the study stops?

This is the first study of FST at 1 year after stroke.



Will my taking part in the study be kept confidential?

Yes, all the information about you and your participation in the study will be kept strictly confidential. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in **Part 2** (p.12).











This completes Part 1 of the information sheet.

If this information interests you and you are considering taking part, please continue to read additional information in Part 2 before making any decision.



If you have **any queries** you can contact the Research Physiotherapist, **Kath Mares** or **Jane Cross** the Principal Investigator.

Contact details:

			
<p>Kath Mares Research Physiotherapist</p>	<p>The Queens Building University of East Anglia Norwich</p>	<p>k.mares@uea.ac.uk</p>	<p>01603 593099 / 07927</p>
			
<p>Dr Jane Cross Principal</p>	<p>The Queens Building University of East Anglia Norwich</p>	<p>j.cross@uea.ac.uk</p>	<p>01603 50262</p>

Independent Contact Details:

If you wish to discuss this study with someone who is not involved in the research then you contact the Research and Development Office, Norfolk and Norwich University Hospital:

	
<p>rd@nuth.norfolkandnorwich.nhs.uk</p>	<p>01603 296644</p>

Part 2



What happens if new information about the research therapy comes along?

Sometimes in research, new things are found out about new therapies. Very few studies have been done about this therapy (FST) and this study is to find evidence to justify a larger study. If however, new information is published



What happens if I no longer wish to continue study?

You may withdraw from the study **at any time** without giving a reason. If you withdraw from the study, we will need to use the data collected up to when you withdrew.

Withdrawing from the study will not affect your treatment now or at any time in the future by any healthcare team



Will anyone else know I am doing this?

With your consent the research team will contact your **GP** to inform them you are **taking part in the study**.

If the Research Team are concerned at any time about your health during your participation in this study they will **report these concerns** to your **GP** or the appropriate **health care professional**.

complain



What if there is a problem or something goes

If you have any **concerns** about this study, you should first contact **Kath Mares** or **Jane Cross**, who will do their best to **answer your questions** or **resolve the problem**. (Contact details given at end of Part 1).

If you are still unhappy or wish to make a **formal complaint** you may do this through the **NHS Complaints Procedure**. Details can be obtained from the hospital.

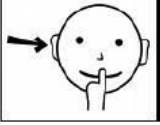
In the event that something does go wrong and you are harmed during the research study there are **no special compensation arrangements**.

Who is organising/funding the research?



The Stroke Association have awarded a **grant** to enable the trial to be funded. The Research Team at the **University of East Anglia** are responsible for **organising** and **running** the trial.


confidential



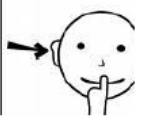
Will my taking part in this study be kept

The research team will only have access to information about you that is relevant to the study. All information will be kept **strictly confidential**.

Information may include details such as your **date of birth** and the **date** and **diagnosis of your stroke**. Personal information such as your **address** will also be required to allow us to visit you at home.

You will be given a **trial number** for the purpose of ~~collecting and analysing data~~. This means you will remain anonymous 

confidential



How will my information be stored?

Data will be **stored securely** in the **research office** during the study and for **5 years** after the study. Long term data is then stored in a secure room in the **NHS Clinical trials Research Unit** at UEA for **25 years**.

All procedures for **handling, processing, storage and destruction of data** are compliant with the Data Protection Act 1998.



What will happen to the results of the research study?

The results of the trial will be **analysed** and used to justify **whether or not a larger scale study** is required to prove effectiveness of this therapy.

The results will be **published in an academic journal** but individual participants will **not be identifiable**. Participants can be sent trial report at the end of the study. Part of this study will contribute to a PhD for Kath Mares (Research Physiotherapist).

Who has reviewed the study?

The Trial has been reviewed by **The Stroke Association** and **Stroke Survivors** at our **Patient Forum**. All were **positive** about the proposed trial and **feedback** has been incorporated into this **research plan**.

The **Cambridgeshire 2 Research Ethics Committee** has approved the study and it will be monitored by a **Trial Management Group**.

End of Part 2

Thank you for taking the time to **read this information**. If you choose to participate, you will **keep a copy** of this **participant information sheet** and the **signed consent form**.

Appendix P Festival Informed Consent

University of East Anglia, version 5 1/4/2011



Participant Name:

Participant Identification Number for this trial:

Consent Form

Title of Project: Functional Strength Training to improve walking and upper limb function in people later after stroke: a phase II Trial



Name of Researcher:

1)



I confirm that I have **read and understood** the information sheet dated 1/4/2011, Version 5 for the above study.

I have had the opportunity to consider the information and have had the

I have read and understood the information sheet	
 Yes	 No

Please initial the relevant box

Please initial or tick the relevant box as able

2)

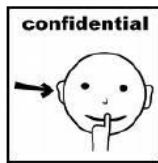


I understand that my **participation is voluntary** and that I am **free to withdraw at any time**, without giving any reason, without any future medical care or legal rights being

I understand I can stop at any time

Yes	No

3)



I understand that **some information about my stroke may be held by individuals from the University of East Anglia**. These may be people outside of the research team who may

My information can be seen



Yes	No

4)



I agree that my **GP** can be **informed of my participation** in the study. I agree for my GP to be asked **whether or not I am fit** to take part in this study. I agree that my GP can be **informed** if there are any

My GP can be told I am in the study



 Yes	 No
--	--

5)



I consent to the use of audio visual equipment for the purposes of recording my interviews if I am selected for that part of this

I consent for my interviews to be recorded



 Yes	 No
--	--

6)



I agree to take part in the study

I agree

	
Yes	No

Name of participant Date Signature

Researcher
(Person taking consent) Date Signature

When completed; 1 for patient; 1 for researcher site file; 1 (original)

Appendix Q GP letter



Faculty of Health
Queens Building
University of East Anglia
Norwich
NR4 7TJ

Date:

Dear Dr

I am writing to you to inform you that your patient (name) has consented to take part in a trial that is currently underway at the University of East Anglia. This trial is called Functional Strength Training later after Stroke (FeStlvAIS) and has been funded by the Stroke Association. We are aiming to recruit 58 participants who have had a stroke between 6 months and 5 years ago to take part in a functional strength training programme which will target either their upper or lower limb, depending on group allocation.

Please find a one page copy of the protocol attached to this letter.

We would be grateful if you could let us know of any medical reason why this patient may not be included in this study. If we have not heard from you within 10 working days from the receipt of this letter, then we will go ahead and include (name) in the study.

If you require any further information about the study then please contact either myself (Kath Mares) or the Principal Investigator, Dr Jane Cross.

Kath Mares
k.mares@uea.ac.uk
01603 593099

Jane Cross
j.cross@uea.ac.uk
01603 593315

Yours sincerely

Kath Mares
Research Physiotherapist

Kath Mares
Research Physiotherapist FeST1vAIS (ISRCTN71632550)
Ethics reference:
k.mares@uea.ac.uk
01603 593099

1

Appendix R GP protocol

Version 2: 03/06/2010

Functional Strength Training Later After Stroke (FeSTivAIS)

Description of Intervention:

Functional Strength Training (FST) is a 'hands-off' progressive, resistive low intensity exercise during functional activity. FST is designed to increase ability to produce voluntary muscle force throughout joint range and increase ability to modulate force in muscles/muscle groups appropriate for the activity being trained and improve functional ability. Activities are progressed by increasing the number of repetitions, increasing range of joint motion required and increasing the load to be moved. The intervention will be carried out in people's homes by a Research Physiotherapist four times a week for six weeks. Portable equipment (e.g. free weights and steppers) will be used as appropriate. Participants will be encouraged to use the paretic limb (upper or lower as allocated) in everyday functional activity.

Research study primary objective:

- To estimate if there is sufficient efficacy to justify subsequent trials of Functional Strength Training (FST) for upper and lower limb motor recovery in people who are between six months and five years after stroke.

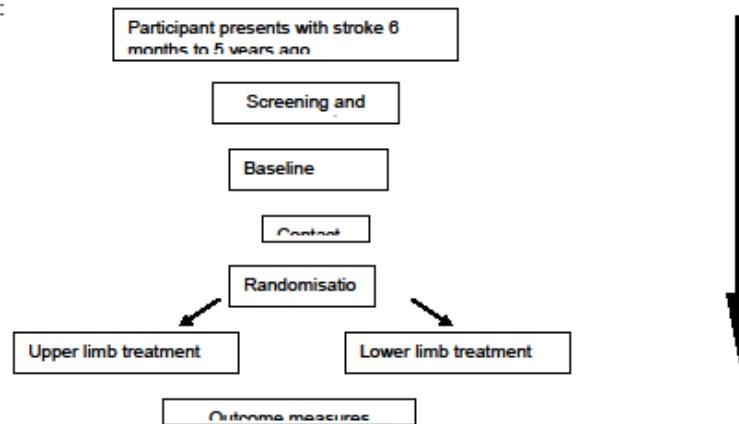
Inclusion criteria:

- adults aged 18+ years, 6 months to 5 years after stroke in anterior circulation (infarct or haemorrhage)
- be able to walk 4 steps with continuous support from one person and/or assistive devices, but unable to step on and off a block with either the affected or unaffected leg more than 14 times in 15 seconds.
- be able to take paretic hand from position on lap and place on table top in front, but unable to pick up four £1 coins individually from a tabletop and stack them evenly in a pile.
- can follow a 1-stage command i.e. sufficient communication/orientation for interventions in this trial

Exclusion criteria:

- known pathology which excludes participation in the low intensity exercise training involved in functional strength training.

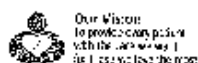
Study design:



Adverse events are not expected in this intervention but there is a small possibility of an overuse syndrome resulting in limb pain. This will be considered to have occurred if a participant reports or exhibits limb pain (behavioural signs) to the Research Physiotherapist on 4 consecutive treatment days. If pain occurs then participants will be withdrawn from their allocated treatment.

Kath Mares
Research Physiotherapist FeSTivAIS (ISRCTN71632550)
Ethics reference: 09/H0308/147
k.mares@uea.ac.uk
01603 593099

Appendix S Festival signed NNUH approval



Norfolk and Norwich University Hospitals 
NHS Foundation Trust

Dr Phyo Myint
Norfolk & Norwich University Hospital
Medicine for the Elderly
Level 2, East Block
Colney Lane
Norwich
NR4 7UY

Research & Development Office
Level 3 East
Norfolk & Norwich University Hospitals NHS Foundation Trust
Colney Lane
Norwich
NR4 7UY

direct dial: 01603 247826
direct fax: 01603 285820
e-mail: rdoffice@nnuh.nhs.uk
website: www.nnuh.nhs.uk

26 May 2011

Dear Dr Myint,

Re: R&D Reference Number: 2009MFE09M (192-11-09)
Project Title: Functional strength training to improve walking and upper limb function in people at least 1 year after stroke. A Phase II Trial. FESTIVAIS

Thank you for recent correspondence regarding substantial amendment 7 (REC #9) for the above study. It was noted that the amendment has already received a favourable opinion from the NRES Committee East of England - Cambridge Central.

Following review of the documentation I am pleased to inform you that Trust approval has been given for these changes.

The documents reviewed and approved are as follows:

- **Participant Consent Form, Version 5, 01 April 2011**
- **Participant Information Sheet, Version 6, 01 April 2011**
- **Protocol, Version 4, 01 April 2011**

If you have any queries regarding this or any other project please contact Clare Ingamells Research Facilitator, at the above address. Please note, the reference number for this study is **2009MFE09M (192-11-09)** and this should be quoted on all correspondence.

Yours sincerely

Professor Garry John
Director of Research & Development
Consultant Clinical Biochemist, NNUH

Carbon Copy: (CI) Dr Jane Cross. J.Cross@uea.ac.uk

Norfolk & Norwich University Hospitals NHS Foundation Trust

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please enter a short title for this project (maximum 70 characters)
Functional strength training one year after stroke -FeST1vAIS

1. Is your project an audit or service evaluation?

Yes No

2. Select one category from the list below:

- Clinical trial of an investigational medicinal product
- Clinical investigation or other study of a medical device
- Combined trial of an investigational medicinal product and an investigational medical device
- Other clinical trial or clinical investigation
- Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- Study involving qualitative methods only
- Study limited to working with human tissue samples, other human biological samples and/or data (*specific project only*)
- Research tissue bank
- Research database

If your work does not fit any of these categories, select the option below:

Other study

2a. Please answer the following question(s):

- a) Does the study involve the use of any ionising radiation? Yes No
- b) Will you be taking new human tissue samples (or other human biological samples)? Yes No
- c) Will you be using existing human tissue samples (or other human biological samples)? Yes No

3. In which countries of the UK will the research sites be located?(Tick all that apply)

- England
- Scotland
- Wales
- Northern Ireland

3a. In which country of the UK will the lead R&D office be located?

- England
- Scotland



National Research Ethics Service
NRES Committee East of England - Cambridge Central

Victoria House
Capitol Park
Fulbourn
Cambridge
CB21 5XB

Tel: 01223 507685
Fax: 01223 507645

19 April 2011

Dr Jane Cross
Senior Lecturer
University of East Anglia
Queens Building
University of East Anglia
Norwich
NR4 7TJ

Dear Dr Cross

Study title: Functional strength training to improve walking and upper limb function in people at least 1 year after stroke. A Phase II Trial.
REC reference: 09/H0308/147
Protocol number: R16844
Amendment number: Amendment 7 (REC #0)
Amendment date: 04 April 2011

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Consent Form	5	01 April 2011
Participant Information Sheet	5	01 April 2011
Protocol	4	01 April 2011
Notice of Substantial Amendment (non-CITMPs)	Amendment 7 (REC #0)	04 April 2011
Covering Letter	Kath Mares	01 April 2011

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

*The Research Ethics Committee is an advisory committee to the East of England Strategic Health Authority.
The National Research Ethics Service (NRES) represents the NRES Directorates within
the National Patient Safety Agency and Research Ethics Committees in England.*

Appendix T FMA Protocol

FUGL-MEYER Motor Assessment

Equipment:

Tennis ball
Plastic mug diameter 8cm
Pen
Paper
Stopwatch
Reflex hammer
Chair with back

General Rules:

- Subject should be verbally instructed as well as with a demonstration of the test;
- Subject should perform with the non-affected side first;
- Do not assist subject, however if the initial position cannot actively attained by the subject the limb may be passively placed therein;
- verbal encouragement is permitted;
- movement may be repeated up to 3 times to enable observation.

UPPER EXTREMITY

I. **SHOULDER / ELBOW / FOREARM:** subject in sitting position aiming for 90° hip and 90° knee flexion.

- **Chair:**description
-
- cm
-

1.1. Reflex activity: test non-affected side first

0 = No reflex activity

- 2 = reflex activity present

a.

1.2. Volitional movement

- 0 = cannot be performed
- 1 = detail performed partially
- 2 = detail performed faultlessly
-

1.2.1. Within synergies

Flexor synergy: *Starting position:* Hand from contralateral knee (shoulder adduction/ internal rotation, elbow extension, forearm fully pronated) to ipsilateral ear (shoulder abduction at least 90°/ external rotation, elbow flexion, forearm supination).

Instruction: Touch your ear with your hand

- **Extensor synergy:** *Starting position:* Hand from ipsilateral ear to contralateral knee.

- Instruction: Move your hand from your ear to your opposite knee....

-

1.2.2.....Mixing

synergies Hand resting on lap.

- **Hand to lumbar spine:** *Starting position:* subject has to move forward on the chair and support for balance may be given.

- *Instruction:* Put your hand behind your back

- Cannot be performed (hand in front of ASIS) 0

- Hand behind ASIS (no compensation) 1

- Hand to lumbar spine higher than ASIS (no compensation) 2

-

- **Shoulder flexion 0-90°:** *Starting position:* elbow at 0°, forearm mid-position

- *Instruction:* Lift your arm straight up, keeping your thumb pointing up

- Immediate abduction or elbow flexion 0

- Abduction or elbow flexion during the movement 1

- Elbow completely extended 2

-

- **Forearm Pro/supination:** *Starting position:* elbow 90°, shoulder 30-90° flexion

- *Instruction:* Turn your palm face up and down

- Cannot be performed 0

- Limited pronation/supination, maintains position 1

- Full pronation/supination, maintains position 2

-

1.2.3.....Without synergies

- **Shoulder abduction 0-90°: Starting position:** elbow at 0°, forearm pronated
- *Instruction:* Lift your arm out to the side
- Immediate supination or elbow flexion0
- Supination or elbow flexion during movement1
- Abduction 90°, maintains extension and pronation2
-
- **Shoulder flexion 90-180°: Starting position:** elbow at 0°, forearm mid position
- *Instruction:* Lift your hands towards the ceiling, keep your elbow straight and thumb pointing up
- Immediate abduction or elbow flexion0
- Abduction or elbow flexion during movement1
- Complete flexion, maintains elbow extension 2
-
- **Pronation/supination: Starting position:** elbow at 0°, shoulder 30-90° flexion
- *Instruction:* Turn your palm face up and down, with your elbow straight
- Cannot be performed0
- Limited pronation/supination, maintains extension..... 1
- Full pronation/supination , maintains elbow extension2
-

1.1. Normal reflex activity: tested only if full score (6 points) achieved on part 1.2.3.

- Test as in section 1.1
- Biceps, triceps, finger flexors
- 0 = No full point section 1.2.3. or 2 of 3 reflexes markedly hyperactive
- 1 = 1 reflex markedly hyperactive or at least 2 reflexes lively
- 2 = maximum of 1 reflex lively, none hyperactive

WRIST Support may be provided at the elbow to take or hold the position, no support at wrist, check the passive range of motion prior testing.

1. Stability at 15° dorsiflexion: *Starting position:* elbow at 90°, forearm pronated

- *Instruction:* Lift your hand and hold it there, keep your elbow bent
- Less than 15° active dorsiflexion 0
- Dorsiflexion 15°, no resistance 1
- Maintains position against light resistance 2

2. Repeated dorsiflexion / volar flexion: Starting position: elbow at 90°, forearm pronated, slight finger flexion

- *Starting position:* Lift your hand up and down, keeping your elbow bent
- Cannot performed 0
- Limited active range of motion 1
- Full active range of motion, smoothly 2

3. Stability at 15° dorsiflexion: *Starting position:* elbow at 0°, forearm pronated, shoulder 30° flexion

- *Instruction:* Lift your hand and hold it there, keep your elbow straight
- Less than 15° active dorsiflexion 0
- Dorsiflexion 15°, no resistance 1
- Maintains position against light resistance 2

4. Repeated dorsiflexion / volar flexion: *Starting position:* elbow at 0°, forearm pronated, slight finger flexion, shoulder 30° flexion

- *Instruction:* Lift your hand up and down, keep your elbow straight
- Cannot performed 0
- Limited active range of motion 1
- Full active range of motion, smoothly 2

5. Circumduction: *Starting position:* should first perform with non affected arm

- *Instruction:* Move your hand around with smooth alternating movements, keep your arm still and your elbow bent
- Cannot perform volitionally 0

- Jerky movement or incomplete.....
.....
.....1
- Complete and smooth circumduction.....
.....
..... 2
-
-

II. HAND support may be provided at the elbow to take or hold the position, no support at wrist, check the passive range of motion prior testing

a. **Mass flexion** *Starting position:* from full active or passive extension

- *Instruction:* Make a fist
- No flexion
.....
.....0
- Some but not full finger flexion
.....
..... 1
- Full flexion
.....
.....
.....2

b. **Mass extension** *Starting position:* from full active or passive flexion

- *Instruction:* Stretch out your hand
- No extension possible
.....
..... 0

- Some but not full finger extension
.....
.....1

- Full extension
.....
.....
.....
.....2

c. **Distal finger Grasp** flexion in PIP and DIP extension in MCP

- *Instruction:* Grip my finger and hold
- Cannot be performed.....
.....
..... 0

- Can held position but weak.....
.....
..... 1

- Can held against resistance.....
.....
.....
.....2

-

d. **Thumb adduction Grasp** *Instruction:* Grip the paper between your thumb and hand

- Cannot be performed.....
.....
..... 0

- Can held paper but not against tug
.....
.....1

- Can held paper against tug
.....

.....
.....2

e. **Thumb to index finger Grasp** *Instruction:* Hold the pencil between thumb and index

- Cannot be performed.....
.....
..... 0
- Pencil can be held but not against tug.....
.....
.....1
- Pencil held against tug.....
.....
..... 2

f. **Cylinder Grasp:** plastic mug diameter 8cm

- *Instruction:* Hold the mug – keep it there
- Cannot be performed.....
.....
..... 0
- Mug can be held but not against tug.....
.....
.....1
- Mug held against tug.....
.....
..... 2

g. **Spherical Grasp:** Tennis ball

- *Instruction:* Hold the ball – keep it there
- Cannot be performed.....
.....
..... 0

- Ball can be held but not against tug
.....
.....1
- Ball held against tug
.....
..... 2
-

III. COORDINATION and SPEED after one trial with non-paretic arm, blind-folded, tip of the index finger from knee to nose, 5 times as fast as possible. Each test is timed.

- In case of complete paralysis, observe for any indication of tremor and dysmetria that may be evident elsewhere (face, vive). If there are no indications of tremor or dysmetria, then score these items 2 and score speed 0.
- If active ROM of affected limb is significantly less than the unaffected limb, patients should be scored 0 for speed.

- - a. **Tremor** 2 = NO Tremor
 - 1..... = Slight Tremor

- 0 = Marked Tremor
-

1. Dysmetria 2 = NO Dysmetria

- 1 = Slight Dysmetria
- 0 = Marked Dysmetria

2. Speed 2 = maximum difference of 1 second between sides

- 1 = 2-5 seconds slower than non affected side
- 0 = more than 5 seconds slower than non affected side

-

LOWER EXTREMITY

I. **HIP / KNEE / ANKLE** all test in supine position are applied first to allow the patient to rest

1.1. Reflex activity: test non-affected side first

- 0 = No reflex activity
- 2 = reflex activity present

1.2. Volitional movement

- 0 = cannot be performed
- 2 = detail performed partially
- 2 = detail performed faultlessly

1.2.1. Within synergies subject in supine position

Flexor synergy: *Starting position:* leg fully extended

Instruction: bring your knee to the chest

- **Extensor synergy:** *Starting position:* Hand from flexor synergy to the hip extension/adduction, knee extension and ankle plantar flexion. Slight resistance is applied to ensure active movement, evaluate both movement and strength.
- *Instruction:* Push your foot down

II. **COORDINATION and SPEED** supine, after one trial with both leg, blind-folded, heel to knee cap of the opposite leg, 5 times as fast as possible. Each test is timed.

-

- 1. Tremor** 2 = NO Tremor
 1 = Slight Tremor
 0 = Marked Tremor

-

- 2. Dysmetria** 2 = NO Dysmetria
 1 = Slight Dysmetria

- 0 = Marked Dysmetria
-
- **3. Speed** 2 =
maximum difference of 1 second between sides
- 1 = 2-5 seconds slower than non affected side
- 0 = more than 5 seconds slower than non affected side
-

1.2.2.....Mixing

synergies *Starting position:* sitting knee 10cm from the edge of the chair/bed.

- **Knee flexion beyond 90°:** from active or passive extension.
- *Instruction:* Pull your knee back under the chair
- No active motion 0
- No flexion beyond 90°, palpate tendon of hamstring..... 1
- Knee flexion beyond 90°, palpate tendon of hamstring 2
- Ankle dorsiflexion:
- *Instruction:* Keep your heel on the floor and lift your front foot
- No active motion 0
- Limited dorsiflexion 1
- Complete dorsiflexion 2

1.2.3.....Without

synergies *Starting position:* standing, hip 0°, balance support is allowed

- **Knee flexion to 90°** Instruction: Keeping your hip still, kick your bottom with your heel
- No active motion or immediate hip flexion 0
- Less than 90° knee flexion or hip flexion during movement..... 1
- At least 90° knee flexion without hip flexion 2
- Ankle dorsiflexion: Knee extended
- Instruction: Keeping your knee extended and your heel on the floor, lift your foot
- No active motion
.....
..... 0
- Limited dorsiflexion
.....
..... 1
- Complete dorsiflexion
.....
..... 2

1.3. Normal reflex activity: tested only if full score (4 points) achieved on part 1.2.3.

- Test as in section 1.1
- Knee flexors, Achilles patellar
- 0 = No full point section 1.2.3. or 2 of 3 reflexes markedly hyperactive
- 1 = 1 reflex markedly hyperactive or at least 2 reflexes lively
- 2 = maximum of 1 reflex lively, none hyperactive

Appendix U FMA evaluation sheet

FMA Evaluation sheet

SHOULDER / ELBOW / FOREARM: subject in sitting position aim for 90° hip and 90° knee.

Reflex activity:

Flexors: biceps and finger flexors

Non-affected arm

Affected arm

Extensors: triceps

Subtotal (max 4):

Volitional movement

Within synergies

Non-affected arm

Affected arm

Flexor synergy:

Shoulder retraction (scapula)

Shoulder elevation

Shoulder abduction

Shoulder external rotation

Elbow flexion

Forearm supination

Extensor synergy:

Shoulder adduction/ internal rotation

Elbow extension

Forearm pronation

Subtotal

(max

18):

Mixing synergies

Hand to lumbar spine:

Shoulder flexion 0-90°:

Pronation-supination elbow at 90°:

Subtotal

(max

6):

Without synergies

Shoulder abduction 0 - 90°:

Shoulder flexion 90 - 180°:

Pronation/supination elbow at 0°:

Subtotal

(max

6):

Normal reflex activity

Biceps, triceps, finger flexors

--	--

Subtotal (max 2):

WRIST

Non-affected arm Affected arm

Stability at 15° dorsiflexion: elbow at 90°
 Repeated dorsiflexion / volar flexion: elbow at 90°
 Stability at 15° dorsiflexion: elbow at 0°
 Repeated dorsiflexion / volar flexion: elbow at 0°
 Circumduction:

90°

Subtotal (max 10):

HAND

Mass flexion
 Mass extension
 Distal finger Grasp
 Thumb adduction Grasp
 Thumb to index finger Grasp
 Cylinder Grasp
 Spherical Grasp:
 Mass flexion

Subtotal (max 14):

COORDINATION and SPEED after one trial with non-paretic arm, blind-folded, tip of the index finger from knee to nose, 5 times as fast as possible. Each test is timed.

Time Non affected side: T1

Time Affected side: T1 T2 T3

T4 T5

Non-affected arm Affected arm

**Tremor
 Dysmetria
 Speed**

Subtotal (max 6):

LOWER EXTREMITY

HIP / KNEE / ANKLE

Reflex activity: Non-affected arm Affected arm

Flexors: knee flexors
Extensors: patellar, Achilles

Subtotal (max 4):

Volitional movement

Within synergies

Flexor synergy:

Hip flexion
 Knee flexion
 Ankle dorsiflexion

Non-affected arm

Affected arm

Extensor synergy:

Hip extension

 Hip adduction

 Knee extension
 Ankle plantar flexion

Subtotal (max 14):

COORDINATION and SPEED supine, after one trial with both leg, blind-folded, heel to knee cap of the opposite leg, 5 times as fast as possible. Each test is timed.

Time Non affected side: T1

Time Affected side: T1 T2 T3

T4 T5

Tremor
Dysmetria
Speed

Subtotal (max 6):

Mixing synergies

Knee flexion beyond 90°:
 Ankle dorsiflexion:

Subtotal (max 4):

Without synergies

Knee flexion to 90°:
 Ankle dorsiflexion:

Non-affected arm

Affected arm

Subtotal (max 4):

Normal reflex activity:

Knee flexors, Achilles patellar

--	--

Subtotal (max 2):

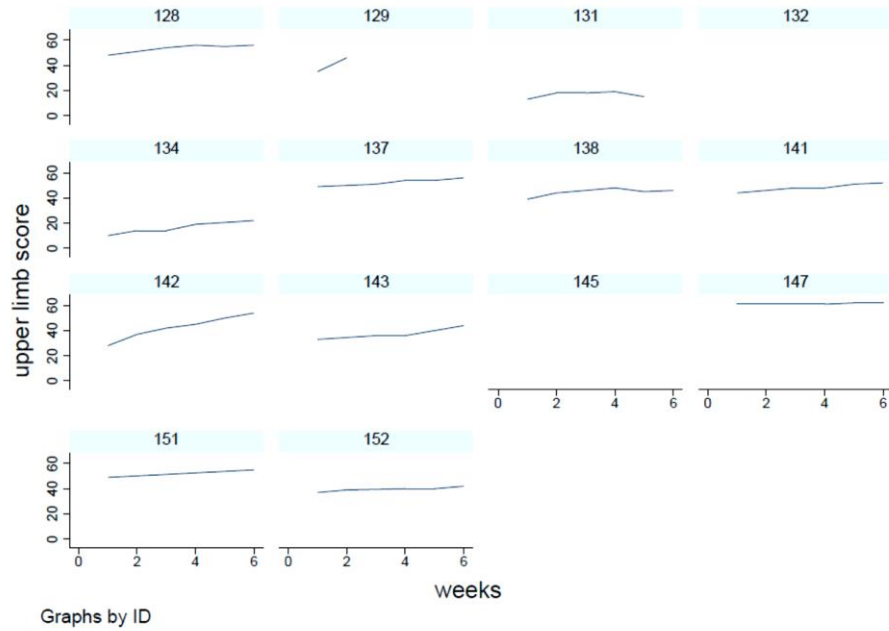
TOTAL SCORE

Upper limb score:

Lower limb score:

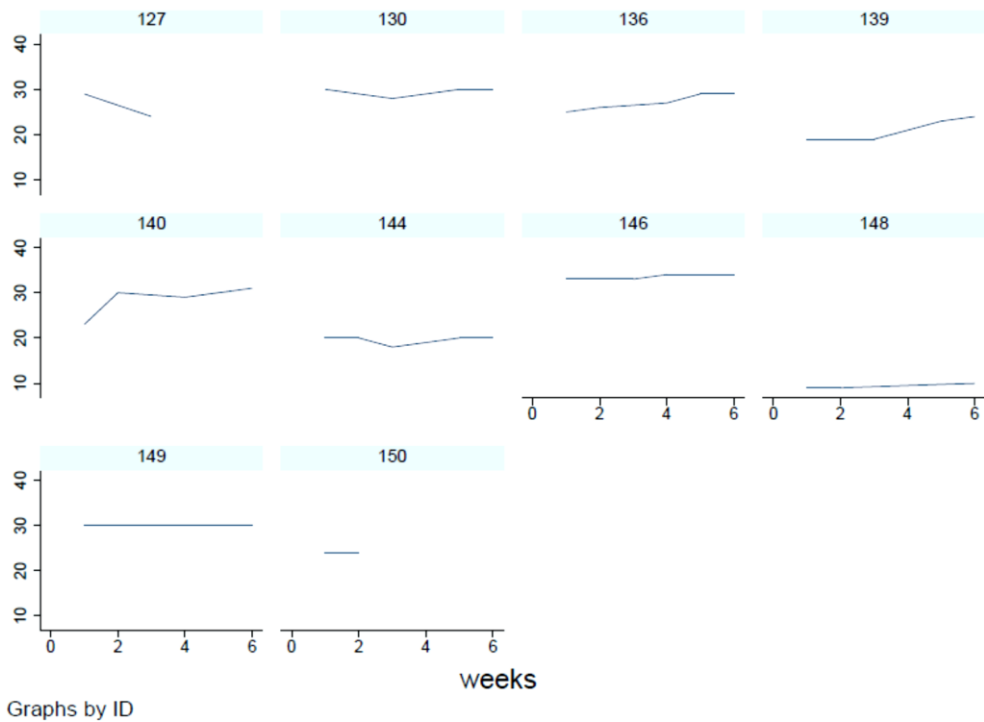
Appendix V FMA subjects' trend over time

Trends over time of FMA-UL score for each participant randomized to receive FST-UL



Note: x-bar=weeks; y-bar= FMA-UL score; participants' trial identification number (ID) is reported above each graph.

Trends over time of FMA-LL score for each participant randomized to receive FST-LL



Note: x-bar=weeks; y-bar= FMA-LL score; participants' trial identification number (ID) is reported above each graph.

Appendix W Sample size

The data coming from this feasibility study are used to make a power calculation for the upper and lower limb groups assuming that the FMA is used as a primary outcome measure⁶⁹.

Retrospectively, I used the data gathered at week six for the upper limb group. To have 80% power at 5% significance to detect a change of 5.25 points on the FMA upper limb score and a standard deviation of 11.3 and a loss of patients at follow-up of 30%, it is estimated that 118 participants per group are needed. A total of 236 participants are then required.

Retrospectively, I used the data at week five, for the lower limb, as the week which seemed related to the higher outcome. To have 80% power at 5% significance to detect a change of 10% on the FMA lower limb score and a standard deviation of 4.8 and a loss of patients at follow-up of 30%, it is estimated that 82 participants are needed per group. A total of 164 participants are then required.

⁶⁹ The sample size calculation is generally made on the study primary outcome.