A GLOBAL APPROACH TO UPPER EXTREMITY IMPAIRMENT POST-STROKE

TITLE PAGE

INCREASING INDEPENDENT PRACTICE EARLY POST-STROKE TO ENHANCE UPPER EXTREMITY FUNCTION: A GLOBAL APPROACH

By

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Abstract

Introduction

Post-stroke activity limitation secondary to upper-extremity motor impairment is common, and increasing. We do not currently have effective, globally applicable interventions to improve activity limitation. The burden of post-stroke disability is rising in low and middle-income countries, resulting in an immediate need for effective interventions that can be implemented throughout the world.

Purpose

This program of research was structured to address three important questions, 1) In all parts of the world, do people with stroke experience similar degrees of activity limitation secondary to upper extremity motor impairment? 2) Are there simple interventions that can be initiated by health care workers, but autonomously sustained by people with stroke, that can improve activity limitation secondary to upper extremity motor impairment? and 3) Are these interventions effective?

Methods

To address the first question, data from an international stroke study were used to quantify the amount of post-stroke upper extremity weakness and characterize the people. For the second question, a systematic review was conducted to identify current evidence on the effectiveness of simple, task-

based practice. To address the third question a protocol was developed for an outcome study.

Results

Post-stroke upper extremity weakness is common throughout the world, ranging from 67.3% of those with stroke in high-income countries to 97.3% in low-income countries. There is inconclusive, but promising evidence on the effectiveness of simple, task-based practice to improve upper-extremity motor impairment. It is likely that multiple interventions are needed to address the problem and a two-by-two factorial design trial, evaluating simple, task-based practice or a motor enhancing pharmacological agent, implemented in all regions of the world, would be a novel and efficient means of addressing the question.

Conclusions

The answers to these questions have provided novel information that is a required next step to providing effective, globally applicable interventions for people with stroke.

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I would like to start by thanking my supervisor, Dr. Laurie Wishart. She has truly been a mentor, one that I hope to emulate. Her consistent support and encouragement, her content knowledge that continually pushed me in new directions and her constant reminders of the importance of the work, even when I lost sight, will never be forgotten and is truly appreciated. Dr. Martin O'Donnell provided me the opportunity of a lifetime, to work on the INTERSTROKE database. He is also a rare internist who thinks function is as important as clinical outcomes, and has encouraged me to think beyond the usual limits in trying to understand functional outcomes and what is important to people. And Dr. Lehana Thabane rounded out the committee, providing the insights of not only a statistician, but also a seasoned researcher and mentor. I could not have asked for a better committee and I am hoping that this is just the beginning of our research endeavors together.

There are also my colleagues at the PHRI who have supported me throughout. Dr. Salim Yusuf, who not only encouraged my efforts, but has come to appreciate function as an outcome. Dr. Janice Pogue, who patiently addresses my never-ending statistical questions, and Dr. Hertzel Gerstein, who was always a willing and detailed reviewer. And I would like to thank my colleagues at the School of Rehabilitation Science who have also been extremely supportive of this endeavor.

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DECLARATION OF ACADEMIC ACHIEVEMENT

The following summary details all author contributions to each of the manuscripts contained within this thesis.

Chapter 2: Jackie Bosch identified the research question, and had assistance refining the question from all three committee members. Jackie performed all of the statistical analysis and wrote the manuscript with editorial assistance from all committee members.

Chapter 3: Jackie Bosch identified the study question, developed the systematic review protocol with input from Susan Barreca, Dr. Laurie Wishart and Dr. Martin O'Donnell. Jackie Bosch received assistance from Shannon Buckley to complete the initial searches and then Jackie replicated all searches again before final analysis. Jackie Bosch and Susan Barreca performed first and second reviews on all articles. Dr. Laurie Wishart and Dr. Martin O'Donnell assisted with a final review. The listed authors provided editorial assistance

Chapter 4: Jackie Bosch wrote the protocol paper and received feedback on all aspects from all committee members. She received guidance preparing the statistical analysis section from Dr. Janice Pogue. Elements of the UPPER intervention were based on work with Dr. Laurie Wishart and Dr. Vincent DePaul from the IMPACT (Independent Mobility and Physical Activity Training) manual.

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CHAPTER 1: INTRODUCTION

Stroke mortality rates have declined over the last two decades, but incidence has remained the same (Feigin et al., 2014), which means more people are living with stroke. Some stroke survivors, in particular those left totally dependent for all activities, do not consider life after stroke to be much better than death (Luengo-Fernandez, Gray, Bull, Cuthbertson, & Rothwell, 2013). Approximately 20% of stroke survivors are left completely dependent; while somewhere between 30 and 65% have persistent mild to moderate disability (Go et al., 2014; Luengo-Fernandez, Paul, et al., 2013). While there are many contributing factors to post-stroke disability, motor weakness and loss of motor control is a common, persistent problem. In particular, loss of upper extremity function has a devastating effect on independence in daily activities and is estimated to occur in about 48-77% of stroke patients (Lawrence et al., 2001; Persson, Parziali, Danielsson, & Sunnerhagen, 2012). To try and perform daily activities, patients often spontaneously use only their non-affected extremity, even if they have partial movement in their affected extremity (Takeuchi & Izumi, 2013). This combination of impairment and disuse sets up a vicious cycle that perpetuates motor impairment in the affected extremity and limits the ability to perform activities requiring the use of both hands, issues referred to throughout this document as motor impairment and activity limitation, using the World Health Organization International Classification of

Functioning, Disability and Health (World Health Organization, 2002). According to stroke survivors, researchers and clinicians, identifying effective interventions to improve upper extremity function and related activity limitation is one of the top five most important research priorities (Pollock, St George, Fenton, & Firkins, 2014).

This chapter is the first of five included in this dissertation. The thesis will describe three specific research activities that contribute to a program of research dedicated to developing effective motor recovery interventions to improve functional recovery post-stroke. The first section of this chapter will discuss the current evidence on interventions to improve post-stroke upper extremity motor impairment. This is followed by a discussion of potential mechanisms to enhance neuroplasticity, a key driver of motor recovery and finally a discussion of considerations for developing globally applicable interventions. The goal of this chapter is to set the scene to discuss the objectives of this thesis, as well as the thesis component pieces, which have been designed to provide the knowledge that is needed to develop effective, globally applicable interventions.

Interventions for Upper Extremity Motor Impairment and Activity Limitation

Although the importance of identifying effective upper extremity stroke rehabilitation interventions is well recognized, there has been difficulty doing so. This is not for lack of trying. In the last 30 years, half of all stroke

rehabilitation studies have tested interventions to improve motor impairment (both upper and lower extremity) and activity limitations secondary to motor impairment (McIntyre, Richardson, Janzen, Hussein, & Teasell, 2014). The problem with these studies is that they have traditionally been small (McIntyre et al., 2014) and methodologically flawed (Santaguida et al., 2012; Stinear, Ackerley, & Byblow, 2013), resulting in many studies providing inconclusive results. The absolute number of studies conducted has led to a large number of systematic reviews on upper extremity motor interventions, including task-based practice (Bosch, Donnell, Barreca, Thabane, & Wishart, 2014), intensity of practice (Sehatzadeh, 2013), virtual reality (Laver, George, Thomas, Deutsch, & Crotty, 2012) repetitive task training (French et al., 2010), bilateral arm training (Latimer, Keeling, Lin, Henderson, & Hale, 2010), bilateral mechanical and robotic training (van Delden, Peper, Kwakkel, & Beek, 2012), specific interventions for those with severe upper extremity paresis (Hayward, Barker, & Brauer, 2010), rehabilitation started early (Lynch, Hillier, & Cadilhac, 2014) and home-based therapy programs (Coupar, Pollock, Legg, Sackley, & van Vliet, 2012). Each one was inconclusive. Systematic reviews on constraint induced movement therapy do support the potential effectiveness, although recognize that these results are not consistent across studies, dominated by a large trial that demonstrated a clear effect, and that the question of appropriate dosage remains

(McIntyre et al., 2012; Nijland, Kwakkel, Bakers, & van Wegen, 2011; Sirtori, Corbetta, Moja, & Gatti, 2009). Therefore despite these research efforts, there is no definitive answer to inform best practice. Perhaps part of the problem is inherent in the interventions we are studying and the methods for evaluating.

Pollock et al., (2014) emphasized that a key problem in stroke rehabilitation research is the use of "compartmentalised, named approaches" (p. 2) instead of testing theoretically based, evidence supported and well-described interventions. To create and test a well-described intervention, researchers need to have a clear understanding of the pathophysiology causing the motor impairments, possible mechanisms through which the intervention will address the problem and ideally some evidence that the hypothesis is accurate. Although we don't have all the answers, there is compelling evidence that post-stroke motor impairment is caused primarily by damage to the motor cortex as well as the corticospinal tract (Grefkes & Fink, 2011; Groisser, Copen, Singhal, Hirai, & Schaechter, 2014; Nudo, Plautz, & Frost, 2001; Ward, 2011). The resultant loss of motor control occurs through a combination of loss of central direction and associated motor unit disturbance and muscle weakness (Shepherd, 2001). This in turn results in activity limitation and motor impairment (*see Figure 1 for a schematic diagram of this process*).

Mechanisms of Motor Recovery After Stroke

Motor recovery is thought to occur through a variety of mechanisms including spontaneous injury-induced recovery (Cramer, 2008; Nudo, 2013) and experience-dependent neuroplasticity (Cooke, Mares, Clark, Tallis, & Pomeroy, 2010; Kleim & Jones, 2008). Ideally an intervention would target both injury and experienced-induced neuroplasticity, but unfortunately at present, there is no way to influence spontaneous, injury-induced recovery after stroke. Instead we must target experienced-induced neuroplasticity to promote upper extremity motor recovery, and in particular, motor control and skill acquisition, as these are pivotal for regaining the functional use of the upper extremities. Therefore experience-dependent motor recovery should be a key component of a post-stroke upper extremity motor recovery intervention (see Figure 1). This concept is strongly supported by practice guidelines in both Canada and the UK (Dawson et al., 2013; National Institute for Health and Care Excellence, 2013).

Ideally, we also want to “prime” the neural system to be more receptive or efficient when using experience to drive neuroplasticity. There are some data to indicate that pharmaceutical agents could enhance experience-dependent neuroplasticity (Dimyan & Cohen, 2011). Serotonin re-uptake inhibitors and monoaminergic drugs have both been identified as having the potential to help “prime” the motor cortex and the basal ganglia

(Dimyan & Cohen, 2011), which may lead to greater effects when combined with rehabilitation interventions working through experience-dependent neuroplasticity. The potential for benefit exists, but is yet to be proven. Additional considerations for a pharmacological agent of choice would be the safety and tolerability of the drug, the ease of administration (e.g. is regular blood monitoring required) and the expense.

Careful choice of interventions, based on the best available data on the potency of effect is appropriate. This could mean either rehabilitative or pharmacological interventions that promote neuroplasticity may be the most potent drivers of drivers of motor recovery (Bowden, Woodbury, & Duncan, 2013; Kleim & Jones, 2008). However, if interventions are to be globally applicable, consideration must also be given to the feasibility of delivery in both resource rich and resource poor settings (Bethge, von Groote, Giustini, & Gutenbrunner, 2014).

Systems Issues in Implementing Globally Applicable Stroke Interventions

The issue of the global necessity for stroke interventions is now coming to the forefront of research agendas, as the international burden post-stroke disability is better understood (Feigin et al., 2014). Clinical guidelines on stroke rehabilitation acknowledge the importance of the amount of practice, using the amount of rehabilitative therapy time as a surrogate for dose (Dawson et al., 2013). These guidelines do not address two important

"system" considerations; i) inpatient stroke rehabilitation is not available in most parts of the world (Bernhardt & Cramer, 2013), and ii) in places where there is organized stroke care, there are limited resources available. Many of the interventions previously described require equipment or specific training or careful monitoring of the patient. While the need for simple, globally applicable stroke rehabilitation interventions is evident, to date interventions have primarily been developed for countries with some type of organized stroke rehabilitation system. Interventions are needed that are applicable in a variety of settings, recognizing that in some places the intervention may be all that is available, while in others it may be an adjunct to therapy.

Next Steps: Thesis Goals

The intent of this dissertation is to provide the relevant information needed to develop and test a globally applicable intervention to improve post-stroke activity limitation secondary to upper extremity motor impairment. Three main questions are addressed:

1. Is post-stroke upper extremity motor impairment common throughout the world? Lacking is an understanding of the characteristics of people with stroke in various parts of the world. Is activity limitation post-stroke the same worldwide? Are the causes of activity limitation post-stroke the same in various parts of the world? As basic as these questions might be, until there is some picture of the similarity (or dissimilarity) of post-stroke

impairment and activity limitation internationally, it would be difficult to develop an intervention that is applicable to all. As a first step, data are needed to help understand the presentation of post-stroke motor impairment and activity limitation in different countries and parts of the world.

2. Based on currently available evidence, does simple task-based practice improve post-stroke upper-extremity motor impairment? The theoretical rationale, along with promising evidence from constraint induced movement therapy interventions (which use a type of task-based practice), indicate that task-based practice could be an effective intervention. But what does task-based practice actually look like? In the simplest form, it means using a task or activity (e.g. buttoning a shirt, pouring a glass of water) as the means to practice, opposed to, for example, an exercise (lift your arm to shoulder height). Some studies have declared task-based practice as the experimental intervention (French et al., 2010), however rarely is enough information provided about the intervention to understand specifically what was done. When information is provided, it is evident that the interventions differ in underlying theoretical frameworks, methods of delivery, amount, etc. Lacking are data on the effectiveness of well-defined, well-quantified, simple task practice, including the amount of effortful practice that is required to drive motor recovery (Birkenmeier, Prager, & Lang, 2010). An understanding of what information is available

is key before going the next step and developing a simple task-based intervention.

3. Is it possible to design a globally applicable, efficient trial that could test the effectiveness of interventions to improve post-stroke upper extremity motor impairment and activity limitation? Once the interventions are identified, they need to be tested in a well designed clinical trial, that can clearly determine effectiveness, a practice suggested by the UK Medical Research Council in their guidance document on Developing and Evaluating Complex Interventions (Craig et al., 2008). These questions led to the specific objectives covered in this dissertation.

Thesis Objectives

The specific objectives of this thesis are to:

1. Describe the global variation in post-stroke upper extremity weakness and activity limitations, to understand if this issue is important in all parts of the world.
2. Understand the current evidence on task-based practice and whether a “dose response” is detectable.
3. Design a trial to efficiently test the most promising, globally applicable, intervention(s) for upper extremity motor weakness following stroke.

These specific objectives are part of a larger research program that also examines similar issues for the lower extremity (the IMPACT: Independent Mobility and Physical Activity Training trial).

Description of the Thesis

A sandwich thesis approach was chosen as the most appropriate method for presenting this material. The questions raised are of significant importance and publication of the work will add substantially to the body of knowledge in this area. A brief description of each objective follows.

Chapter 2: Understanding Upper Extremity Weakness Activity Limitation Post-Stroke on a Global Level

INTERSTROKE is the largest case-control study on stroke in the world (O'Donnell et al., 2010), led by Dr. Martin O'Donnell (a member of my thesis committee) and Dr. Salim Yusuf. The purpose of the study is to examine the risk factors associated with stroke and determine the frequency of these risk factors in various parts of the world. The trial was designed to be large (over 26,000 participants in total, 13,000 cases and 13,000 controls, in 32 countries) and simple, and therefore data collection was kept to a minimum. The researchers asked a few questions about impairment and activity limitation before, at the time of, and after stroke in all participants. These data allowed us to globally examine the incidence of upper extremity weakness and activity limitation after stroke. Data collection for the main study was completed in January 2014 and study

results will be published in the latter half of 2014. This manuscript will be submitted for publication only after the main study results have been published, and the thesis will be embargoed until such publication.

Chapter 3: Understanding the Effectiveness of Task-Oriented Practice

We conducted a systematic review to understand whether basic task practice, i.e. task-practice that can be implemented without knowledge of specific techniques or additional equipment, can be effective in improving upper extremity motor impairment post-stroke. Building on the understanding of the global prevalence of upper extremity weakness post-stroke, the intent of this review was to provide an estimate of the effect of task-based practice and ideally to determine the appropriate amount of practice needed to restore motor function. This manuscript has been published.

Chapter 4: Testing Optimal Interventions for Motor Recovery Post-stroke

With an understanding of the best evidence on the effect of task-based practice, coupled with data on the prevalence of post-stroke upper extremity motor impairment across the globe, we designed the PROOF (Post-stroke Recovery Of Optimal Function) trial. PROOF tests whether a simple, task-based, intervention to increase practice, in addition to therapy (if available), can improve upper extremity motor recovery post-stroke. PROOF is designed to clearly demonstrate a result, and will therefore be one of the largest trials of stroke rehabilitation interventions ever

conducted. Given such a unique opportunity, the trial is designed to maximize the information gained, and uses a factorial design to also test whether the supplementation of dopamine through use of carbidopa-levodopa (which is converted to dopamine in both the peripheral circulation and the central nervous system) may also be effective in improving motor impairment and activity limitations after stroke.

Chapter 5: Discussion

The discussion will allow a more thorough exploration of some of the methodological and practical challenges faced in each of the topic areas. Related research studies that are currently underway will be discussed as will the potential impact of the results on the research described in this thesis. And finally, a discussion of the larger research program will be provided along with some insights gained from these endeavours.

Content Overlap Between Manuscripts

Each chapter presents a unique aspect of the issue of determining optimal interventions in stroke rehabilitation. Understanding who is affected, and whether, based on available data, a simple intervention can work and creating the study to definitively test the question are essential components of the overall program of research. Overlap in content occurs mainly in the introduction and background sections, where the scope of the problem and knowledge on the existing interventions is provided.

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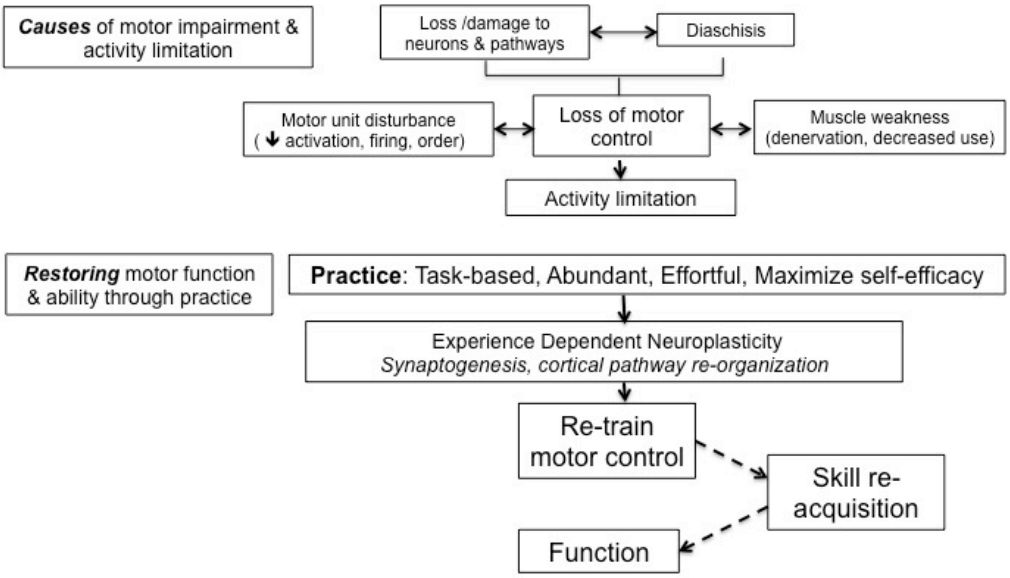
Chapter 1 - Figure 1: Mechanisms of Motor Impairment & Recovery



Adapted from Shepherd 2001, Birkenmeier 2010, Grefkes, 2011, Ward 2011

CHAPTER 2: UPPER EXTREMITY WEAKNESS AND FUNCTIONAL DEFICITS POST-STROKE: A GLOBAL PROFILE FROM 32 COUNTRIES BASED ON THE INTERSTROKE STUDY

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Abstract

Background

While data are available on stroke incidence, mortality and disability rates in many countries, there is little available on the prevalence of post-stroke upper extremity activity limitation and motor impairment across the globe.

Aims

To determine the incidence of post-stroke upper extremity motor impairment in various regions and countries, and the degree of activity limitation in those with arm weakness.

Methods

Using data available from the 32 country INTERSTROKE Study, the key baseline characteristics, incidence of upper extremity impairment at the time of stroke and degree of activity limitation, at the time of and one month after stroke, were calculated. Data were also grouped according to country income level (high (HIC), upper middle income (UMIC), lower middle (LMIC) and low income (LIC)) for each country.

Results

After first stroke, arm weakness was present in 77.9% of all patients (67.3% from HIC, 74.4 % from UMIC, 89.4% from LMIC and 97.3% from LIC). Post stroke, 47.3% of all patients reported moderate to severe activity limitation and 25.5% reported the same at 1 month.

Conclusions

These data confirm that in every country and at every country income level, there are large percentages of patients with upper extremity weakness that have moderate to severe activity limitation one month post-stroke, and this is more common in LMIC and LIC compared to UMIC and HIC.

Commonly Used Abbreviations

mRS	modified Rankin Scale
HIC	High income country
LIC	Low income county
UMIC	Upper middle income country
LMIC	Lower middle income country
UEW	Upper extremity weakness
GNI	Gross national index

Introduction

Research articles on stroke usually begin by describing the associated morbidity and mortality, as the figures are startling. Indeed the most recent data indicate that stroke is the second leading cause of mortality and seventh leading cause of disability adjusted life years (DALY)—a measure that combines years of life lost due to premature mortality and years lost because of disability (Feigin et al., 2014). Over the last twenty years there has been an increase in both the absolute number of strokes, as well as the DALYs incurred, meaning that more people are living after stroke, and in particular living with disability after stroke, with the most significant increase in low and middle income countries (Ferri et al., 2011; Krishnamurthi et al., 2013; Sousa et al., 2009). While the DALY provides a measure of disease burden, it lacks specificity in terms of the type or cause of disability. To better understand post-stroke disability, researchers and clinicians measure impairments (including motor weakness) and activity limitations (such as functional decline) (World Health Organization, 2002). It is estimated that between 40% and 60% of stroke survivors have permanent activity limitations, (Hankey et al., 2007) with either no improvement or worsening limitations up to ten years after stroke (Dhamoon, Moon, Paik, Sacco, & Elkind, 2012; Wolfe et al., 2011). Upper and lower limb motor impairments are common post-stroke (Lawrence et al., 2001), and it is likely that these impairments are strongly associated

with activity limitation. Research on post-stroke interventions has primarily focussed on the lower extremity rather than the upper extremity, probably because outcomes are easier to quantify, and interventions are somewhat easier to deliver. Upper extremity motor impairment, and the associated activity limitation, is equally important. Studies indicate that upper extremity motor impairment is at least as common as lower extremity impairment, with up to 75% of patients reporting impairment immediately after stroke (Lawrence et al., 2001), and between half and three-quarters of patients experiencing long term upper extremity impairment (Au-Yeung & Hui-Chan, 2009; Lai, Studenski, Duncan, & Perera, 2002). While these data on activity limitation and upper extremity impairment provide an idea of the type and cause of post-stroke disability, there are a few key limitations: a) *Limited generalizability:* The detailed information on upper extremity impairment was collected almost exclusively in high-income countries. Results from recent studies show that over the past two decades, disability associated with stroke is actually on the decline in high income countries (HIC), while there is a substantive increase in DALYs in both low and middle-income countries (Feigin et al., 2014), b) *Underestimate of activity limitation*: In low and middle income countries, strokes occur in those who are younger, and potentially still working (Feigin et al., 2014). The DALY does not consider the effect of stroke on employment or income, as the DALY calculations used for the 2010 Global

Burden of Disease study measures health loss as opposed to welfare loss (Salomon et al., 2012). The DALY is then an underestimate of the effect of post-stroke disability, especially in low and middle-income countries, c) *Heterogeneity of outcome measures of upper extremity impairment:* The previously mentioned studies that have quantified post-stroke upper extremity impairment have used different measures to do so, making it difficult to compare data across studies. In order to obtain an accurate global profile, consistent eligibility criteria and outcome measures need to be used in each country. These data can then provide an accurate estimate of the global profile of post-stroke upper extremity motor impairment, and can be used to inform the development of globally applicable interventions to improve motor impairment and activity limitation, as well studies to test the effectiveness. The urgent need to develop and test stroke rehabilitation interventions is currently one of the top priorities in stroke research (Hachinski et al., 2010).

Objectives

The primary objective of this paper is to describe the frequency of post-stroke upper extremity motor impairment and activity limitations among patients admitted to hospital with first stroke, in various regions of the world, using data from the INTERSTROKE Study (O'Donnell et al., 2010). INTERSTROKE, a case-control study designed to determine the extent to which traditional and novel risk factors contribute to the development of

stroke, is the largest study of it's kind, having collected data on over 26,000 participants (half cases and half controls) from 32 countries.

Characteristics of People with Stroke and Upper Extremity Impairment or Activity Limitation

In addition to understanding the prevalence of the problem, we wanted to examine various characteristics of people with stroke and upper extremity impairment and activity limitation, *overall, by country income level* and where noted*, by country*, for the following:

i) Frequency of key characteristics of those with post-stroke upper extremity impairment, that might affect either adherence or response to an intervention, (e.g. age, sex, type of stroke, pre-morbid physical activity levels and past medical history (Dashe, 2014)),

ii) Prevalence of major motor, sensory or speech impairments in those with upper extremity impairment (defined as motor weakness for this analysis), to understand the frequency of co-existing post-stroke impairments,

iii) Distribution of activity limitations after stroke by country, in those with upper extremity impairment, to understand the prevalence of the problem in each country,

iv) Distribution of activity limitations, for those with upper extremity impairment, before, at the time of, and 1 month post-stroke, to

demonstrate activity limitation trends by country income level at each time point,

v) Number of post-stroke patients with upper extremity impairment receiving rehabilitation four weeks after stroke, to get an understanding of the amount of post-stroke intervention provided.

Methods

The INTERSTROKE Study

The rationale and design of the INTERSTROKE Study have been presented elsewhere (O'Donnell et al., 2010). Briefly, INTERSTROKE is a multi-centre, multi-national, case-control study designed to understand the incidence and prevalence of key risk factors for stroke, and how these differ internationally. Eighty-four centres recruited participants from 32 countries (a list of the participating countries can be found in Table 1). Overall, 27,531 participants were recruited between April 2007 and January 2014, of which 13,725 were cases and 13,806 controls. Given the aim of this paper, only case data were used for these analyses. Cases were those with a first stroke, had persistent symptoms (> 24 hours) in the preceding five days that were most likely attributable to a stroke, were within 72 hours of being admitted to hospital and had a Computed Topography (CT) scan or a Magnetic Resonance Imaging planned within the next week. Participants were not eligible if they were in hospital for an

acute coronary syndrome, if the stroke was not of vascular aetiology or if the stroke survivor or their proxy would not provide consent.

Data Collection

Details of all demographic data that were collected are described in the design paper (O'Donnell et al., 2010). Study personnel collected the case data and were instructed on how to administer the measures. Data were obtained primarily through patient interview (i.e. no direct observation), however proxy respondents (spouse or first degree relative) could provide information if the participant was unable to communicate. The following baseline data were used for these analyses, a) date of birth (or age), b) educational level achieved, c) past medical history, d) physical activity level, divided into four categories to describe their pre-stroke physical activity level either at work or during leisure time (mainly sedentary, minimal walking/mild exercise, mainly walking/moderate exercise, heavy physical labour/strenuous exercise), e) existence of symptoms lasting 24 hours or more post-stroke, including one question each on weakness or paralysis of the arm/hand, leg or face. Of importance to this analysis is that participants were questioned on the existence of arm or hand weakness (yes or no) rather than motor impairment, and therefore results are presented for upper extremity weakness, f) activity limitation, measured using the modified Rankin Scale (mRS). This is a widely used, simple, reliable and valid seven-point scale (0 = no activity limitation, 6 =

death). A score of 2 or less indicates slight to no disability (Banks & Marotta, 2007; Quinn, Dawson, Walters, & Lees, 2009), scores of 3-4 indicate moderately/severe disability and 5 is considered severe disability. Participants were asked about functional activity before stroke, at baseline (within days of stroke) and at one month and these data were used to complete the mRS for each time point. Physicians provided the diagnosis of stroke based on both clinical presentation and neuroimaging. Follow-up occurred at one month, at which time it was determined whether the participants were alive, discharged from the initial hospital admission or still in hospital. If discharged, participants were asked if they were at home, in a rehabilitation or long-term care facility or elsewhere. If still in hospital, participants where asked if they were on an acute, rehabilitation or long-term care unit.

Statistical Analyses

The percentage of participants with upper extremity weakness was calculated using the total number of cases as the denominator. Country income level was chosen as the regional grouping factor because of it's association with stroke, and because it is an indicator of health expenditure, which could influence post-stoke outcomes (Higashida et al., 2013; Sposato & Saposnik, 2012). The World Bank's measure of gross national income (GNI), from July 1, 2007 – June 30, 2012, was used to group countries, as this is when recruitment occurred (World Bank Group,

2014). The GNI is a measure of both domestic and foreign output claimed by nationals living inside and outside of the country. The World Bank categorizes GNI levels per capita by country as follows; low income (LIC) = <+$1,035 USD; lower middle income (LMIC) = $1,036 - $4,085 USD; upper middle income (UMIC) = $4.086-12,615 US; high income (HIC) = >$12,615 USD. Countries were classified based on the median category during the recruitment time frame or if there were two medians, the median GNI during 2009-2012, as this is when the majority of recruitment occurred.

Key baseline characteristics as well as presence of motor, sensory and speech impairments are presented as the percentage of those with upper extremity weakness overall, and the percentage in each income level. Where provided, a Pearson's chi squared test was calculated to determine the association between income level and categorical variables; for continuous variables, an analysis of variance was used. p values of less than 0.05 are considered statistically significant.

The data on the modified Rankin Scale provided in Figures 3b and 3c, were adjusted for age, gender, type of stroke, past medical history or heart disease, hypertension, diabetes and atrial fibrillation, using a partial proportional odds model (since the proportional odds assumption was violated). All data were analysed using STATA 13.1 for Mac (StataCorp, Texas, USA).

Results

A total of 13,639 cases were recruited from 32 countries. From these cases, 10,621 (77.9%) had upper extremity weakness after stroke, and form the cohort used in these analyses, which will be referred to as the upper extremity weakness (UEW) group. Those in the UEW group were divided amongst the country income group levels as follows, 17.4% (n=1,850) from HIC, 46.9% (n=4,983) from UMIC, 30.7% (n=3, 257) from LMIC and 5.0% (n=531) from LIC. Baseline assessments were completed within a median of 2 days of stroke (1st quartile [Q1] -3rd quartile [Q3], 1-3 days) and 1-month assessments were completed within a median of 31 days of the baseline assessment (Q1-Q3: 29-39 days).

Primary Objective - Frequency of post-stroke upper extremity weakness: At the baseline assessment, of the 10,621 (77.9%) with UEW, arm weakness was present in 67.3% from HIC, 74.4 % from UMIC, 89.4% from LMIC and 97.3% from LIC. Figure 1 illustrates the percentage of upper extremity weakness by country.

Results from each of the five questions characterizing the population are presented below:

Frequency of key baseline characteristics: Table 2 describes the baseline characteristics of the sample. The overall mean age of the UEW group was 61.9 years (standard deviation (SD), 13.7 years), with the youngest participants coming from the LMIC and LIC (59.2 years (SD 13.3) and 58.7

years (SD 14.8) respectively ($p<0.001$)). Overall, 40.5% of the UEW group were women, with the largest percentage from LIC (n=268, 50.5%) and just about 40% from the three other income level groups ($p<0.001$). Over 80% of the study population had at least some education, with only 3.3% in the HIC reporting no education, compared to about 15% in the UMIC and LIC groups, and close to 29% in the LMIC group ($p<0.001$). About 40% of the UEW group was working at the time of stroke, and in those, more men were working at the time of stroke (51.2%) compared to women (23.0%) The majority of working men were in LMIC and LIC countries, while the majority of women who were working at the time of their stroke were in the LIC group. Approximately 75% of the overall UEW cohort reported minimal to no physical activity prior to stroke, either during leisure or work time. There were fewer in the LIC group who described their behaviour as sedentary (53.7%) compared to about 75% in the other groups ($p<0.001$). Ischemic stroke accounted for 74.4% of all strokes, although this ranged from 60.0% in the LIC group to 91.6% in the HIC group. Twenty-three point 8 percent had intracerebral haemorrhage, while very few had subarachnoid haemorrhage (1.0%). Over half of the UEW group had hypertension (55.6%) with the highest percentage in the LIC group (63.5%) and lowest in the LMIC group (45.5%). High cholesterol and diabetes were reported by 13.0% and 17.2% respectively, with the highest percentages of each in the HIC group. Therefore, the UEW group

as a whole are fairly young, more likely to be male and have had an ischemic stroke. Educational levels achieved, physical activity levels and the number who are employed at the time of stroke differ by region.

Prevalence of major motor, sensory or speech impairment: Leg weakness was the most common post-stroke symptom, occurring in 89.2% overall, over 90% of those in UMIC, LMIC and LIC groups (Table 3) and 73.5% in HIC. Sensory changes ("numbness") were reported in just over half of the UEW group, and aphasia in about one third. Therefore, post-stroke symptoms are common in all regions, however LIC participants experienced the highest percentages.

Distribution of activity limitation after stroke: The degree of post-stroke activity limitations was measured using the mRS. In Figure 2, the countries are ordered according to those countries with largest percentage of the UEW group reporting slight to no disability (an mRS score 0-2). For example, Denmark is first because they reported the highest percentage of participants with an mRS score of 0 or 1. This figure demonstrates the variation in mRS scale score by country, with between 31% and 94% in the UEW group reporting moderate disability (mRS ≥3) after stroke. Over half (52.4%) of those in the UEW group had a post-stroke mRS score of 3 or 4, with percentages ranging from 18% (Ireland) to 82% (Russia). Overall, there was a large percentage of patients with UEW who have

activity limitations post-stroke, with 47.3% reporting moderate to severe activity limitation (mRS 3 or 4) post-stroke and 25.5% at 1 month.

Distribution of activity limitation before, at the time of and 1 month after stroke: The mRS was used to quantify activity limitation before, at the time of and after stroke. Figure 3 provides the mRS data by country income level, before stroke (3a), post-stroke (3b) and 1 month after stroke (3c). In each region, the majority of patients were functioning independently and without limitation prior to first stroke (3a). Figure 3b describes the degree of activity limitation among participants after stroke, by country income level. At 1 month (3c), there is a shift towards less activity limitation, however this is more pronounced in the HIC, as there are more with an mRS of 0 or 1 compared to the other regions. The UMIC, LMIC and LIC groups continue to have more participants with an mRS of 3 or 4 compared to the HIC, and more died in each of these regions as well.

Number of post-stroke patients receiving rehabilitation: The majority of patients were discharged from their initial admission by the 1-month follow-up assessment (86.7%); 7.8% had died and 4.4% remained in hospital (Table 4). Of those discharged, the majority went home (92.8%). This discharge location was particularly common in the UMIC where 86.2% of those discharged went home, the LMIC where 98.1% went home and the LIC where 95.3% went home, compared to 76.0% of the patients in the HIC (where 20% of the participants were discharged to a

rehabilitation centre). The majority of the participants that remained in hospital and in rehabilitation were primarily from the HIC (73.4% of those still in hospital). At one month, a total 714 out of the 9,687 participants (7.4%) remained in rehabilitation (either discharged to a facility or still in hospital from initial admission). Therefore rehabilitation post-stroke occurs primarily in the HIC, although for a relatively small proportion (23%); the majority of stroke participants with UEW are at home one month after stroke.

Discussion

The purpose of these analyses were to describe a) the prevalence of upper extremity weakness after first hospitalized stroke in an international cohort, b) the key baseline characteristics of post-stroke participants with UEW, c) the amount of activity limitation experienced by post-stroke participants with UEW, and d) whether this cohort receives rehabilitation after stroke. The results of these analyses indicate that a) arm weakness post-stroke is prevalent in all regions and countries, although higher in LIC, b) the baseline characteristics of those with UEW differ based on country income level, c) activity limitations are, to varying degrees, present after stroke regardless of country income level, d) one month post-stroke, activity limitations are diminished, but remain, and this is more evident in LMIC and LIC compared to UMIC and HIC, and e) overall, few participants with UEW are receiving rehabilitation 30 days post-stroke, and those

participants are primarily in HIC, however even in HIC, very few receive rehabilitation. While studies have reported on UEW and disability after stroke, these are the first data assembled from one international cohort that included HIC, MIC and LIC settings. These data confirm that in every country and at every country income level, there are large percentages of patients with UEW that have moderate to severe activity limitation one month post-stroke.

These are the first data to describe the cohort of post-stroke patients with UEW. In addition to understanding the characteristics of these patients, they have provided insight about important considerations for implementing interventions and potential confounders to consider when designing studies. For example, age and type of stroke are usually considered important predictors in terms of activity limitations (Dashe, 2014). Our data demonstrate that compared to HIC and UMIC patients, those in LMIC and LIC tend to be slightly younger and experience more intracerebral haemorrhages (both related to better outcomes), but they are also more likely to be female, less educated, and have hypertension (related to poorer outcomes). These are important considerations when implementing interventions (historically designed and evaluated primarily in HIC). For example, some interventions use a behavioural contract, which requires that the patient be able to read and write. Alternative methods for establishing a contract, such as a pictorial representation of

the concepts, need to be developed for those who are not literate. When designing studies, researchers can use these data to consider the potential effect of these confounders on the effectiveness of the intervention, and should adjust study procedures, and potentially sample size, accordingly. Data collection should include an ability to quantify the existence of the confounders to understand any imbalances that may occur and, if required, adjust for such imbalances.

Another important finding is that the majority of men who have a stroke in UMIC, LMIC and HIC countries were working prior to having their stroke. It is likely that these men were important contributors to household income and that they are no longer able to earn these same wages. Family income can be further limited if other family members must stay home to care for patients who require constant assistance with activities of daily living, and there are no socialized support systems, as is the case in many of these countries. Enabling patients post-stroke to independently overcome motor impairment and activity limitation may have an important effect not only on the individual but also on the family as a whole.

These data also confirm that the initial activity limitations seen post-stroke remain for many one month after stroke, with about 65% of the cohort reporting some deficit at one month (mRS of 2 or greater). This rate is similar to previous data indicating about 68.5% of patients in a HIC experienced moderate disability at the time of hospital discharge (Arboix et

al., 2003). Therefore, activity limitation persists for those with UEW, emphasizing the need for rehabilitative strategies to improve upper extremity impairment and activity limitations.

The number of patients receiving rehabilitation at one month is fairly low (7.3%) given the degree of residual activity limitations, and the majority of the patients (60%) in rehabilitation are from HIC, although in absolute numbers this is also relatively few. Even within HIC, the existence of organized stroke units is not consistent. The key message to consider is that post-stroke rehabilitation needs to be designed so that patients can carry out the activities in a hospital or home environment, likely with minimal if any health team support. Interventions need to be designed so they can be initiated by trained health care workers (e.g. doctors, nurses, rehabilitation specialists), but should be sustainable by the patients. Effective interventions that are currently available to address upper extremity motor impairment and activity limitation, such as Constraint Induced Movement Therapy or virtual reality, all require allied health professionals to provide the intervention and some require additional equipment. Countries that have limited health care resources have limited opportunity to provide organized post-stroke rehabilitation, leaving patients with motor impairment and activity limitations without any means of remediating the deficit. As health professionals we need to respond to the

real world situation experienced by post-stroke patients and develop interventions that are safe, sensible and sustainable.

Although post-stroke upper extremity motor recovery interventions may be needed globally, to date intervention testing (clinical trials) has occurred almost exclusively in HIC. At present we do not have data on the effectiveness of either known or novel interventions in UMIC, LMIC and LIC. Based on our analyses, recruitment to intervention trials is feasible, as potentially eligible participants exist in all INTERSTROKE countries. Usually, inclusion criteria for post-stroke upper extremity intervention studies require that participants have some upper extremity movement. This inclusion criteria is based on predictive models that indicate these patients are more likely to regain some movement compared to those who initially have no movement (Nijland, van Wegen, Harmeling-van der Wel, Kwakkel, & EPOS Investigators, 2010; Stinear, Barber, Petoe, Anwar, & Byblow, 2012). In the INTERSTROKE UEW group, those most likely to have some movement (i.e. those who scored between 2 and 4 on the mRS), accounted for 52% of the UEW group, with slightly more patients in UMIC, LMIC and LIC compared to HIC. Therefore, even when the UEW population is restricted to those who might best respond to the intervention, a large percentage remain potentially eligible.

While the data from INTERSTROKE provides much needed information regarding the severity of activity limitation and upper extremity motor

impairment across many countries, there are some limitations that affect the interpretation of the data, such as biased selection of participants, issues with recall bias with participant reported measures, and accuracy of measurement of activity limitation. First, as with any case-control study, there is the potential for selection bias. There is the potential that cases differ across countries. As evidenced by the post-stroke mRS scores, strokes in LMIC and LIC result in more profound activity limitation. It is possible that in these countries, only those who have a severe stroke present to hospital, and that these patients may have been previously experiencing milder strokes or TIAs (i.e. this is not the first stroke) but not sought medical care. If so, these patients may have not only the immediate consequences of the current stroke, but may also have deconditioning and even mild activity limitation as a result of the prior stroke. mRS scores before stroke showed no difference between countries in the number reporting “no disability” (88.5% in LIC versus 90.1 in HIC), however in the LIC, more reported “any disability” compared to HIC (11.0 versus 8.3%), but this was primarily at an mRS level of 1 (slight disability not affecting activity). Interestingly, more UEW patients were working in LIC prior to stroke, indicating that UEW patients were not limited in activity to a degree that would prevent their ability to work. Therefore it seems that disability levels before stroke do not substantially differ between countries.

Second, there is also the potential for recall bias of items such as previous physical activity or past medical history, as UEW patients were asked to provide much of the data and it is possible that their recent stroke affected patients' ability to recall. Patients were assessed, on average, 2 days after stroke, and 33% reported aphasia at that time, and impressively, there were very few missing data. However, any statistically significant differences noted should be viewed cautiously.

Third, there are also important considerations when interpreting the mRS scores. First, there is contradictory information on the reliability of the measure, with some studies demonstrating good reliability while others question it, suggesting a structured interview method to improve reliability (11, 12). Study coordinators and physicians were instructed on how to administer the mRS, however there was no standardization of administration across sites. Scoring of certain categories may be difficult to assess without direct observation (i.e. through patient report), such as clarifying differences between a score of 1 (no significant disability) and 2 (slight disability). Furthermore, upper extremity impairment is not a key component of the mRS score, but the intention is to consider upper extremity impairment when assessing the ability to perform activities. Patients post-stroke with complete hemiplegia of the affected upper extremity can be taught to perform most activities using the unaffected upper extremity. Therefore it is possible there are more patients with upper

extremity motor impairment in the groups that scored 1 or 2 on the mRS. These measurement limitations underscore the importance of using these data as a guide, and are the reason why further assessment of amount of change and modeling of predicted outcomes were not undertaken.

Conclusions

Although there are limitations in the data, the intent of the analyses was to report a general overview of an international cohort of patients with UEW after first stroke. These data clearly indicate that post-stroke upper extremity impairment is common in all parts of the world, that people with upper extremity weakness also commonly experience activity limitations even at one month post-stroke, and that the majority of these patients are not receiving any sort of longer term rehabilitation at one month. From these data, it is evident that there is an unmet clinical need to develop and evaluate interventions to improve functional upper extremity motor recovery post-stroke, that are not heavily reliant upon health care resources, and that this need is applicable to all regions.

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The list of the INTERSTROKE Study investigators will be included in published version of the manuscript.

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Chapter 2 -Table 1: Percentage of patients with weak arm, by country

Country	GNI Category	n	Arm Weak n (%)
Australia	1	123	68 (55.3)
Canada	1	312	204 (65.4)
Croatia	1	61	50 (82.0)
Denmark	1	42	32 (76.2)
Germany	1	339	211 (62.2)
Ireland	1	25	17 (68.0)
Kuwait	1	5	2 (40.0)
Poland	1	429	336 (78.3)
Saudi Arabia	1	40	23 (57.5)
Sweden	1	166	104 (62.7)
United Arab Emirates	1	206	169 (82.0)
United Kingdom	1	1002	634 (63.3)
Argentina	2	151	111 (73.5)
Brazil	2	387	310 (80.1)
Chile	2	106	82 (77.4)
China	2	4079	3094 (75.9)
Colombia	2	272	210 (77.2)
Ecuador	2	591	371 (62.8)
Iran	2	122	58 (47.5)
Malaysia	2	272	221 (81.3)
Peru	2	143	101 (70.6)
Russia	2	132	95 (72.0)
South Africa	2	100	95 (95.0)
Thailand	2	31	24 (77.4)
Turkey	2	297	211 (71.0)
India	3	2525	2253 (89.2)
Nigeria	3	56	49 (87.5)
Pakistan	3	184	146 (79.3)
Philippines	3	571	508 (89.0)
Sudan	3	308	301 (97.7)
Mozambique	4	281	279 (99.3)
Uganda	4	265	252 (95.1)
Total*		13623	10621 (78.0)

GNI, Gross National Income;
1=High (H) income = >$12,615 USD; 2=upper middle (UM) income = $4.086-12,615 US; 3= lower middle income (LM) = $1,036 - $4,085 USD; 4= Low (L) income = <+$1,035 USD;

- data on upper extremity weakness were not available on 16 cases (9 from Ecuador, 6 from China, 1 from unknown)

Chapter 2 -Table 2: Baseline Characteristics in Those with Upper Extremity Weakness: Overall and by Regional Income Level

	Overall		Income Level								
	n=10,621		HIC n=1,850		UMIC n=4,983		LMIC n=3,257		LIC n=531		P*
	mean	**SD**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**	
Age, years	61.9	13.7	65.8	13.9	62.7	13.3	59.2	13.3	58.7	14.8	<0.001
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Gender- Female	4,297	40.5	742	40.0	2,060	41.3	1,227	37.7	268	50.5	<0.001
Education level											
None	1,856	17.5	61	3.3	779	15.6	938	28.8	78	14.7	<0.001
1-8 years	4,040	38.0	312	16.9	2,494	50.1	980	30.1	254	47.8	
9-12 years	2,804	26.4	799	43.2	1,095	22.0	789	24.2	121	22.8	
Trade school	839	7.9	252	13.6	436	8.8	130	4.0	21	4.0	
College/University	1,082	10.2	426	23.0	179	4.0	420	12.9	57	10.7	
Currently Working											
Men	3,244	51.2	468	42.4	1,417	48.5	1,172	57.8	187	71.1	<0.001
Women	1,001	23.3	140	19.0	480	23.3	221	18.0	160	59.7	<0.001
Physical Activity (minimal/no activity, work or leisure)	7,915	74.5	1,194	64.5	3,909	78.5	2,527	77.6	285	53.7	<0.001
Stroke type (baseline)											
Ischemic	7,905	74.4	1,676	90.6	3,698	74.2	2,213	68.0	318	60.0	<0.001
Intracerebral haemorrhage	2,528	23.8	147	8.0	1,220	24.5	965	29.6	196	36.9	<0.001
Subarachnoid haemorrhage	103	1.0	3	0.2	55	1.1	41	1.3	4	0.8	<0.001
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Past Medical History											
Hypertension	5,933	55.6	1,100	59.5	3,014	60.5	1,482	45.5	337	63.5	<0.001
High cholesterol	1,381	13.0	629	34.0	558	11.2	177	5.4	17	3.2	<0.001

	Overall		Income Level								
	n=10,621		HIC n=1,850		UMIC n=4,983		LMIC n=3,257		LIC n=531		P*
Diabetes	1,826	17.2	379	20.5	865	17.4	520	16.0	62	11.7	<0.001
Peripheral arterial disease	143	1.4	77	4.2	59	1.2	4	0.1	3	0.6	<0.001
Atrial fibrillation/flutter	447	4.2	256	13.8	153	3.1	29	0.9	9	1.7	<0.001
Angina	566	5.3	260	14.1	235	4.7	69	2.1	2	0.4	<0.001
Myocardial infarction	424	4.0	194	10.5	163	3.3	65	2.0	2	0.4	<0.001
Transient ischemic attack	228	2.2	129	7.0	52	1.0	40	1.2	7	1.3	<0.001
Stroke	21	0.2	4	0.2	12	0.2	2	0.06	3	0.6	0.22
HIV	38	0.4	0	0	10	0.2	2	0.06	26	4.9	<0.001
Tuberculosis	180	1.7	33	1.8	58	1.2	68	2.1	21	4.0	<0.001

HIC, high-income countries; UMIC, upper middle income countries; LMIC, lower middle income countries; LIC, low income countries; HIV, human immunodeficiency virus

* calculated using the Chi-squared test for all variables except age, for which ANOVA was used to calculate the p value

Chapter 2 - Table 3: Symptoms Occurring After Stroke in Those with Upper Extremity Weakness: Overall and by Income Level

	Overall		Income Level								P*
	n=10.621		HIC n=1,850		UMIC n=4,983		LMIC n=3,257		LIC n=531		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Leg weakness	9,471	89.2	1,360	73.5	4,585	92.0	3,009	92.4	517	97.4	<0.001
Numbness	5,725	53.9	886	47.9	2,732	54.8	1,788	54.9	319	60.1	<0.001
Aphasia	3,478	32.8	421	22.8	1,373	27.6	1,399	43.0	285	53.7	<0.001
Unsteady Gait	3,986	37.5	583	31.5	1,635	32.8	1,384	42.5	384	72.3	<0.001
Vertigo	1,582	14.9	146	7.9	694	13.9	625	19.2	117	22.0	<0.001
Homonymous Hemianopsia	789	7.4	176	9.5	306	6.1	264	8.1	43	8.1	<0.001

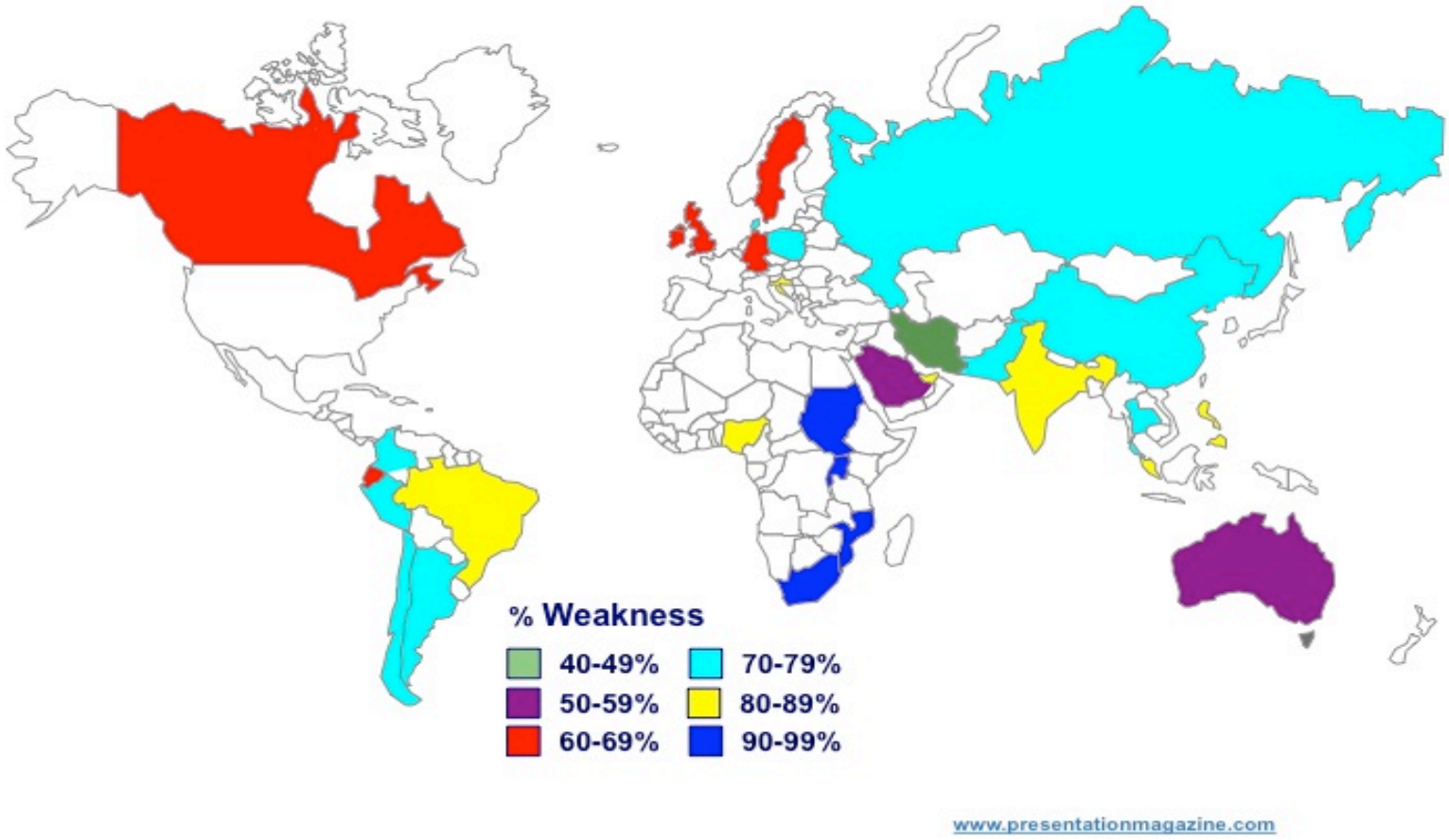
HIC, high-income countries; UMIC, upper middle income countries; LMIC, lower middle income countries; LIC, low income
* *calculated using the Chi-squared test

Chapter 2 -Table 4: Discharge Status at 1 month in Those with Upper Extremity Weakness: Overall and by Income Level

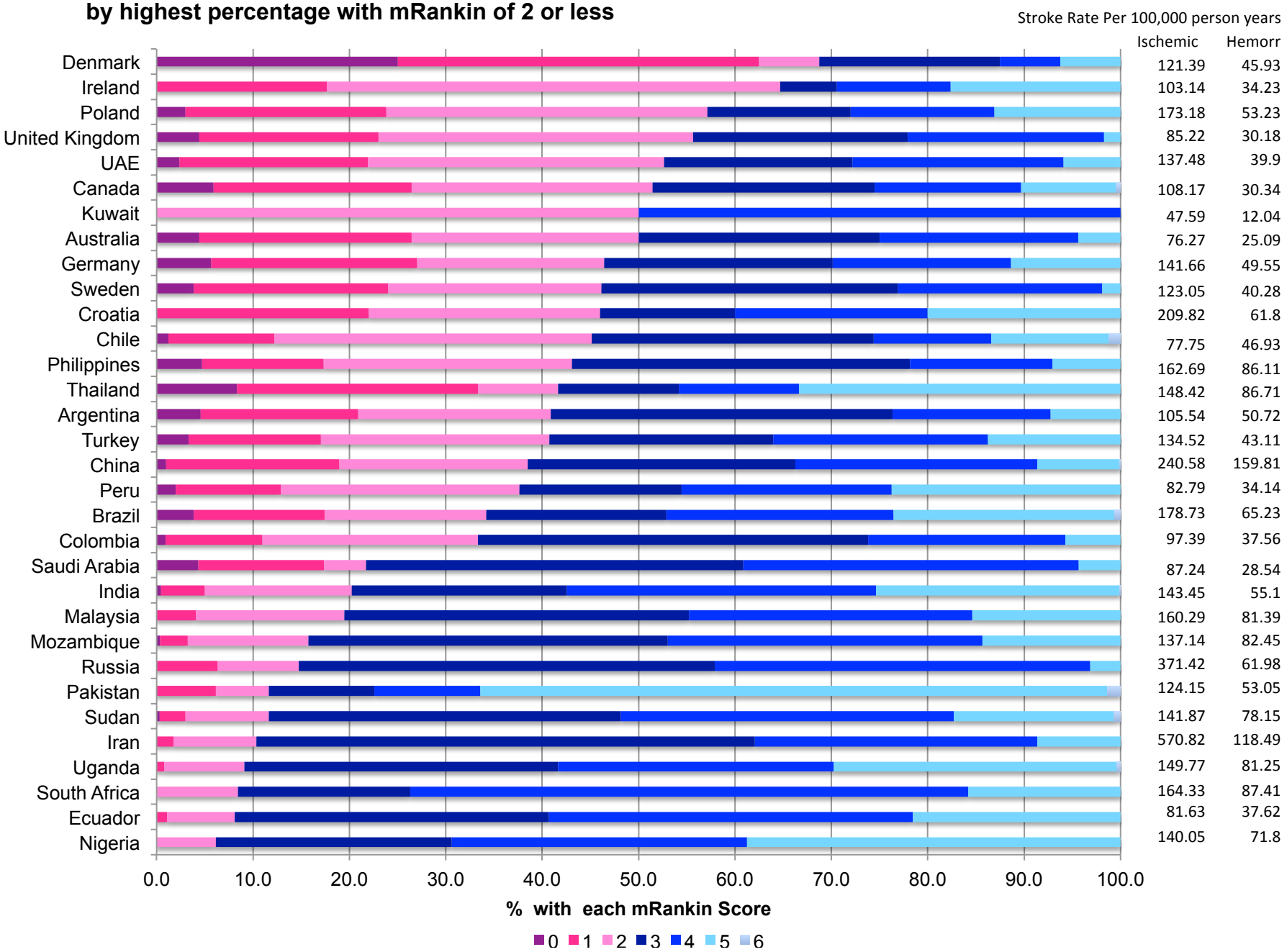
	Overall		Income Level								P*
	n=10,621		HIC n=1,850		UMIC n=4,983		LMIC n=3,257		LIC n=531		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Discharged	9,208	86.7	1,689	91.3	4,293	86.2	2,805	86.1	421	79.3	<0.001
Home	8,549	92.8	1,284	76.0	4,113	95.8	2,751	98.1	401	95.3	
Rehabilitation Centre	459	5.0	337	20.0	85	2.0	20	0.7	17	4.0	
Institutional Care	96	1.0	23	1.4	48	1.1	25	0.9	0	0	
Other	98	1.1	44	2.6	43	1.0	9	0.3	2	0.5	
Still in hospital	470	4.4	109	5.9	327	6.6	26	0.8	8	1.5	
Acute	128	27.2	27	24.8	88	26.9	9	34.6	4	50.0	
Rehabilitation	255	54.3	80	73.4	166	50.8	7	26.9	2	25.0	
Long term care facility	86	18.3	1	0.9	73	22.3	10	38.5	2	25.0	
Dead	830	7.8	40	2.2	320	6.4	385	11.8	85	16.0	

*calculated for “discharged”, using the Chi-squared test

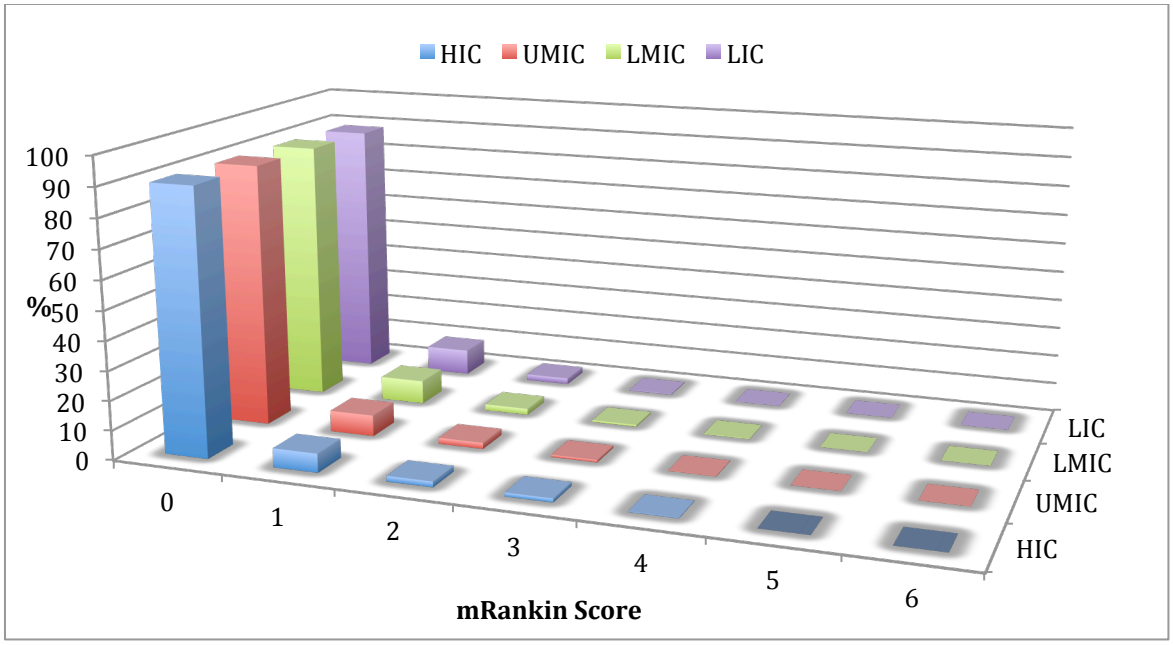
Chapter 2 - Figure 1: International Distribution of Upper Extremity Weakness Immediately After Stroke



Chapter 2 - Figure 2: mRankin in those with upper extremity weakness, immediately after stroke, sorted by highest percentage with mRankin of 2 or less

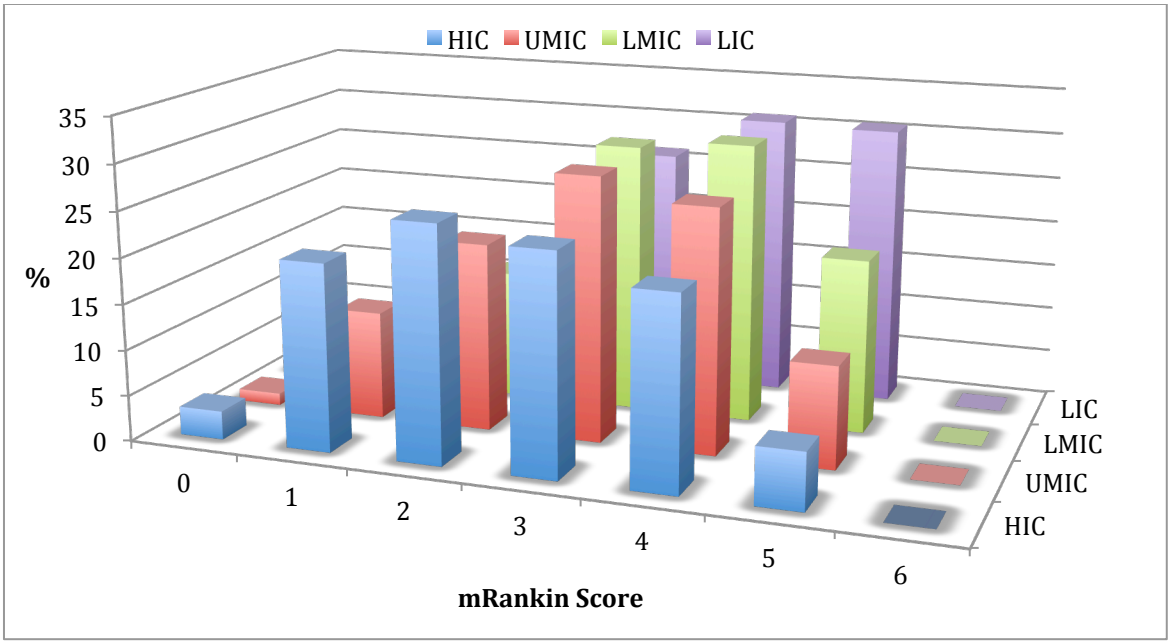


Chapter 2 - Figure 3a: mRankin score by income category in those with arm weakness, before stroke



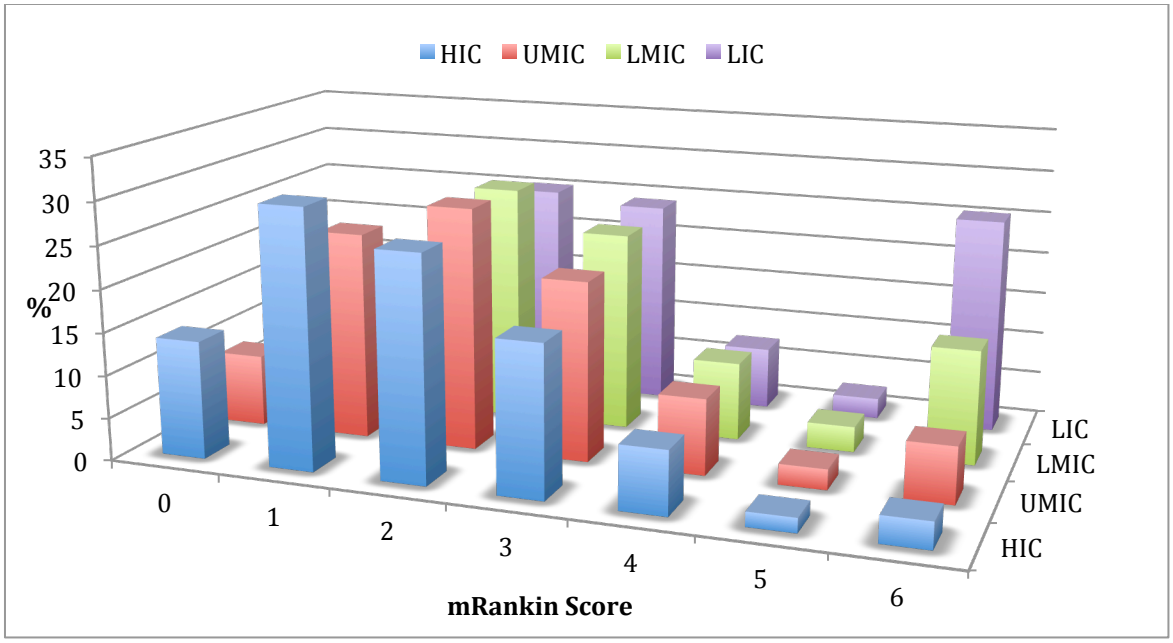
HIC= high income countries, UMIC = upper middle income countries, LMIC= lower middle income countries, LIC = low income countries

Chapter 2 - Figure 3b: mRankin score by income category in those with arm weakness, after stroke^



HIC= high income countries, UMIC = upper middle income countries, LMIC= lower middle income countries, LIC = low income countries
^ adjusted for age, gender , type of stroke, past medical history of heart disease, hypertension, diabetes and atrial fibrillation

Chapter 2 - Figure 3c: mRankin score by income category in those with arm weakness 1-month after stroke^



HIC= high income countries, UMIC = upper middle income countries, LMIC= lower middle income countries, LIC = low income countries
^ adjusted for age, gender , type of stroke, past medical history of heart disease, hypertension, diabetes and atrial fibrillation

CHAPTER 3: DOES TASK-ORIENTED PRACTICE IMPROVE UPPER EXTREMITY MOTOR RECOVERY AFTER STROKE? A SYSTEMATIC REVIEW

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Abstract

Background: Stroke commonly affects upper extremity motor abilities, yet there has been very limited success in developing effective rehabilitation interventions to remediate motor impairments, particularly for the upper extremity.

Objective: To determine if task-oriented practice administered soon after stroke, is more effective than usual care in improving post-stroke upper extremity motor recovery and to explore the optimal amount of practice.

Methods: A systematic review of the literature was performed from 1950 to November 2012, to identify randomized controlled trials of task-oriented practice compared to usual care, or to different amounts of task-oriented practice to improve motor impairment and activity. Studies were excluded if specific types of interventions were used as comparators or if they were of poor methodological quality.

Results: Six studies met the review criteria. Three of the six studies demonstrated a statistically significant effect of task-oriented practice. Study results could not be pooled because of a lack of homogeneity in populations and intervention.

Conclusions: The results demonstrate that an increase in the amount of task-oriented practice after stroke may result in less upper extremity impairment; further research on both effect and required dosage is needed, as results are inconsistent.

1. Introduction

Stroke is the fifth leading cause of disability internationally (Johnston, Mendis, & Mathers, 2009) and it is likely that this is an underestimate of the absolute level of functioning that is lost, especially in low-income countries (Hong & Saver, 2009). Stroke results in disability through loss of function from motor, cognitive or sensory impairments either individually or in combination. Although stroke survivors can compensate for some of these losses, they often experience substantial residual functional deficits. Motor impairment is the most common deficit post-stroke and the major contributor to functional limitations (Langhorne, Coupar, & Pollock, 2009). Motor impairments are a principal target of rehabilitation interventions, and many novel therapeutic approaches for motor recovery have emerged in recent decades (Bonaiuti, Rebasti, & Sioloi, 2007; Cooke, Mares, Clark, Tallis, & Pomeroy, 2010; Ferrarello et al., 2011; French et al., 2010; Hayward, Barker, & Brauer, 2010; Henderson, Korner-Bitensky, & Levin, 2007; Kwakkel et al., 2004; Langhorne et al., 2009; Latimer, Keeling, Lin, Henderson, & Hale, 2010; Laver, George, Thomas, Deutsch, & Crotty, 2011; Oujamaa, Relave, Froger, Mottet, & Pelissier, 2009; Peurala et al., 2012; Timmermans, Spooren, Kingma, & Seelen, 2010; Urton, Kohia, Davis, & Neill, 2007; Veerbeek, Koolstra, Ket, van Wegen, & Kwakkel, 2010; Zimmermann-Schlatter, Schuster, Puhan, Siekierka, & Steurer, 2008). Research has focused on lower limb motor impairment more than

upper limb, partly because lower limb interventions are more easily described, outcomes are more easily quantified and because mobility is considered a key functional consideration after stroke. However, among those who have had a stroke, upper limb recovery is also considered important because it is integral to independence in many activities of daily living (Barker & Brauer, 2005). Therefore, interventions designed and tested specifically for upper extremity motor recovery are required. Motor recovery interventions have been developed based on a variety of theoretical paradigms. Interventions may look similar, however the expected mechanism of effect differs. Rigorous evaluation of novel interventions has been a major challenge due to the complexity of the interventions (Craig et al., 2008) and the variability of the post-stroke populations (e.g. acute, subacute, and chronic). Furthermore, the methodological limitations of completed trials (e.g. small sample sizes) have resulted in studies that are underpowered to detect the modest effects expected from rehabilitation interventions (Santaguida et al., 2012). In situations where there are numerous underpowered clinical trials, meta-analysis may prove useful in estimating a potential treatment effect. However, conducting and interpreting meta-analyses of clinical trials evaluating interventions for upper limb recovery has been challenging because of the heterogeneity of interventions and outcomes. This has

made interpretation of the evidence difficult for guideline committees as well as clinicians trying to determine “best practice”.

One promising upper extremity motor recovery intervention is task-oriented practice (Arya et al., 2012; French et al., 2010; Langhorne et al., 2009; Winstein & Wolf, 2009). While the role of task practice in improving general motor performance has long been recognized as important (Schmidt & Lee, 2011), the evidence to support its effect on post-stroke motor recovery is based on small clinical trials and observational studies. A meta-analysis of clinical trials evaluating task-oriented practice has reported modest benefits in functional outcomes for lower limb motor, but not for upper limb impairments (French et al., 2010). The studies included in the meta-analysis were small, heterogeneous in terms of population and outcome, and some used active comparators that may have also used task practice. Therefore, it is not surprising that an effect on upper extremity impairment was not evident.

Determining whether task-oriented practice is effective depends in part at least, on understanding the “amount” of practice necessary to improve motor performance, or as it has been called by some, the “dosage” of task-oriented practice. Dosage is a commonly used term when prescribing pharmaceuticals, and it describes the concentration of the active ingredient as well as the frequency and duration of administration. Although the application of this concept to rehabilitation therapies was first

proposed over 15 years ago (Kwakkel, Wagenaar, Koelman, Lankhorst, & Koetsier, 1997), implementation in clinical and research settings has been slow, potentially because of a lack of consensus regarding the definition (Page, Schmid, & Harris, 2012). Most rehabilitation clinicians and researchers agree that the frequency and duration of an intervention can be quantified using minutes per day and number of days over which an intervention is administered. There is less agreement about the definition of intensity, with some considering the more physiologic interpretation (e.g., the energy expenditure, which can be measured by scales such as Metabolic Equivalent of Task (MET)) (Kwakkel, 2006; Wallace et al., 2010) while others define it as the minutes per day on a prescribed protocol, where the goal is the maximum amount of task practice in the time provided (Bowden, Woodbury, & Duncan, 2013; Winstein et al., 2013). Given that intensity describes the concentration of the active ingredient in task-oriented practice, time on task, as opposed to the energy expended on task, is the more appropriate measure. The argument is however somewhat academic, as studies generally do not measure intensity. In their systematic review, Langhorne et al. (Langhorne et al., 2009) noted that high-intensity rehabilitation may be beneficial, however the available data did not allow for quantification of the level of intensity, a conclusion that is consistent with other studies and reviews (Birkenmeier, Prager, & Lang, 2010; French et al., 2010; Langhorne, Bernhardt, & Kwakkel, 2011;

Oujamaa et al., 2009; Wallace et al., 2010). Therefore, although there is recognition of the importance of understanding the elements of dosage, studies to date have not been able to clearly determine the parameters, and in particular to quantify intensity. This limitation, along with the methodological limitations of many studies, may lead to inaccurate conclusions, such as those reported in a recent review, that higher intensity rehabilitation does not improve functional recovery (Sehatzadeh, 2013).

Studies providing upper extremity task-oriented practice, given during the subacute phase (prior to the development of long-term compensatory strategies), in an inpatient setting (most likely the highest dosage) where the comparator group is usual practice (as opposed to other interventions that have not proven effective), would provide the most accurate estimate of the effect of task-oriented practice on upper extremity motor recovery in the first months after stroke and may allow for quantification of a threshold dose for motor recovery. Therefore we performed a systematic review a) to determine if task-oriented practice, administered early after stroke, is more effective than usual care in improving post-stroke upper extremity motor recovery and, b) to explore whether there is a 'dose' response within clinical trials in terms of duration, frequency and intensity.

2. Methods

2.1 Inclusion/Exclusion Criteria

Studies considered for inclusion in this systematic review met the following criteria:

(a) randomized participants (i.e., randomized controlled trials (RCTs)), as these studies provide the most valid estimate of effectiveness;

(b) included an adult population with upper extremity motor deficits, three months or less after stroke (with or without lower extremity deficits);

(c) used upper extremity task practice as the intervention, with enough information to quantify the amount of upper extremity task practice (not necessarily the intensity, but at least frequency and duration);

(d) used at least one outcome measure that quantified upper extremity motor recovery (either at the International Classification of Functioning and Health level of Body Function or Activities and Participation (World Health Organization, 2002));

(e) published in full in English.

Studies were excluded from the review if they met the following criteria:

(a) used any specific intervention method (e.g. NeuroDevelopmental Therapy, Motor Relearning Program, Constraint Induced Movement Therapy, exercise, Virtual Reality, Mental Imagery, Therapeutic

Electrical Stimulation, Transcranial Magnetic Stimulation), for either the intervention or control groups. Studies comparing specific interventions were excluded because it is difficult to quantify the amount of task performance and task is not necessarily the focus of the intervention or the "active ingredient";

(b) were of poor methodological quality that is, a score of <4 using the Centre for Evidence Based Medicine, Randomized Controlled Trial Critical Appraisal Sheet (http://www.cebm.net/index.aspx?o=1157) which assesses internal validity. This scale is similar to other scales of clinical trial quality, but focuses specifically on issues of internal validity that are key to obtaining valid results.

2.2 Information Sources, Search and Study Collection

The search for studies was done in multiple phases. Given the lack of consistency in the use of both subject headings and keywords, an initial search was performed using the following terms in various combinations; "stroke", "motor learning", "task", "arm" and similar terms (e.g. cerebrovascular accident, motor recovery, practice, arm), in the following databases; CINAHL (EBSCO Host, 1981- November 2012), MEDLINE R (Ovid)(1950- November 2012), EMBASE (OvidSP, 1980 – November 2012). Two reviewers (Jackie Bosch (JB), Susan Barreca (SB)) independently reviewed the list of titles, and chose articles for abstract review based on the inclusion criteria provided above. The same two

researchers (JB, SB) independently reviewed the abstracts and if selected by either reviewer, the articles went for complete text review. Full articles were then reviewed against the inclusion and exclusion criteria, and the methodological quality of the studies was appraised using the Centre for Evidence Based Medicine Randomized Controlled Trial Critical Appraisal sheet (http://www.cebm.net/index.aspx?o=1157). Agreement rates for study inclusion were 85%, and a consensus approach was again used when there was discrepancy.

A final review of the remaining articles was performed by Laurie Wishart (LW) and Martin O'Donnell (MO) to confirm appropriateness for inclusion.

2.3 Data Collection Process, Data Items and Risk of Bias in Individual Studies

Data were extracted from studies by JB and independently reviewed by LW and MO. Data included mean age, inclusion criteria for upper extremity movement, time since stroke, amount of practice in each group (minutes per day, days per weeks, and number of weeks), upper extremity motor recovery outcome measures (either at the Body Structure or Activities and Participation level, based on the International Classification of Functioning Disability and Health by the World Health Organization (2001)) and timing of the assessment of the primary outcome measure. If the authors did not indicate which outcome was primary, measures were chosen based on the expected sensitivity to the intervention and

administration time in closest proximity to the end of the intervention period, as this is when the largest effect is expected to occur, opposed to weeks or months thereafter. All data were extracted from publications.

2.4 Risk of Bias within and across Studies

Using the Centre for Evidence Based Medicine Randomized Controlled Trial Critical Appraisal sheet (http://www.cebm.net/index.aspx?o=1157, internal validity section), one point was given for a "yes" to each question, with a maximum score of 6 for each study. Because of the nature of the interventions, participants were not blinded to their treatment group in any study; however, outcome assessment was often completed by assessors who were blinded to treatment allocation and in such circumstances, one point was given for blinded outcome assessment.

In terms of potential for bias across the studies, there is always a risk of publication bias; that is, studies that are positive are more likely to get published. Half of the studies in this review demonstrated a statistically significant effect (3 out of 6).

2.5 Data Synthesis

The reporting of the results of this review is done in accordance with the PRISMA guideline (Liberati et al., 2009). Studies meeting the inclusion criteria were heterogeneous in study population (i.e. amount of upper extremity motor deficit) and interventions evaluated (i.e., different task-oriented approaches); and such as, the authors concluded that meta-

analysis would not be appropriate. Therefore the results are reported descriptively with some narrative summaries.

3. Results

3.1 Study Selection

The initial search resulted in a list of 309 titles, of which 60 were excluded and 299 abstracts were reviewed. A hand search of bibliographies resulted in an additional 62 citations for review. A total of 361 abstracts were reviewed of which 136 (38%) were found eligible for full text review. From the full review, 23 (17%) studies were eligible for inclusion and underwent a third review by a second set of reviewers, who excluded an additional 17 articles. The remaining 6 articles represent 6 unique studies that were included in the review (see Figure 1).

The three most common reasons for excluding articles/studies were (a) use of a specific intervention as a comparator (38%), (b) the article was a review (critical or systematic) (23%), and (c) the study design was not a randomized controlled trial or practice was not used as an intervention (20%).

3.2 Study Characteristics

The key characteristics of the six studies included in this review are provided in Table 1. The mean age for the participants varied from 50 to 75 years. All studies required participants to have motor impairment in the affected upper extremity and two also required that participants had some

upper extremity movement. Although tools used to measure severity of deficits at baseline varied across studies, results indicated moderate upper extremity impairment in each study. Participants were recruited within about six weeks of stroke onset. Ethics approval from the local institution was obtained for each study and informed consent was obtained from each study participant.

All studies provided a brief explanation of the experimental (E) and control (C) interventions, with functional task practice and repetition as key elements of the experimental intervention. Strength training was also included in the experimental intervention for 5 of the 6 studies (Blennerhassett & Dite, 2004; Donaldson et al., 2009; Han, Wang, Meng, & Qi, 2012; Harris, Eng, Miller, & Dawson, 2009; Kwakkel, Wagenaar, Twisk, Lankhorst, & Koetsier, 1999). Additional details on the experimental intervention protocol were publically available for one study (Harris et al., 2009)(http://www.neostrokenetwork.com/newportal/Portals/0/Education%20Documents/videoconf%20handout/GRASP_Manual11492.pdf), while two authors indicated that protocols were developed but were not publically available (Kwakkel et al., 1999; Winstein et al., 2004). One study formally evaluated different durations of the same intervention (Han et al., 2012). In this three arm study, the same intervention was given for 1, 2 and 3 hours per day to each of the groups, 5 days per week for six weeks.

The most commonly used outcome assessment was the Action Research Arm Test (ARAT) which uses usual activities and movements to assess grasp, grip, pinch and overall upper extremity movement. It was the primary outcome measure in three of the studies (Donaldson et al., 2009; Han et al., 2012; Kwakkel et al., 1999) and a secondary outcome measure in another (Harris et al., 2009), and was therefore the outcome measure reported for each of these studies, to allow for comparison between studies. The remaining two studies used measures of upper extremity motor recovery after stroke as the primary outcome, and data for each of these measures were provided (Blennerhassett & Dite, 2004; Winstein et al., 2004).

All studies included in this review received a score of 4 or higher using the Centre for Evidence Based Medicine Randomized Controlled Trial Critical Appraisal sheet (see Table 2). The most common limitations in the studies were lack of complete follow-up of participants at study end (five studies), followed by an imbalance of key prognostic variables between groups at baseline (three studies).

3.3 Study Outcomes

Table 3 provides both the baseline score and end of intervention score for each of the studies. In three of the six studies, statistically significant between group differences in the ARAT at study end were demonstrated in favour of additional, deliberate, task-oriented practice ($P \leq 0.01$) (Han et

al., 2012; Harris et al., 2009; Kwakkel et al., 1999). Two other studies suggested an improvement in the task-oriented practice group (versus control), however this was not statistically significant (Donaldson et al., 2009; Winstein et al., 2004). One study did not show any significant difference (Blennerhassett & Dite, 2004).

The issue of the effect of differing amounts of therapy was addressed by one study, where a dose response effect was suggested with higher dosages of task-oriented practice resulting in improved activity, although a statistically significant difference was evident only between the lowest and highest dose group (Han et al., 2012).

4. Discussion

4.1 Main Findings

Based on the six studies identified in this systematic review, there is some evidence of a potentially beneficial effect of task-oriented practice in upper extremity motor recovery after stroke. Results of the study by Han et al. (Han et al., 2012) indicate there may be a dose response relationship, suggesting that more practice results in better post-stroke upper extremity motor recovery. However, data were limited and we were unable to conclude if there is a minimum threshold of practice that will result in improved upper extremity motor function after stroke.

4.2 Strengths and Limitations

Data from the available studies are promising, but have been interpreted with caution, as there are limitations of this review. First, developing both sensitive and specific search criteria to identify appropriate articles was difficult. Ideally, search criteria will identify articles based on the population, intervention, outcomes and methodology of interest. While a post-stroke population could be identified, initial attempts to use search strategies to identify any specific types of post-stroke interventions were unsuccessful, primarily because of a lack of consistency in the use of subject headings or keywords. The decision was made to use broad search terms that would provide a sensitive, albeit unspecific list of studies and this resulted in the large number of titles initially searched. This issue emphasizes the need for diligence by authors in using consistent terminology when submitting studies in this field. The search was further enhanced by hand searching bibliographies, which has been shown to be an effective supplement to electronic searches (Hopewell, Clarke, Lefebvre, & Scherer, 2007). Therefore, while we believe the search is thorough, it is possible that other studies exist, especially in languages other than English. Second, an important aspect of our questions was whether the active ingredient of task produced better outcomes than usual therapy. It was clearly evident that the definition of task is not consistent across studies, ranging from exercise to reaching activities to the practice of usual daily activities like dressing. A lack of clarity in terms of definition as well as

terminology (e.g., task specific training, task-oriented training, and functional training) made it difficult to accurately identify studies of task-oriented practice. We chose to focus on studies comparing task-oriented practice as defined by Winstein and Wolf (2009), which focuses on remediating activity limitations, as opposed to individual upper extremity impairments and skill development opposed to movement. Studies that described the use of another type of intervention in either the experimental or control group (e.g. NeuroDevelopmental Therapy or Constraint Induced Movement Therapy) were excluded since they were not evaluating task-oriented practice per se; however, it is possible that some element of task-oriented practice was used in these interventions. Although we suspect that this is not a likely scenario, without thorough and detailed descriptions of the interventions in each study, it is possible.

Third, while all studies scored four or above in the methodological evaluation, only one study was free from bias (Harris et al., 2009), while three studies had a lack of similarity in baseline characteristics, probably due to small sample sizes (Blennerhassett & Dite, 2004; Donaldson et al., 2009; Han et al., 2012). These baseline differences, especially in upper extremity motor function, may have made it difficult to demonstrate a statistically significant effect (and there was no indication whether statistical adjustments were made in the analysis). In addition, four of the six studies did not have complete follow-up of participants (one of the

studies had less than 80% follow-up (Winstein et al., 2004)). The methodological problems of small sample size and differences in baseline characteristics between groups was most likely compounded by loss to follow-up, further decreasing the likelihood of finding an effect.

Fourth, not all studies identified a primary outcome measure so we chose to use the measure that theoretically should show the greatest effect, and that was administered at the end of the intervention period. This approach provided results under ideal circumstances (i.e., outcomes measured after the largest dose of the intervention and with the most sensitive tool) and could as a result increase the potential for Type 1 error. Of the three studies that demonstrated a statistically significant effect of practice, two had identified the ARAT as a primary outcome measure (Han et al., 2012; Kwakkel et al., 1999) so the results of the third study by Harris et al. should be interpreted cautiously (Harris et al., 2009).

Finally, although each of the studies used deliberate task-oriented practice as the fundamental component of the intervention, there was variation in how interventions were delivered. For example, the study by Harris et al., (2009) used a self-administered intervention, while the intervention in the study by Kwakkel et al. (1999) was therapist administered. The lack of consistency between interventions made it inappropriate to meta-analyse study results, and therefore a minimum threshold of task-oriented practice could not be determined.

Although there are issues in terms of the design, conduct and analysis of some of the studies, it should be noted that five out of the six journals in which the studies were published have adopted the CONSORT statement for reporting clinical trials, and adherence to the statement is intended to improve the quality of reporting (Ghimire, Kyung, Kang, & Kim, 2012).

4.3 Clinical Perspectives

Although there are limitations to this review, it highlights two key messages; the use and definition of task varies greatly in clinical studies as well as clinical practice, and that we do not know the optimal "dose" (intensity, frequency and duration) of task to improve upper extremity motor impairment. The problem of lack of clarity in defining task has been discussed previously in this review and by other authors (Bowden et al., 2013). The issue of the optimal dose remains important and unanswered. Studies on the use of task in clinical settings report that task is used in only about half of the therapy sessions (Lang et al., 2009) and for about 1/3 of the length of the session (De Wit et al., 2007). It is possible that a lack of clarity in terms of "what is task "and "minimum dose" is leading therapists to underutilize task-oriented practice. Implementing a treatment regimen based on frequency and duration alone is not difficult, but the quantification and implementation of intensity remains problematic due to these uncertainties and is further complicated if therapists are uncertain of the specifics of task-based practice. Recent efforts to define intensity in

terms of post-stroke motor rehabilitation offer a definition based on the amount of work the patient performs (Page et al., 2012). This definition does not consider the amount of the "active ingredient" included in the intervention. For task-oriented practice, quantification of intensity has to incorporate the amount of task practice occurring. Working harder will only produce better post-stroke motor recovery if the work (i.e., task-oriented practice) is aimed at producing the desired neurophysiologic changes and subsequent improvement in activity, and does not invoke adverse effects. In summary, we chose to look specifically at the effect of task-oriented practice on post-stroke upper limb motor recovery compared to usual care, using randomized controlled trials of patients in the sub-acute phase post-stroke, a group that is understudied but most likely to benefit from interventions aimed at maximizing neuroplasticity (Bowden et al., 2013). The criteria for review do not seem outwardly restrictive and yet they resulted in only six studies eligible for consideration. The differences between included studies, specifically the intervention and dosage of the intervention, made it inappropriate to further combine these data in any statistical manner. These considerations highlight the need for research that (a) clearly defines the intervention, (b) clearly defines the intensity, frequency and duration of the intervention (dosage), and (c) uses similar outcome measures.

While the results of this review are inconclusive, they do provide evidence of a possible effect of task-oriented practice, although a specific amount required could not be quantified. These conclusions are consistent with Canadian and international guidelines that either provide minimum amounts of therapy required, with little evidence in terms of effect, or call for increased intensity in therapy without further clarification or quantification of the meaning of increased or intensity (Foley et al., 2012; Lindsay et al., 2010). With limited rehabilitation resources, governments need to support well-designed clinical trials that address the question of intensity, frequency and duration of task-oriented practice. Alternative solutions for enabling additional practice must be considered such as self-administered task-oriented practice as was shown effective by Harris and colleagues (Harris et al., 2009). Standardized protocols, along with studies designed and powered to examine the dose response, will provide the needed information in terms of the effect and the optimal dosage threshold.

5. Conclusions

There are few studies that have looked solely at the effectiveness of task-oriented practice on post-stroke upper extremity motor recovery in the subacute phase. The available evidence indicates that task-oriented practice may result in improved motor recovery and may ultimately result in improvements in post-stroke activity. Large, well designed and

conducted randomized controlled trials, using standardized protocols with consistent definitions, that examine the response to various doses of task-oriented practice, are required to confirm the effect of task-oriented practice and to determine a minimum threshold of practice at which motor recovery occurs.

Conflict of Interests

The authors declared they have no conflict of interest.

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Chapter 3 - Table 1: Characteristics of Included Studies

First Author, Year	n participants, Description	Description of Intervention Experimental (E), Control (C)	Additional Deliberate U/E Practice	U/E or Functional Outcome Measures
Blennerhasset, 2004	n=30, 2 groups 55 yrs (mean) No u/e entry criteria 43 days post-stroke (avg)	In addition to usual care; E: *Upper Limb Group*, functional tasks to improve reach, grasp, coordination, n=15 C: *Mobility Group*, sit-to-stand, walking, stairs, n=15	A: Upper Limb Group: 5 hours per week for 4 weeks C: Mobility Group: No additional upper extremity practice	Motor Assessment Scale (MAS) Upper Limb/Extremity^ MAS Hand Jebsen Hand Function Test (3 subsets)
Donaldson, 2009	n=30, 3 groups 72.8 yrs (mean) Some mov't in paretic u/e required 20 days post-stroke (avg)	In addition to usual care; E: Functional upper extremity training, using progressive task training, n=10 C1: Additional session of usual (exercise based) care, n=10 C2: Nothing in addition to usual (exercise based) care, n=10	A: 4 hours per week for six weeks C1: 4 hours per week for six weeks C2: No additional upper extremity practice	Action Research Arm Test (ARAT)^ Nine Hole Peg Test (9HPT) Grip force Pinch force Elbow flexion/extension force
Han, 2012	n=32, 3 groups 50.2 yrs (mean) u/e impairment, no spasticity, no pain 40 days post-stroke (avg)	In addition to usual care, strength training and functional activity practice in three doses: E: 3 hours/day, 5 days/week, n=11 C1: 2 hours/day, 5 days/week, n=10	A: 15 hours/week for 6 weeks C1: 10 hours/week for 6 weeks C2: 5 hours/week for 6	ARAT^ Fugl-Meyer (arm items) Barthel Index

First Author, Year	n participants, Description	Description of Intervention Experimental (E), Control (C)	Additional Deliberate U/E Practice	U/E or Functional Outcome Measures
		C2: 1 hour/day, 5 days/week, n=11	weeks	
Harris, 2009	n=103, 2 groups 69 yrs (mean) u/e impairment, some mov't 20 days post-stroke (avg)	In addition to usual care: E: Task-oriented, unsupervised home- based exercise program C: Education program	A: 3.75 hours/week for 4 weeks C: 0.75 hours/week for 4 weeks	Chedoke Arm and Hand Activity Inventory (CAHAI)^ ARAT Motor Activity Log-14 (MAL) Grip strength Short Form-12 (SF-12) Pain Visual Analog Scale Fatigue Severity Scale
Kwakkel, 1999	n=101, 3 groups 66 yrs (mean) some u/e impairment 7 days post-stroke (avg)	In addition to usual care: E: Intense arm training, functional exercises, n=33 C1: Intense leg training, sitting/standing/walking activities, n=31 C2: Control (air splint), n=37	A: 2.5 hours per week, 20 weeks C1: No additional upper extremity practice C2: No additional upper extremity practice	ARAT^ Barthel Index Nottingham Health Profile Sickness Impact Profile Frenchay Activities Index

First Author, Year	n participants, Description	Description of Intervention Experimental (E), Control (C)	Additional Deliberate U/E Practice	U/E or Functional Outcome Measures
Winstein, 2004	n=64, 3 groups Mean age, 95% between 35 and 75 years Upper extremity impairment (inferred from FIM score) 16 days post-stroke (avg)	In addition to usual care: E: Functional Task Practice (FTP) (repetitive and progressive), n=22 C1: Strength and Motor Control Training (ST), exercise based, n=21 C2: Usual Care (UC), n=21	A: 5 hours per week for 4 weeks (task) C1: 5 hours per week for 4 weeks (exercise) C2: No additional task-oriented practice	Functional Test of the Hemiparetic Upper Extremity (FTHUE)^ FIM Fugl-Meyer Upper Extremity (motor, sensory, ROM) Grip force Pinch force Shoulder/elbow/wrist torque FIM Self-care

n=sample size, u/e = upper extremity; OT = occupational therapy; PT = physical therapy; ROM = range of motion; FIM = Functional Independence Measure; yrs =years, avg = average
^ primary outcome

Chapter 3 - Table 2: Assessment of the Risk of Bias

First Author, Year	Randomized?	Similarity of groups?	Groups treated equally?	All participants accounted for?	Analysed in group assigned?	Outcome measure blinded?	Score(/6)
Blennerhasset, 2004	Y	N	Y	Y	Y	Y	5
Donaldson, 2009	Y	N	Y	N	Y	Y	4
Han, 2012	Y	N	Y	N	Y	Y	4
Harris, 2009	Y	Y	Y	Y	Y	Y	6
Kwakkel, 1999	Y	Y	Y	N	Y	Y	5
Winstein, 2004	Y	Y	Y	N	Y	N	4

Y: Yes; N: No; Total score = sum of Y's

Chapter 3 - Table 3: Results for Primary Outcome Measures

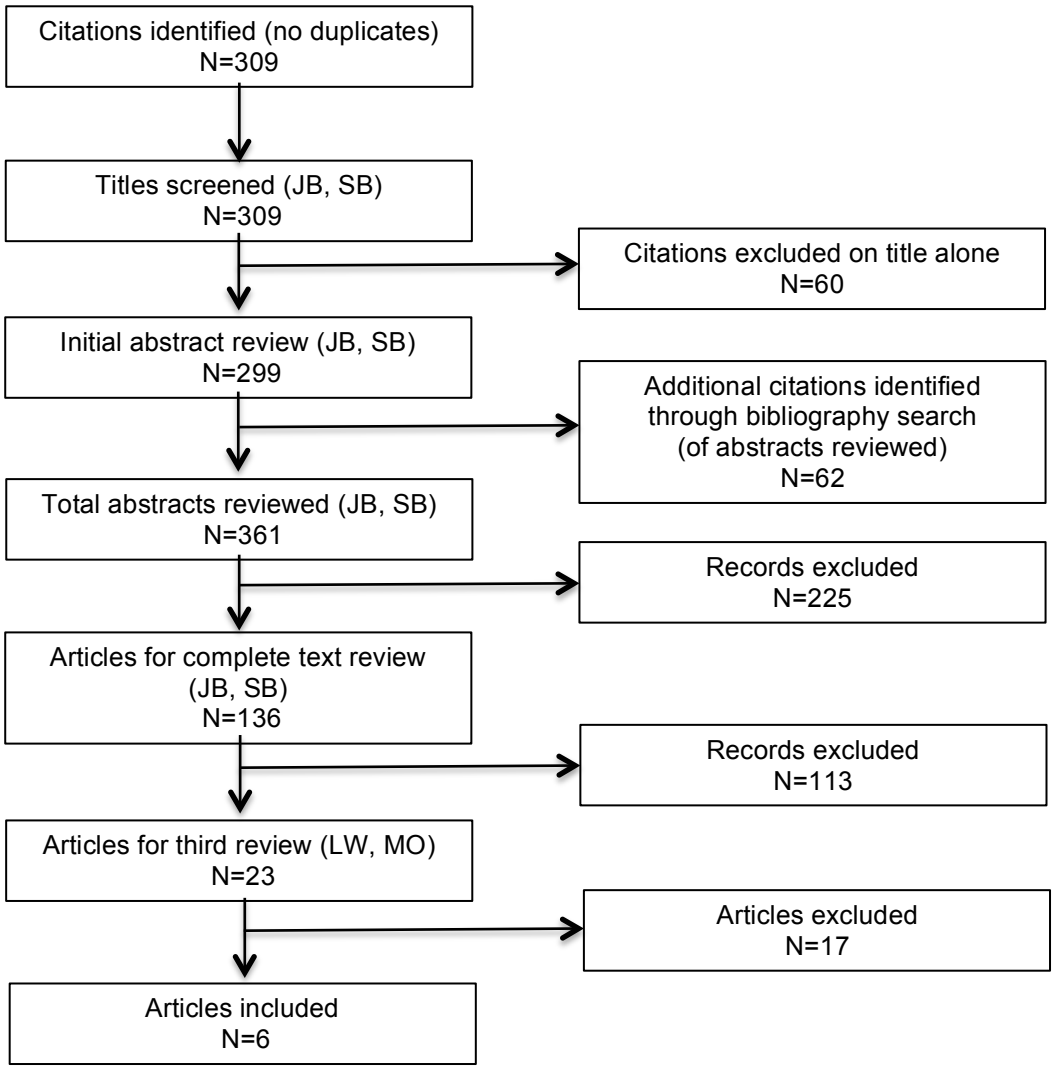
First Author, year	Primary Outcome	Timing of Measurement	Statistic	Results: Experimental (E), Control (C)			
Blennerhasset, 2004	MAS Upper Limb/Extremity			E: 5 hrs/wk n=15	C: No addl deliberate U/E practice n=15		p
		Baseline	Median Q1-Q3	5 (2-5)	5 (1-6)		NR
		4 weeks post rand (end of intervention)	Median Q1-Q3	6 (5-6)	6 (4-6)		NR
Donaldson, 2009	ARAT^			E: 4 hrs/wk task n=10*	C1: 4 hrs/wk exercise n=10	C2: No addl U/E practice n=8	p
		Baseline	Median Q1-Q3	27.0 (11.0)	34.5 (26.0)	28.0 (17.0)	-
		6 weeks post rand (end of intervention)	Median (Q1-Q3 change)	19.50 (22.00)	8.00 (13.25)	11.50 (21.00)	0.232

First Author, year	Primary Outcome	Timing of Measurement	Statistic	Results: Experimental (E), Control (C)			
Han, 2012				E: 15 hrs/wk n=10	C1: 10 hrs/wk n=10	C2: 5 hrs/wk n=10	p
	ARAT	Baseline	Mean (SD)	1.10 (1.52)	1.50 (1.58)	0.80 (1.14)	0.386
		6 wks post rand (end of intervention)	Mean (SD)	10.90 (3.60)	8.70(4.62)	5.30 (3.40)	0.008
Harris, 2009				E: 3.75 hrs/wk n=50	C: 0.75 hrs/wk n=53		p
	ARAT	Baseline	Mean	31.1	31.0		-
		4 wks post rand (end of intervention)	Mean (SD)	42.8 (9.20)	38.0 (9.47)		0.025
Kwakkel, 1999				E: 2.5 hrs/wk n=29	C1: No add'l U/E n=26	C2: No addl u/e extremity n=34	p
	ARAT	Baseline	Median (Q1-Q3)	0 (0-1)	0 (0-6)	0 (0-0)	-
		20 weeks post rand (end of intervention)	Median (Q1-Q3)	9 (0-39)	2 (0-56)	0 (0-2)	0.01

First Author, year	Primary Outcome	Timing of Measurement	Statistic	Results: Experimental (E), Control (C)			
Winstein, 2004				E: 5 hrs/wk Task n=20	C1: 5 hrs/wk Exercise n=20	C2: No addl U/E practice n=20	p
	FTHUE	Baseline	Mean (SD)	4.30 (5.35)	5.15 (5.97)	5.40 (4.30)	0.83
		4 weeks post rand (end of intervention)	Mean (SD)	4.70 (4.27)	4.25 (4.33)	3.35 (3.63)	0.61

* Note, Ns provided in this section may differ from Table 1 as these are the numbers used for analysis, ^ ARAT: higher score = better outcome
n=sample size, wk = week, avg = average
MAS Upper Limb/Extremity: Motor Assessment Scale, Upper Limb/Extremity section (score range of 0-18, high score indicating normal ability)
Q1=1st quartile, Q3 = 3rd quartile
NR= Not reported
ARAT: Action Research Arm Test (score range of 0-57, high score indicating normal ability)
addl = additional
SD = standard deviation
FTHUE: Functional Test of the Hemiparetic Upper Extremity (score range of 0-17, high score indicating normal ability)

Chapter 3 - Figure 1: Flow diagram of the literature search



CHAPTER 4: THE POST-STROKE RECOVERY OF OPTIMAL FUNCTION (PROOF) STUDY: A FACTORIAL, PARTIAL CLUSTER RANDOMIZED CONTROL TRIAL TO EVALUATE TWO SIMPLE INTERVENTIONS TO IMPROVE UPPER EXTREMITY MOTOR IMPAIRMENT

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Abstract

Background

Stroke is the third leading cause of disability, and disability rates are increasing in low and middle-income countries. Effective interventions, rehabilitative and pharmacological, that are applicable in all parts of the world are needed to address the problem. These interventions need to be designed so they can be implemented in a variety of settings with minimal training.

Design

This manuscript describes the protocol for an international, randomized, two-by-two factorial trial with partial cluster randomization. A simple rehabilitation intervention using task-based practice was developed to maximize the amount of effortful practice in the first weeks after stroke. The UPPER (Upper-extremity Practice Post-stroke in Early Recovery) intervention will be compared to usual practice using cluster randomization of the sites. Simultaneously, continued release carbidopa-levodopa (25/100mg, daily) will be compared to placebo using individual patient randomization. The interventions will be initiated early after stroke (within 4-10 days) and will be evaluated four weeks later to determine the effect on activity limitation secondary to upper extremity motor impairment as measured by the Action Research Arm Test (ARAT). Secondary outcomes include the amount of arm movement as measured by accelerometer, self-

efficacy, and general health status. The study will be conducted in 32 sites, equally divided between high income, upper middle income, lower middle income and low-income countries. Each site will recruit 13 participants over 18 months. With 416 participants, the study will have 80% power to detect a 7.4 difference in ARAT score in the UPPER versus usual care comparison and a 5.4 difference in ARAT in the carbidopa-levodopa versus placebo comparison. Recruitment for the study is expected to start in 2015, once funding for the trial has been secured.

Discussion

The PROOF trial uses a novel and efficient design to study two clinically important questions to address post-stroke disability. The vast majority of post-stroke rehabilitation intervention trials have been conducted in high-income countries and very few have identified interventions that are realistic for resource poor settings. PROOF is designed to determine effectiveness of both of these interventions in a variety of settings, recognizing the need for globally applicable interventions.

Background

Stroke is the third most common cause of adult disability adjusted life years (Hankey, 2013). Disability is not only common after stroke, but the rate of disability continues to rise, especially in low and middle income countries (Krishnamurthi et al., 2013). Disability for stroke survivors often includes difficulty performing usual daily activities (Lai, Studenski, Duncan, & Perera, 2002), and motor impairment, and in particular upper extremity motor impairment, is the most common cause (Lawrence et al., 2001). Researchers and clinicians have been trying for decades to develop interventions to improve functional deficits secondary to post-stroke upper extremity motor impairment. As yet, we do not have clearly effective rehabilitation interventions to improve either activity limitations or motor impairment (Langhorne, Coupar, & Pollock, 2009), Traditionally, rehabilitation interventions, provided by occupational therapists, physical therapists or speech and language therapists, have been considered the primary method for remediating post-stroke deficits (Langhorne, Bernhardt, & Kwakkel, 2011). In addition to rehabilitation, there has recently been growing interest in the use of pharmacological agents to restore motor function (Chollet, 2013; Oczkowski, 2013). The research conducted in both of these areas of neuro-restorative therapy has encountered similar problems. Studies are usual small with fairly major methodological flaws, resulting in inconclusive or contradictory results (McIntyre, Richardson,

Janzen, Hussein, & Teasell, 2014). The need for studies to clearly address important questions is evident (Hachinski et al., 2010), however the reality is that post-stroke rehabilitation research funding is very limited. This means that researchers must design efficient studies to clearly answer clinically important questions, ideally using any opportunity to answer as many clinically important questions as possible.

Simultaneous evaluation of behavioural and pharmacological interventions has been proposed as a possible approach to answering two important stroke rehabilitation questions (Bowden, Woodbury, & Duncan, 2013; Hachinski et al., 2010), and this could be achieved using a factorial design. As long as the interventions chosen to study are not expected to interfere with each other, it is appropriate to study them together, but analyse them independently (Couper, Hosking, Cisler, Gastfriend, & Kivlahan, 2005; Hart & Bagiella, 2012; McAlister, Straus, Sackett, & Altman, 2003). This design has been used in clinical trials for many years (McAlister et al., 2003), and is chosen for a variety of reasons, including situations where there is the potential for multiple pathways of effect and where there may be incremental gains from interventions that each have modest treatment effects, but collectively they may have larger effects (Hosking et al., 2005; Montgomery, Peters, & Little, 2003). Therefore the factorial design seems optimal in evaluating rehabilitation interventions, and will allow the simultaneously study of both a behavioral and pharmacological

intervention. However, careful consideration must be given to the specific choice of each intervention.

Keeping with the goal of efficiency, ideally the interventions chosen to be included in a factorial design should be widely applicable, so that the largest number of people with the condition will benefit from the study results. Historically, post-stroke upper extremity rehabilitation studies have been conducted almost entirely in high-income countries and the interventions almost always require additional resources. Recent data indicate that those who experience stroke in low and lower middle-income countries have greater post-stroke disability (Bosch, O'Donnell, et al., 2014), and a large percentage experience upper extremity weakness (77.9%). This ranges from 67.3% in high-income countries to 97.3% in low-income countries. The same study also identified that the majority of patients with stroke and upper extremity weakness were not receiving rehabilitation one month after stroke, indicating that it is unlikely that intervention could be provided through health systems for the majority of the world. A simple rehabilitation intervention that requires minimal, if any, training to provide and can be independently sustained by patients is urgently needed.

Similar considerations should be given to the choice of pharmacological intervention. Ideally, the drug would not only have evidence to support its use, but would have an established safety profile (to minimize the amount

of data collection required on safety), be easily available and inexpensive so that if effective, it is affordable for most. A generic drug is most likely to meet these criteria. In general, for post-stroke rehabilitation and pharmacological interventions to be globally applicable, they must be simple for health care providers to implement and allow patients to easily comply. With these basic criteria in mind, the following interventions were selected for use in PROOF.

A simple task-based upper extremity post-stroke rehabilitation intervention

Using best available evidence to maximize the likelihood of effectiveness, the rehabilitation intervention a) is based on fundamental principles of motor learning (Schmidt & Lee, 2014) , b) uses key elements of self-efficacy theory (Jones & Riazi, 2011; Korpershoek, van der Bijl, & Hafsteinsdottir, 2011) and c) is introduced early to maximize neuroplasticity.

The fundamental principles of motor learning used in the rehabilitation intervention are intensity, or amount, of practice and the use of task (or experience) to practice, and were chosen because they have the most evidence of effect (Arya et al., 2012; Hubbard, Parsons, Neilson, & Carey, 2009; Kitago & Krakauer, 2013; Krakauer, 2006). The effect of practice on skill acquisition has been recognized for almost a century, such that performance improves rapidly when practice begins and diminishes (but continues) as the learner becomes skilled at the task (Kitago & Krakauer,

2013; Schmidt & Lee, 2014). While the exact amount (intensity) of practice that is required to improve activity limitation is not known (Bosch, Donnell, Barreca, Thabane, & Wishart, 2014; Kwakkel, 2006; Nijland et al., 2010; Pollock et al., 2014), based on available outcome and safety data in people with stroke (Han, Wang, Meng, & Qi, 2012; Harris, Eng, Miller, & Dawson, 2009), the practice target should be a minimum of 60 minutes, with a goal of closer to 3 hours per day. Furthermore, practice should occur through completion, in part or whole, of tasks to promote experience-based neuroplasticity (Nudo, 2013; Winstein & Wolf, 2009). The type of tasks should be varied, challenging, adaptive to learning (i.e. made progressively more difficult, with frequent opportunity for success) and engaging, such that the learner wants to complete the task. These basic principles of abundant, effortful practice and use of task will encourage neuroplasticity, and in particular maximize processes such as synaptogenesis and cortical pathway re-organization, that are expected to lead to the permanent cortical changes required for skill re-acquisition (Buma, Kwakkel, & Ramsey, 2013; Dimyan & Cohen, 2011; Takeuchi & Izumi, 2013).

Strategies to enhance self-efficacy, defined as one's belief in their own ability to perform a task (Bandura, 1977) are incorporated in the intervention to maximize the amount of autonomous practice, through engagement and motivation (Jones & Riazi, 2011). Strategies include the

use of client-centered goal setting to determine what is important to the participant in terms of upper extremity function, and also the activities to be practiced. Negotiating the activity choice with the patient is meant to enhance confidence in task conduct and subsequently functional performance (Jones & Riazi, 2011), through an increase engagement with the intervention (Epstein & Street, 2011).

While these principles of practice, and specifically task-based practice form the active ingredients of the intervention, the timing of delivery is another important consideration. There is evidence that the neurophysiologic processes that occur in the days following stroke actually prime the injured brain for recovery, and may work synergistically with other efforts to maximize neuroplasticity (Cramer & Riley, 2008; Johansson, 2000). Stroke rehabilitation, where available, usually begins in the weeks following stroke, however stroke rehabilitation studies most often enroll participants 3-6 months after stroke (Stinear, Ackerley, & Byblow, 2013). Concerns over early initiation of intervention arose after one study of an upper extremity motor intervention (constraint induced movement therapy) initiated immediately after stroke (4.5 days) concluded there was less motor improvement at 90 days in the early initiated group, based on differences in the Action Research Arm Test (ARAT) scores (Dromerick et al., 2009). The overall ARAT scores demonstrated a difference that was dominated by grip and pinch scores, while there was

no difference in grasp and gross motor scores. The results are odd as these movements are closely related and therefore one would expect a consistent result across all four domains. Furthermore, the upper limb component of another functional outcome measure (the Functional Independence Measure) did not demonstrate a difference. This inconsistency in the study outcomes means results should be interpreted cautiously. More studies on early initiated intervention, started after the patient is medically stable, are required as doubt remains as to the best timing of intervention (Bernhardt, Indredavik, & Langhorne, 2013).

Based on these core motor learning principles as well as self-efficacy theory, and with consideration of best timing, we developed the "Upper-extremity Practice Post-stroke in Early Recovery" (UPPER) intervention to be one of the factorial arms in the PROOF study (specific details on the intervention are provided in the methods section).

Using Dopamine to Treat Post-stroke Upper Extremity Motor Impairment

To choose the appropriate intervention for the second arm of the factorial design, we reviewed the literature on the effect of pharmacological agents on post-stroke motor recovery (Berends et al., 2009; Rosser & Floel, 2008). Although there is limited efficacy data, carbidopa-levodopa (which is converted to dopamine in both the peripheral circulation and the central nervous system) was chosen because of it's effect, through dopamine, on learning and movement (Schultz, 2007). The effect on motor control and

learning is mediated through dopaminergic pathways emanating from the basal ganglia and working through mid-brain structures (thalamus and globus pallidus) to influence the motor cortex (nigrostriatal pathway) (Leisman, Melillo, & Carrick, 2013). There is also evidence of dopaminergic projections to the motor cortex, indicating that dopamine may have a direct effect on motor activity (Luft & Schwarz, 2009; Middleton & Strick, 2000; Molina-Luna et al., 2009) with data from animal studies supporting the hypothesis of a direct effect on motor learning (Beeler et al., 2010; Hosp & Luft, 2013). Therefore, dopamine plays an important role in movement, and in particular in skill acquisition, theoretically making it an ideal candidate for the second arm of a factorial design aimed at improving activity limitation secondary to upper extremity motor impairment.

Data from animal studies on the effect of dopamine on motor function has been promising, although limited, (Rosser & Floel, 2008), while data from human studies have been inconclusive. There have been two studies in humans that have administered short courses (1-3 days) of carbidopa-levodopa therapy to people with stroke with chronic motor impairment. Each study demonstrated an effect (thumb movement, n=9, finger movement, n=18)) (Floel, Hummel, Breitenstein, Knecht, & Cohen, 2005; Rosser et al., 2008). Two other studies randomized people with stroke and chronic motor impairment to longer courses of levodopa treatment (100

mg for five weeks, n=10; 125 mg for three weeks in combination with methylphenidate in a factorial design, n=100) (Acler, Fiaschi, & Manganotti, 2009; Lokk, Salman Roghani, & Delbari, 2011). Improvement in arm function and functional activities was seen in the levodopa group in each study. Another study administered carbidopa-levodopa (100 mg levodopa, n=53) with physiotherapy in the first three weeks after stroke, and demonstrated improvement in upper extremity motor impairment and activity limitation (Scheidtmann, Fries, Müller, & Koenig, 2001). On the whole, these studies are small and heterogeneous in design, making it difficult to draw any absolute conclusions about effectiveness (Acler & Manganotti, 2013), however there is a trend towards effect. There is one large study currently underway (n=572), evaluating the effect of co-calredopa on walking outcomes at 8 weeks (arm function is a secondary outcome) (Bhakta et al., 2010). This trial has completed recruitment and results are expected within the next six months. While the results will be of interest for both efficacy and safety outcomes, the hospital-based design coupled with provision of rehabilitation based on the United Kingdom (UK) National Health Service system, limits the generalizability of results beyond the UK.

Based on the potential physiological mechanisms and the limited data available, carbidopa-levodopa (25mg- 100mg) shows promise in terms of remediating post-stroke motor impairment. The specific mechanism of

effect is not clear as it could either be through increasing norepinephrine concentration (dopamine converts to norepinehphrine) or actually supplementing depleted dopamine stores (Scheidtmann, 2004). Lower doses have been used in previous studies of post-stroke motor impairment and there are extensive safety data available for this dose, which show minimal side effects (Block, Liss, Reines, Irr, & Nibbelink, 1997). As an added consideration, the formulation intended for use in the study (controlled release carbidopa-levodopa 25mg/100mg) is off patent, meaning the drug is available fairly inexpensively worldwide. Carbidopa-levodopa seems like an appropriate choice to include as the pharmacological agent since there are promising data on effect, it is available in all parts of the world (for relatively little cost) and is fairly easy to administer (minimal safety concerns).

The following protocol describes a randomized, factorial, partial cluster clinical trial of additional, upper extremity, supported, independent task practice compared to usual care, and carbidopa-levodopa compared to placebo to test the hypothesis that either of these interventions will improve post-stroke upper extremity activity limitation due to motor impairment.

Study Objectives

The primary objectives of the PROOF trial are to determine:

1. If a structured upper extremity practice program (UPPER),

improves upper extremity activity limitation due to motor impairment in the affected upper extremity, as measured by the Action Research Arm Test, after four weeks, compared to usual care.

2. If 30 days of sustained release carbidopa-levodopa (25 mg-100 mg) daily, improves upper extremity activity limitation due to motor impairment in the affected upper extremity, as measured by the Action Research Arm Test, compared to placebo.

Exploratory analysis will include:

If the combination of a structured upper extremity practice program (UPPER) and sustained release carbidopa-levodopa (25 mg- 100 mg) improves upper extremity activity limitation due to motor impairment in the affected upper extremity, as measured by the Action Research Arm Test, compared to usual care and placebo, after four weeks.

Secondary objectives, each analysed according to the three comparisons described above, will determine if there is an:

1. Effect on any of the primary objectives, six months after stroke. Six months was chosen as this will allow an estimate of longer-term functional gain, but it is also short enough to ensure more complete follow-up.
2. Increase in the amount of movement in the affected upper

extremity in the UPPER group compared to usual care, after four weeks, as measured by upper extremity accelerometry (to understand if the intervention results in an increase in the amount of upper extremity activity, the key active ingredient in UPPER).

3. Change in perceived self-efficacy in the UPPER group compared to usual care, after four weeks, as measured by the Stroke Self-Efficacy Questionnaire.
4. Improvement in patient perception of stroke related outcomes, as measured by the Stroke Impact Scale 3.0 (SIS 3.0), at four weeks and at six months (to gain the participants assessment of effectiveness).

Safety outcomes, each analyzed according to the comparisons described in the primary objective, include:

1. For UPPER/usual care arm only: Increase in upper extremity pain, as measured by a visual analog scale (although the intervention activities will be designed to minimize the likelihood of pain).
2. For the carbidopa-levodopa/placebo arm only: Any events that are serious (according to ICH E6 criteria), unexpected (in terms of product labeling or the participant's medical history), and associated with the use of study drug, in the opinion of the

attending physician.

Methods

Study Design

PROOF is a multi-centre, two-by-two factorial design (see Table 1), using cluster randomization for the stroke rehabilitation intervention (UPPER compared to usual care) and individual patient randomization for the pharmacological intervention (carbidopa-levodopa versus placebo). The use of cluster randomization results in an increase in the required sample size, and is therefore not usually preferable, however it is essential in PROOF because of the potential for contamination. In a development study of a similar intervention for the lower extremity, conducted in an inpatient environment, therapists reported that delivery of the intervention changed their practice, such that they began negotiating an outside-of-therapy activity program with each patient. Furthermore, to maximize implementation of the intervention in an inpatient setting may require the participation of the entire team (i.e. not just the attending therapists). Either of these scenarios increases the likelihood for contamination (implementation of the intervention) in the control group, for those participants that are admitted to inpatient rehabilitation services, but could also apply in an outpatient setting. This potential effect of contamination along with the intent to include a small number of participants per cluster, (preferable in cluster designs) makes cluster randomization the

appropriate option for the rehabilitation arm of the trial (Slymen & Hovell, 1997).

For the comparison of carbidopa-levodopa to placebo, patient level randomization is appropriate as double blinding is possible. Carbidopa-levodopa tablets can be over-encapsulated to match placebo, which means that neither the health care provider nor the participant will know which treatment the participant is taking, avoiding any potential bias related to open treatment.

The study design is therefore a unique factorial design, with one arm of the study using cluster randomization (UPPER program versus usual care), while the other arm (carbidopa-levodopa versus placebo) uses individual participant randomization (see Figure 1). Every participant will receive an intervention, including those randomized to usual care + placebo, which may improve overall follow-up since patients have a reason to attend study visits to pick up their pills (opposed to just receiving usual care).

Ethical Considerations

The study was designed in accordance with the Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials (Weijer et al., 2012), Canadian Food and Drug Regulations (Division 5), the International Conference on Harmonization Guideline for Good Clinical Practice (International Conference on Harmonization (ICH), 1996), and the Tri-Council Policy Statement (TCPS2) (Canadian Institutes of Health

Research, Natural Sciences and Engineering Research Council of Canada, & Canada, 2010) and where required, will conform to specific national and local laws. Applications will be made in each to country for regulatory approval and at each site for ethics approval, and the consent form will be translated into the required languages. Participant recruitment will not begin until these approvals have been obtained.

Country and Centre Selection

The 32 sites that participate will be divided evenly between the 4 income regions, with each site recruiting a total of 13 participants over 18 months (n=416). The success of the study will depend on finding investigators who are interested in research and in particular the study questions, and who have the resources required to conduct the study at their site (that is, to recruit and follow participants). Funding will be provided to cover costs, and all study processes will be kept as simple as possible, to minimize efforts required at the site. Ideally each site will identify both a physician (required for the pharmacological component) and an allied health care provider who are interested in the trial, as well as the resources to implement the interventions, collect data and administer assessments. Potential sites will be identified from a variety of sources including known researchers interested in the topic and an established network of stroke research centres from the INTERSTROKE Study (O'Donnell et al., 2010). Countries from high-income regions that might participate include Canada,

Ireland and the United Kingdom; upper middle-income countries include China, South Africa or Brazil; lower middle-income countries include India (although current problems in conducting clinical trials would have to be resolved), the Philippines or Pakistan, and low income countries Mozambique, Uganda and Tanzania (income levels are based on the World Bank's assessment of gross national income for the fiscal year 2012 (World Bank Group, 2014)). Two countries in each region will be selected to participate, based on the response from sites, as this will minimize drug importation and translation costs. In order to minimize between site variation, sites will be asked to describe key parameters that can be used to match sites within a country or region (an example of the types of parameters is provided in Appendix A). Sites will also be asked to describe their experience in other trials and their strategies for achieving the recruitment goals and maintaining adherence. It is important to note that participants will be recruited after being admitted to hospital for stroke, but participants may not stay in hospital for the entire four weeks until initial follow-up. Therefore sites will have to structure activities so that study visits can be completed (both control and intervention sites will be asked to see the participant weekly) and outcome assessments obtained. In some cases this will require asking the participant to return to clinic.

Eligibility Criteria

Participants are eligible if they have:

1. Experienced their first stroke (either ischemic or hemorrhagic) between 4 and 10 days before randomization to the study (this timeframe should ensure the patient is medically stable). The diagnosis of stroke requires confirmation by a physician using clinical evidence, such as sudden onset focal neurological deficits lasting more than 24 hours, and neuroimaging, based on the WHO criteria (WHO Monica Project Principal Investigators, 1988).

2. Hemiparesis in the arm or hand but are able to, at least partially, activate a shrug of their shoulder and extension of at least one of their fingers against gravity on their hemiplegic side. Studies indicate that patients with hemiparesis who are able to perform these movements within 72 hours of stroke are likely to regain more movement (Beebe & Lang, 2009; Kwakkel, Kollen, van der Grond, & Prevo, 2003; Nijland, van Wegen, Harmeling-van der Wel, Kwakkel, & EPOS Investigators, 2010; Smania et al., 2009).

3. Provided a signed informed consent.

4. Identified one functional goal that involves improving movement in the affected upper extremity.

5. Willing to participate in both arms of the trial.

Participants are ineligible if they have:

1. A comorbid medical musculoskeletal, neurological or psychological condition that may preclude or make difficult their participation in an upper

extremity motor impairment recovery program (e.g. Parkinson's disease, severe osteoarthritis of the shoulder or rheumatoid arthritis of the fingers).

2. Cognitive or communication deficits that, in the opinion of the investigator, would prevent the patient from understanding or implementing the intervention.

3. Glaucoma (potential side-effect of carbidopa-levodopa).

4. Undiagnosed skin lesions that are suspicious of melanoma or history of melanoma (potential side-effect of carbidopa-levodopa).

5. A need to take monoamine-oxidase inhibitor or sympathomimetic agents, with the inability to discontinue, as these drugs also increase catecholamines.

6. Known hypersensitivity or contraindication for carbidopa or levodopa.

7. Childbearing potential and are unwilling to practice an effective method of birth control at study entry and during administration of carbidopa-levodopa, or are pregnant at time of recruitment.

Vanguard Phase & Strategies for Recruitment

As a precursor to the large trial, two sites from a high income country and two sites from an upper middle income country will be asked to start 3-4 months before the other sites, as an internal vanguard phase (Friedman, 2013). This will allow us to test out all aspects of the study processes, including the feasibility of implementing both interventions (e.g. timelines of drug packaging and shipping, as well as site set-up for provision of

intervention), and will allow us to make any revisions to processes before the remainder of the sites begin. Both steps are considered important precursors to larger trial implementation (Thabane et al., 2010) and the outcome data from participants recruited during this phase will be used as part of the main analyses (unblinding will not occur in these sites at the end of the Vanguard phase). Furthermore, it will allow a quantification of usual care in these regions (expected to be the regions with the most organized care post-stroke). Feasibility of recruitment in a high-income country (Canada) can be estimated from experience in an ongoing pilot study of additional walking and walking related practice (the Independent Mobility and Physical Activity Training, IMPACT trial). Preliminary (and unpublished) data indicate that sites should be able to recruit at least one participant per month, and therefore asking sites to recruit 13 participants in 18 months allows for potential slow downs during, for example, vacation periods.

Randomization

Cluster: Site randomization will be performed based on information provided by sites (Appendix A). Sites will be grouped into dyads within their region based on similarities and then randomized to either UPPER or usual care. A dyad will only be randomized once ethics approval is obtained at both sites. A statistician not involved in the study will be asked to randomly assign sites to UPPER and usual care, stratified by region.

Individual Participant: A list of treatment allocations for carbidopa-levodopa or placebo (1:1 ratio) will be generated using STATA 13.1(ralloc program), stratified by site and with randomly selected block sizes. Randomization into the trial will only occur after consent is obtained.

Interventions

An outline of the study visit schedule is provided in Appendix B as well as a brief description of the activities that occur at each visit. The specific details of each intervention are detailed below.

*The UPPER (**U**pper-extremity **P**ractice **P**ost-stroke in **E**arly **R**ecovery) Program*

The purpose of the UPPER program is to increase the amount of independent upper extremity task-based practice that occurs outside of therapy time. Recent data emphasize the need for additional practice for patients admitted to inpatient rehabilitation units, as not much occurs outside of therapy time (Bernhardt, Chan, Nicola, & Collier, 2007; Lang, Wagner, Edwards, & Dromerick, 2007; West & Bernhardt, 2012). For those discharged directly home, a lack of confidence in the abilities of the affected arm, coupled with an increase in skill in the unaffected arm results in decreased use of the impaired limb in the home environment (Hidaka, Han, Wolf, Winstein, & Schweighofer, 2012). The UPPER program can be implemented in either the home or hospital environment as PROOF participants may or may not remain in hospital four weeks after stroke (the

timing for the intervention and the primary outcome assessment). The UPPER program can initiated in the home or hospital environment, with follow-up visits occurring in hospital, outpatient clinic or the participants' home. Four weeks was chosen for the length of intervention as this is the average length of stay if admitted to inpatient rehabilitation (Hall et al., 2013) and for those discharged home, it is a reasonable length of time for usual follow-up appointments and therefore may fit with a usual care schedule (if follow-up is available). For those receiving rehabilitative therapies, UPPER is an adjunct to those therapies and the participant will be asked to share their UPPER program with their therapists. When agreed to by the participant, caregivers and family members will be encouraged to be involved, as they too can be effective in helping the participant improve their physical functioning after stroke (Wang et al., 2014).

The key to implementing the UPPER intervention is to make every effort to maximize the dose of the "active" ingredient that the participant receives (Hart & Bagiella, 2012; Winstein & Wolf, 2009). The active ingredient in UPPER is abundant, effortful task-based practice. The challenge is to get participants to practice outside of therapy times if in therapy or practice in general if discharged home. There are many possible reasons why patients do not practice on their own which include physical (pain and fatigue), behavioral (such as decreased self-efficacy or lack of belief in the

ability to practice successfully) (Lequerica, Donnell, & Tate, 2009) and environmental factors, including a lack of things to do especially in the inpatient rehabilitation setting (Gallacher et al., 2013). The UPPER manual for Healthcare Providers (Appendix C) provides a detailed description of how to implement the intervention and guidance on how to address each of these areas. The health care provider (a nurse, physiotherapist, occupational therapist, personal support worker, physician, etc.) will initially identify the participants' goals (related to activity limitation secondary to upper extremity impairment). The list of activities provided in the manual can be used for activity ideas, or other appropriate activities can be identified. It is essential that the goal is identified, and at least 2-3 activities negotiated (including practice time) within the first session. These are recorded on the UPPER Worksheet (Appendix D). The participant should be given the opportunity to practice the activities, review questions and learn how to complete the activity log (Appendix D). Also during this session, participants will be asked to rate their confidence in performing the activities out of 10. If they score less than 8, the activities either need to be renegotiated or further practice provided.

Recognizing that there is a lot of activity during the first session, there are three sessions planned during the first week, where the participant will check in with the health care provider to review activity completion, any questions and ensure an appropriate challenge. At each visit participants

will be asked if the activity challenge is appropriate and will be encouraged to either practice a more difficult version of the current activity or negotiate a new activity, if the activity becomes too easy. Two visits per week will occur for the next three weeks. Baseline and discharge assessments may be done before or after sessions with the health care provider, but should be distinct so that the blinded assessor is not privy to the content of the visits. Baseline and 4-week assessments should preferably be scheduled at the same time of day (i.e. if the baseline assessment is done in the morning, the four week assessment should be completed at the same time). Sites who are randomized to deliver the UPPER program will receive training, the manual and all required materials prior to study start and as required throughout the study. UPPER participants will be asked to wear accelerometers, as described for the usual care group below. All forms that are to be completed by participants will be translated into the appropriate languages.

For UPPER sites, data will be collected during the intervention period and sent centrally to allow for review of activity programs (draft data collection forms and instructions pages are provided in Appendix E). The project office team will provide sites with feedback on the amount of activities negotiated, the amount of practice negotiated and the amount achieved. Regularly, the project team will discuss strategies for improvements in these areas as issues arise. Furthermore, solutions to common problems

as well as novel strategies for enhancing practice will be shared with all intervention sites during the course of the study.

Usual Care

Sites that are randomized to the usual care arm will provide care as usual in terms of the amount of practice a participant receives. If participants are usually provided with activity programs to complete on their own, this practice should continue. Participants will be asked to wear an accelerometer and keep an activity record, and sites will be asked to submit activity records on a weekly basis.

Carbidopa-levodopa/Placebo

All participants will be randomized to receive either carbidopa-levodopa or placebo. An extended release formulation of carbidopa-levodopa (25mg-100mg) will be provided in blister packs. On the first two days post-randomization, participants will receive a half dose of the drug (12.5 mg carbidopa-50 mg levodopa), and this will increase to full dose by day 3, and they will remain on full dose until day 28. Four weeks should provide enough dopamine supplementation to enhance motor recovery. Those randomized to placebo, will receive a matching placebo tablet provided in blister packs. Each drug package will be uniquely numbered, so when a site randomizes a participant (through the web portal) they will be provided with the specific drug package number to provide.

Data Collection and Procedures

The schedule for data collection for the UPPER and usual care sites is provided in Appendix B. Data will be collected at baseline and at the end of each study week. At baseline, key characteristics including stroke type and location, age, gender, hand dominance, past medical history, current medication use, functional status (before and after stroke, using the modified Rankin Scale) and cognitive measures (if available) will be collected (see Appendix E: Case Report Forms). Participant contact details will be collected and stored locally to assist with contacting participants for follow-up. Weekly, sites will be asked to submit the Participant Activity Log and information on adherence and tolerance to the carbidopa-levodopa/placebo arm. At the end of four weeks, additional information will be collected on clinical events that occurred during the study period, the outcome assessments will be repeated and the six-month assessment will be scheduled (note that this assessment may occur either in hospital, at an outpatient clinic or in the participant's home). Data will be collected either by fax, scan or direct entry into a comprehensive data management system (DataFax™, housed at the Population Health Research Institute, McMaster University) that will allow real time identification of data issues for both the project team and site investigators. Sites will be paid based on the receipt of complete and clean data, and therefore data issues will be identified and resolved quickly.

Outcomes

Outcome assessment will occur at baseline, four weeks after study entry and six months after study entry. Sites will be provided with all required equipment and valid translated versions of all questionnaires.

Action Research Arm Test

The primary outcome measure in PROOF is the Action Research Arm Test (ARAT), an upper extremity activity limitation measure designed for people with stroke. The measure uses direct observation of upper extremity activity to quantify limitation and improvement in upper extremity movement and activity post-stroke (Van der Lee et al., 2001). The measure uses 19 activities to evaluate grasp (6 items), grip (4 items), pinch (6 items) and gross arm movement (3 items). The test is out of a total of 57, using a 0-3 rating scale on each of the 19 activities, with 0 indicating no movement and 3 indicating full movement (see Appendix F for an example scoring sheet). The measure is used extensively in post-stroke upper extremity motor function research, and has demonstrated excellent inter-rater reliability, internal consistency in the acute stroke setting (Nijland et al., 2010), as well as construct validity (Platz et al., 2005). The minimal clinically important difference (MCID) is 12 for the dominant hand and 17 for the non-dominant hand (Lang, Edwards, Birkenmeier, & Dromerick, 2008). The measure is only available in English, so validated translations of the instructions will be provided to each site. All required equipment will also be provided. To further

improve the reliability and interpretability of the measure, the ARAT will be administered according to published standardized procedures (Yozbatiran, Der-Yeghiaian, & Cramer, 2008).

Upper extremity accelerometer

Arm accelerometry has been established as a valid measure of upper extremity movement post-stroke (Rand & Eng, 2010; Uswatte et al., 2005). The Actical (STARR Life Sciences Corp.) has been shown to be both reliable and valid at measuring arm movement in previous studies in a subacute stroke population (Rand & Eng, 2012). Participants (in both the UPPER and usual care group) will be asked to wear the accelerometer whenever they are awake (although it should be removed for bathing) to obtain an accurate estimate of activity (measured as number of movements within a 15 second time interval). Each site will be provided with 3 accelerometers, as it is not expected that more than 3 participants would be enrolled simultaneously. Data will be downloaded to the Project Office weekly and will be reviewed for completeness. Participant instructions will be provided in required languages.

Self-Report Measures: The Stroke Self-Efficacy Questionnaire (SSEQ), the Stroke Impact Scale (SIS)

The SSEQ will assess the level of self-efficacy at baseline, 4 weeks and 6-months to determine if the UPPER program is able to increase self-efficacy in the short and long term. This measure consists of 13 items,

representing common functional deficits experienced by people with stroke. Participants are asked to rate their confidence on a scale of 0 (no confidence) to 10 (very confident) (Riazi, Aspden, & Jones, 2014). The measure has demonstrated reliability and validity (Jones, Partridge, & Reid, 2008). Sites will be provided with validated translated verisons.

The Stroke Impact Scale (SIS), version 3.0, will be used to assess the participants perception of their health status in 8 areas (strength, memory, emotions, communication, activities of daily living, mobility, arm/hand function, participate in roles). There are 59 items in total and each domain can be scored separately. The SIS 3.0 has demonstrated good test-retest reliability and construct validity (Lin et al., 2010). The SIS 3.0 has been translated into many languages, and validated translations will be provided if necessary.

Procedures for Assessment

Individuals blinded to the site allocation for the UPPER/usual care comparison will collect all outcome measures. Possible assessors could include rehabilitation professionals from other departments, study coordinators involved in other studies or anyone who could perform the task without being unblinded in their usual daily activities. Assessor training on the ARAT will be a three-phase activity. First, assessors will be provided with detailed training materials (written and visual), including standardized instructions. The assessor will indicate to the study team

when they have completed the review of the materials, and they will be sent five test cases to score for each measure. They will have two days to submit the results of these assessments, and they must demonstrate 95% agreement. If they do not, additional training will be provided, dependent upon the assessment issue identified. At each assessment, blinded assessors will be asked if the blind has been broken.

A participant instruction video will be provided for training the participants on how to wear the accelerometer (it will be a visual aid and no verbal or written language will be used to accommodate those who are illiterate and to avoid the need for translation). Sites will be provided with the details on how to download the accelerometry information on a weekly basis. Assessors will also be provided with the training materials for the two self-report outcome measures (the Stroke Self-Efficacy Questionnaire and the Stroke Impact Scale).

Safety Outcomes

Adverse events likely related to study interventions will result in the discontinuation of a study intervention, either temporarily or permanently. Once per week, reasons for discontinuation of the study treatment will be reported, and unblinded data will be reviewed regularly by the Data and Safety Monitoring Board (DSMB). Likewise data on reasons for not adhering to the UPPER intervention will be reviewed, as will the pain scores for both the UPPER and usual care groups. There is an extensive

amount of available safety data on the extended release carbidopa-levodopa 25mg-100mg, and therefore only those events that are serious (as per the International Conference on Harmonization, E6, Good Clinical Practice, (International Conference on Harmonization (ICH), 1996)), unexpected in terms of the current product labeling and the participant's medical history and believed to be related to continued release carbidopa-levodopa 25mg-100 mg will be reported to health authorities and ethics boards in an expedited manner (within 7 days of reporting to the project team). Data on reasons for not wearing the accelerometer will also be collected.

Statistical Considerations

Sample Size

Sample size calculations were made with consideration of both the cluster randomization and factorial design. The sample size calculation for cluster randomized trials requires the inclusion of an intra-cluster correlation coefficient (ICC) to account for the variation between clusters, and applies an "inflation factor" to the sample (van Breukelen & Candel, 2012).

The following assumptions were made to calculate the required sample size:

i. Expected difference between UPPER and usual care groups at four weeks: The expected difference in mean ARAT scores at one month is between 6-10 points (Arya et al., 2012; Dromerick et al.,

2009; Han, Wang, Meng, & Qi, 2013). .

ii. Mean ARAT score in the usual care group at one month: Data taken from similar patients with hemiparesis indicated a mean score of 39.5 and a standard deviation of 19.7 (Beebe & Lang, 2009). This was supported by comparable data at 14 days.

iii. Number of clusters: As mentioned previously, a total of 16 clusters will participate (32 sites) from 8 countries. The 32 sites will be distributed evenly between high-income, high-middle income, low-middle income and low-income countries (i.e. 4 clusters for a total of 8 sites in each, see Figure 1).

iv. Cluster size: Each site will recruit 13 participants over a period of 18 months. Based on data from pilot work, this is a reasonable estimate for recruitment.

v. Intracluster correlation co-efficient (ICC): Based on data using a similar measure in a similar population, the ICC is estimated to be 0.03 (Frank et al., 2013). ICC was also calculated using a worst case estimate of 0.1 (van Breukelen & Candel, 2012).

vi. Level of significance: 0.05 (two–sided)

vii. No interaction: It is assumed that there will be no interaction between the two interventions in this factorial design, however the analyses to test for interaction will be performed to confirm this assumption.

Using the STATA clustersampsi program (Hemming & Marsh, 2013), the power and detectable difference were calculated for the UPPER versus usual care comparison using various values of the ICC for the main comparisons, as well as for each region. With a total of 384 participants, from 32 clusters (mean cluster size of 12), the study will have 80% power to detect a difference in ARAT scores of 7.56 in the UPPER versus usual care comparison, and 90% power to detect a difference of 8.75 in scores (details are provided in Table 2a, i.). However there are also a variety of elements that could negatively affect study power, that include:

a) Imbalance in cluster size: Although the number of participants expected per site is very reasonable (n=13), based on our experience to date, there is the potential for variation which may negatively affect study power (Eldridge, Ashby, & Kerry, 2006).
b) Lost to follow-up/non-adherence/increase in practice or use of carbidopa-levodopa in the control groups: While every effort will be made to minimize these issues, each could affect study power and needs to be considered (Slymen & Hovell, 1997).
c) Death: The mortality rate at one month is likely to be 10 and 16% (Bosch, O'Donnell, et al., 2014; Dashe, 2014) and those who die will not contribute to the study outcome.

Each of these elements may have a negative effect on power although the exact effect cannot be accurately estimated. To preserve study power in

the presence of any of these factors, the sample size was increased by 7.5%. (n=416). The revised sample size calculations can be found in Table 2 a. ii.

The sample size and cluster structure will also provide 80% power to detect a difference in score of 17.0 between the UPPER and usual care arms *in each of the regions* (high-income, upper middle-income, lower middle-income, low income).

For the carbidopa-levodopa comparison to placebo, there is 80% power to detect a 5.41 difference in ARAT scores, and 80% to detect an 11-point difference in any of the regions (Table 2b.)

Analysis

The primary outcome analysis for all three objectives will be calculated using individual participant data and based on an intention to treat approach. Table 3 provides a brief description of each method of analysis. For the UPPER versus usual care comparison, the analysis and reporting of the results follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines for cluster randomized trials (Campbell, Piaggio, Elbourne, Altman, & Consort Group, 2012). Randomization to UPPER will be done at a site level, however outcomes will be collected and analyzed at the individual participant level. The analysis of both primary and secondary outcomes will account for the between-centre variation using mixed-effects models with centre as a random-effect and treatment group

(UPPER vs. usual care) as a fixed-effect. For example, the effect of intervention on the primary outcome (ARAT score) will be assessed based on a generalized linear mixed effect model with logit link function using centre as random and other factors as fixed in the model, where covariance structure will be determined by examining the unstructured covariance estimates and selecting the most appropriate structure. The results will be expressed as odds ratios with corresponding two-sided 95% confidence intervals and p-values. Given that our unit of randomization is at the centre level for the rehabilitation intervention, there may be imbalances on some key factors at baseline such as age, gender, type of stroke, history of diabetes. We will examine all of these factors for possible imbalances prior to fitting a model and add them as covariates when imbalance across intervention groups is detected.

Linear regression modeling (random effects model) will be used to analyse the carbidopa-levodopa versus placebo comparison, and we will adjust for any imbalances in baseline characteristics (see Table 3 for details). Before performing the model-fitting analysis, the order in which the variables are to be included in the analysis will be identified as suggested by Campbell, Mollison, Steen, Grimshaw & Eccles (2000). If either of the tests at the margin are statistically significant (p values less than or equal to 0.05) then the double active and usual care/placebo comparison will be tested, also at a significance level of 0.05.

In addition to participant baseline characteristics, site characteristics will be reported. The observed ICC will be calculated as will the interaction term for the primary outcomes.

Careful attention will be paid to ensure complete follow-up is obtained on all participants. As noted previously there is the expectation that some participants will die before outcome assessment occurs and therefore it will be impossible to avoid missing outcome data. As suggested by White, Horton, Carpenter & Pocock (2011), a plausible assumption will be made to estimate the value of the missing data. It is expected that the majority of missing data will result from the inability to collect outcomes in those who have died. It is possible that these participants will be sicker and will likely experience decline in functional abilities before their death. Although we won't have outcome data, weekly activity logs will be available and it is likely that activity levels will also decline prior to death. Therefore activity levels will be used to perform multiple imputations to estimate the missing values. Also as suggested by White et al. (2011) sensitivity analyses will be performed if a large proportion of data are missing (>5%). A range of possible differences between observed and missing will be used, such as assuming that there is no improvement from baseline, assuming half the mean change of others in the group or assuming the same change as others in the group.

There is also the potential for differential effect in some participants based

on a variety of reasons. For example, participants from lower income regions will most likely receive less organized post-stroke rehabilitation care, and may do better than those from higher income regions, as this is the only structured practice that they will perform. Age is a risk factor for functional decline and as a result, older participants may not do as well as the younger participants (Saposnik et al., 2008). Finally those with hemorrhagic stroke are thought to have better functional outcomes than those with ischemic stroke, and this will be examined in the PROOF participants also (Paolucci et al., 2003). An interaction term will be used to assess the homogeneity of intervention effect in these subgroups with the main outcome. All subgroup analyses will be reported.

Trial Monitoring and Management

The PROOF trial will convene an independent Data and Safety Monitoring Board (DSMB) to review unblinded data. The DSMB will be comprised of 3 experts in either content, methodology or both. Although the DSMB will set their own charter, it will be recommended that two interim analyses occur, one when 50% of the participants have completed one month of follow-up and the second when 75% have completed one month of follow-up. If there is a clear indication of efficacy at either of these interim reviews (i.e. if there is a reduction of 3 standard deviations ($p=0.0027$) in either arm of the study, the DSMB may recommend that the study be terminated. If there is an indication of effect in just one arm, the other arm will continue.

In addition to the authors listed on this publication, a Steering Committee will provide study oversight and will be comprised of one medical and allied health leader from each of the participating regions, as well as one expert each in neurology (in particular stroke related neurology), stroke rehabilitation and statistics. The Steering Committee will meet monthly, beginning in study start up and continuing until the two manuscripts on the main results have been finalized. Members of the writing group for this paper have extensive experience successfully conducting large, international trials (MO, LT, JB) and will use these skills to guide study activities throughout the process.

Study timelines are dependent upon secured funding. A variety of approaches will be used to obtain the required funding, as it is unlikely that one funding source will provide the total amount required. Each region will be encouraged to apply for independent funding to cover site costs in the region, while in addition to helping regional funding efforts; the project team will work to secure funding for central activities. The authors of this paper have successfully used this funding model in many trials. In addition, the recent funding of large post-stroke rehabilitation studies such as the multicenter, multinational inpatient AVERT trial, which plans to mobilize 2,014 patients within 24 hours of stroke (Bernhardt et al., 2006), and the DARS trial (Dopamine Augmented Rehabilitation in Stroke) of 572 patients with stroke (Bhakta et al., 2010) indicate that obtaining funding for large

international post-stroke rehabilitation trials is possible. Once funding for any region is obtained, it will take six months to get the necessary approvals and import licenses to start.

Discussion

The PROOF trial evaluates two independent interventions that have the potential to improve post-stroke activity limitation secondary to upper extremity motor impairment. This trial is unique in many ways. It is a multi-country, multi-site intervention that will simultaneously evaluate two interventions in high, middle and low-income countries. The rehabilitation intervention will be implemented by health care workers but independently carried out by patients. The study methodology uses a combination of cluster randomization to overcome the bias of an open, motor/behavioural intervention with individual participant randomization to a pharmacological intervention. It will promote collaboration between medicine and allied health care professionals, a practice that happens daily in clinic but rarely in research. Finally, it is designed to clearly answer both questions, with careful thought given to potential impediments. The results of the PROOF trial may not only improve post-stroke function for stroke patients internationally, but may change the way in which future post-stroke rehabilitation trials are conducted.

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Chapter 4- Table 1: The Factorial Study Design

Total n = 416	**UPPER**	**usual care (UC)**	**Carbidopa-levodopa margin**
carbidopa-levodopa	UPPER/ carbidopa-levodopa active n=104	usual care/ carbidopa-levodopa active n=104	**carbidopa-levodopa Active n=208**
Placebo	UPPER/ carbidopa-levodopa placebo n=104	usual care/ carbidopa-levodopa placebo n=104	**carbidopa-levodopa Placebo n=208**
UPPER/UC margin	**UPPER n=208**	**UC n=208**	

Chapter 4 -Table 2: Sample Size Calculations

Table 2a. Sample Size Calculations for Cluster Analysis: UPPER versus Usual Care Comparison

i. 12 participants per site

N Sites	Pts per Site	Usual care ARAT 1-mo mean (SD)	ICC	Power	Detectable Difference
32	12	39.5 (19.7)	0.03	80%	7.56
32	12	39.5 (19.7)	0.03	90%	8.75
32	12	39.5 (19.7)	0.1	80%	10.57
Within Region Comparison					
8	12	39.5 (19.7)	0.03	80%	16.91

Calculated using STATA 13.1, clustersampsi
Pts= Participants, mo=month, SD= standard deviation, ICC=Intracluster correlation coefficient

ii. 13 participants per site

N Sites	Pts per Site	Usual care ARAT 1-mo mean (SD)	ICC	Power	Detectable Difference
32	13	39.5 (19.7)	0.03	80%	7.39
32	13	39.5 (19.7)	0.03	90%	8.56
32	13	39.5 (19.7)	0.1	80%	10.46
Within Region Comparison					
8	13	39.5 (19.7)	0.03	80%	16.53

Calculated using STATA 13.1, clustersampsi
Pts= Participants, mo=month, SD= standard deviation, ICC=Intracluster correlation coefficient

Table 2b. Sample Size Calculations for Individual Participant Analysis: Carbidopa-Levodopa versus Placebo Comparison

n	Usual care ARAT 1-Mo mean (SD)	Power	Detectable Difference
416	39.5 (19.7)	80%	5.41
416	39.5 (19.7)	90%	6.26
Within Region Comparison			
104	39.5 (19.7)	80%	10.82

Calculated using STATA 13.1, clustersampsi
Pts= Participants, mo=month, SD= standard deviation, ICC=Intracluster correlation coefficient

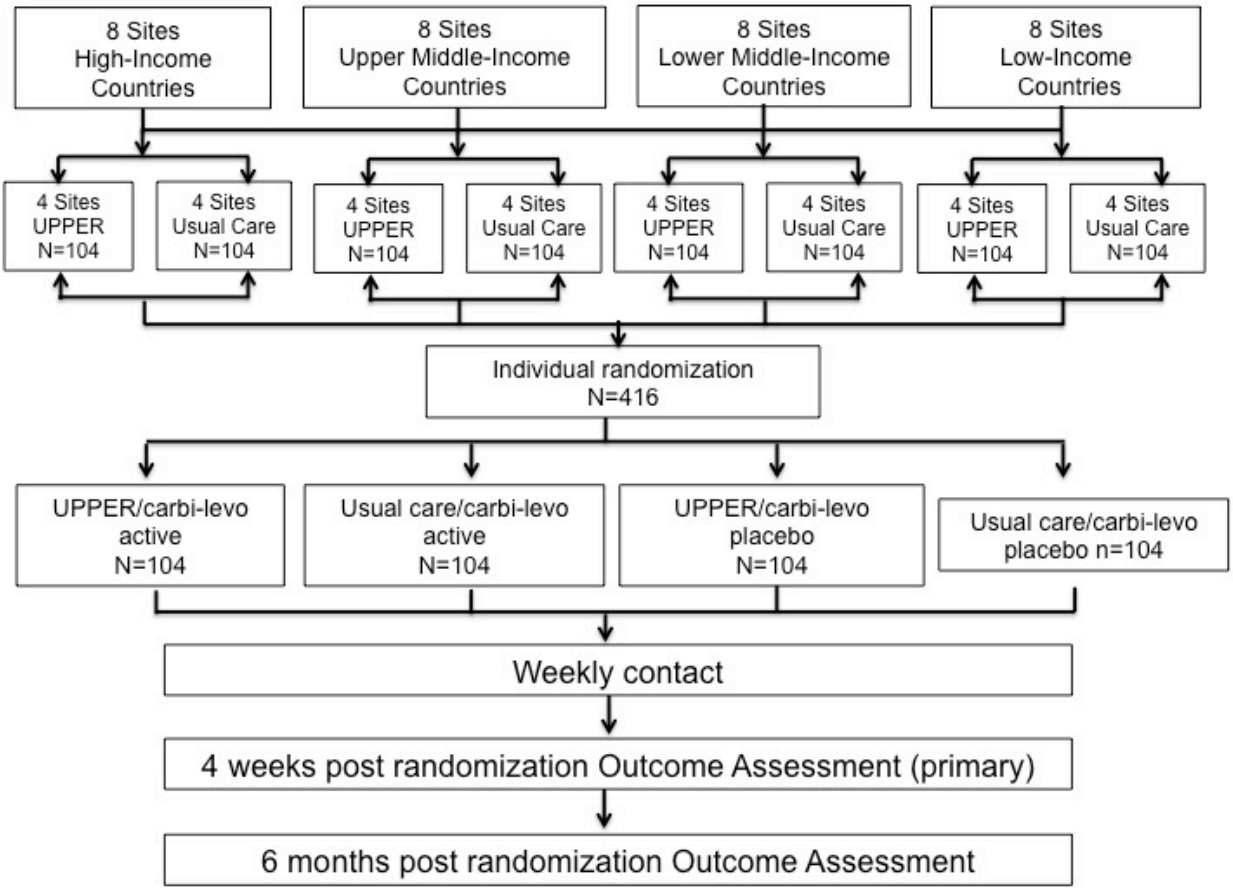
Chapter 4 - Table 3: PROOF Outcomes, Rationale, Measurement Tools & Method of Analysis

Outcome/variable	Hypothesis	Outcome measure	Method of analysis
Primary outcomes			
Affected upper extremity activity limitation one month post-stroke	UPPER > usual care (cluster randomization)	Mean change in ARAT score	Mixed linear regression modelling*
	Carbidopa/levodopa> placebo (Individual patient randomization)	Mean change in ARAT score	Linear regression modelling*
Exploratory analysis			
Affected upper extremity activity limitation one month post-stroke	UPPER + carbidopa/levodopa> usual care + placebo	Mean change in ARAT score	Mixed linear regression modelling*
Secondary Outcomes			
Affected upper extremity activity limitation six months post-stroke	UPPER > usual care	Mean change in ARAT score	Mixed linear regression modelling*
	Carbidopa/levodopa> placebo	Mean change in ARAT score	Linear regression modelling*
	Upper + carbidopa/levodopa> usual care + placebo	Mean change in ARAT score	Mixed linear regression modelling*
Affected upper extremity movement one month post-stroke	UPPER > usual care	Mean (or Transformed mean if non-normal) Actical movement count	Mixed linear regression modelling*
	Carbidopa/levodopa> placebo	Mean (or Transformed mean if non-normal) Actical movement count	Linear regression modelling*
	Upper + carbidopa/levodopa> usual care + placebo	Mean (or Transformed mean if non-normal) Actical movement count	Mixed linear regression modelling*
Self-efficacy	UPPER > usual care	Mean (or Transformed mean if non-normal) SSEQ	Mixed linear regression modelling*
General health status	UPPER > usual care	Mean (or Transformed mean if non-normal) Stroke Impact Scale	Mixed linear regression modelling*
	Carbidopa/levodopa> placebo	Mean (or Transformed mean if non-normal) Stroke Impact Scale	Linear regression modelling*
	Upper + carbidopa/levodopa> usual care + placebo	Mean (or Transformed mean if non-normal) Stroke Impact Scale	Mixed linear regression modelling*
Safety Outcomes			
Affected upper extremity pain	UPPER > usual care	Mean (or Transformed mean if non-normal) Visual Analog Scale	Mixed linear regression modelling*
	Upper + carbidopa/levodopa> usual care + placebo	Mean (or Transformed mean if non-normal) Visual Analog Scale	Mixed linear regression modelling*
Serious adverse events	Carbidopa/levodopa> placebo	Time to event	Cox regression survival analysis

Outcome/variable	Hypothesis	Outcome measure	Method of analysis
	Upper + carbidopa/levodopa> usual care + placebo	Time to event	Cox regression frailty survival analysis (to adjust for cluster rand)
Subgroups			
Regional income groups	Lower income groups will do better because of lack of additional services		Regression methods with interaction term
Age	Younger > older		
Type of stroke	Hemorrhagic > ischemic		

* adjusted if necessary

Chapter 4 - Figure 1: Study Design and Sequence



Appendix A: Sample Site Information Sheet: Criteria for Clustering

	[Site Name]
Average Monthly Admission (N)	
Average Monthly Discharge (N)	
Number of Beds	
Number of OTs	
Average years on any stroke service	
Average years on this stroke service	
Number of OTAs	
Number of OT Students Per Month	
Number of PTs	
Average years on stroke service	
Average years on this stroke service	
Number of PTAs	
Number of PT Students Per Month	
Number of Nurses	
Average years on stroke service	
Average years on this stroke service	
Number of SLP	
Average years on stroke service	
Average years on this stroke service	
Number of Rec Therapists	
Staffing Ratio: OT to pt	
Staffing Ratio: PT to pt	
Staffing Ratio: Nursing to pt	
Staffing Ratio: SLP to pt	
Avg length of time: Stroke – Adm (median)	
Avg length of time in rehab (median)	
Hrs/Day, Days per week of Group Activity Training	
Hrs/Day, Days per week Pool Therapy	
Average admission FIM score (median)	
Average discharge FIM score (median)	

Adm = Admission, Avg = average, Hrs = hours

Appendix B: PROOF: Schedule of Study Activities

Week No.	Day	Visit No.	UPPER	Usual Care
~	~	Screening	• Review chart for eligibility criteria • Complete screening log • If eligible continue	
1	1	1 (within 4-10 days of stroke)	• Confirm eligibility, including upper extremity related activity goal • Obtain consent • Randomize to carbidopa-levodopa/placebo arm: dispense allocated treatment • Instruct on medication schedule • Negotiate realistic goal • Negotiate activities and training schedule • Train family/friends/caregivers if available • Train on how to complete the activity log and wear the accelerometer • Complete case report forms and submit data	• Confirm eligibility, including upper extremity related activity goal • Obtain consent • Randomize to carbidopa-levodopa/placebo arm: dispense allocated treatment • Instruct on medication schedule • Teach how to wear accelerometer • Complete case report forms and submit data

Week No.	Day	Visit No.	UPPER	Usual Care
	1-3	Baseline Assessment (within 2 days of visit 1)	• ARAT (10-20 min) • Visual analog scale for shoulder pain (5 min) • Upper extremity accelerometer • Stroke Self-Efficacy Questionnaire (15 min) • Stroke Impact Scale (20 min) • Complete case report forms and submit data	
	2-4	2	• Review activity log; encourage participant to complete if not doing so • Address any concerns, retrain on or revise activities as required • Train family, friends, caregivers • Check for accelerometer and review instructions • Clarify any questions re: carbidopa-levodopa/placebo • Encourage participant to continue to take daily • Assess for safety outcomes • Complete case report form and submit data	• Check for accelerometer and review instructions • Clarify any questions re: carbidopa-levodopa/placebo • Encourage participant to continue to take daily • Assess for safety outcomes • Complete case report form and submit data
	5-7	3*	• Review activity log; encourage participant to complete if not	• Check for accelerometer and review instructions

Week No.	Day	Visit No.	UPPER	Usual Care
			doing so • Address any concerns, retrain on or revise activities as required • Train family, friends, caregivers • Check for accelerometer and review instructions • Clarify any questions re: carbidopa-levodopa/placebo • Encourage participant to continue to take daily • Assess for safety outcomes • Complete case report form and submit data	• Clarify any questions re: carbidopa-levodopa/placebo • Encourage participant to continue to take daily • Assess for safety outcomes • Complete case report form and submit data
2	8	4	• Review activity log; consider making activity more challenging or increasing amount of activity time • Check for accelerometer and review instructions • Clarify any questions re: carbidopa-levodopa/placebo • Encourage participant to continue to take daily	• Check for accelerometer and review instructions • Clarify any questions re: carbidopa-levodopa/placebo • Encourage participant to continue to take daily • Assess for safety outcomes • Complete case report forms and submit data

Week No.	Day	Visit No.	UPPER	Usual Care
			• Assess for safety outcomes • Complete case report forms & submit	
	11-13	5*	• As in visit 4	• As in visit 4
3	15	6	• As in visit 4	• As in visit 4
	18-20	7*	• As in visit 4	• As in visit 4
4	22	8	• As in visit 4	• As in visit 4
	25-27	9*	• As in visit 4 • Prepare participant for end of study	• As in visit 4 • Prepare participant for end of study
	28	10	• Collect back unused medication • Assess for safety outcomes • Submit final visit case report forms	
	27-30	Four Week Assessment	• ARAT (10-20 min) • Upper extremity accelerometer • Stroke Self-Efficacy Questionnaire (15 min) • Stroke Impact Scale (20 min) • Complete case report forms and submit data	
24	180	11	• Collect data on continued adherence to UPPER program • Collect data on clinical outcomes since four week assessment, discharge location, help required	• Collect data on clinical outcomes since four week assessment, discharge location, help required
		Six Month	• ARAT (10-20 min)	

Week No.	Day	Visit No.	UPPER	Usual Care
		Assessment	• Upper extremity accelerometer • Stroke Self-Efficacy Questionnaire (15 min) • • Stroke Impact Scale (20 min) • Complete case report forms and submit data	

*these visits can be performed by telephone

Appendix C: The UPPER Manual

Upper-extremity **P**ractice **P**ost-stroke in **E**arly **R**ecovery
UPPER
MANUAL
Health Care Provider

2014-MAY-11

To implement the UPPER program follow these steps:

1. *Understand the participant's activity related goal that involves their affected upper extremity*: To do this, ask the participant to identify problems they are currently having conducting their usual activities (activities of daily living). Once you have a determined the activity, ask the participant what they find most difficult (e.g. lifting my arm (limited shoulder flexion), bending my elbow (limited elbow flexion), holding things (limited grasp).

   Then ask the participant if it is important for them to use the arm in the activity, or if they would be happy getting the activity done whatever possible.

   The answers to each of these questions should be recorded on the UPPER Worksheet. These questions can be used as part of the screening process to determine a participant's eligibility for the study. If a potential participant cannot identify an activity goal related to their affected upper extremity or if the use of the affected upper extremity in the task is not important to them, they are not eligible for the study.

2. *Negotiate the type and schedule of activities (Day 1 of study):*

   - The type of activity should depend on the interests of the participant and the available resources. The activity list that follows provides some example activities. The participant should be asked to identify any activities they are interested in and must agree to any activity that is chosen
   - Negotiated activities should include a mix of arm and hand activities
   - Any pain or limitations the participant may have should be considered when choosing activities
   - The schedule for practice should be negotiated with the participant; the amount of practice needs to be at a level that the participant can complete
   - When developing the schedule, consideration should be given to:
     i. The timing of other rehabilitative sessions the participant is receiving
     ii. When the participant is usually most fatigued
     iii. When family members, friends or caregivers may be available to help remind the participant to practice and to offer encouragement

3. *Demonstrate/describe the activities*: Demonstrate each activity for the participant but also provide them sufficient time to practice and feel comfortable with the activities themselves. Use the worksheet to provide a description of the activity and any cues that might be helpful. After allowing the participant a chance to practice, ask them to rate their confidence in performance of each of the tasks. If the score less than 8, review the activity again to determine if it needs to be modified or more practice is required. The participant should leave each session with confidence (8/10 or more) that they can perform each task.

4. *Encourage/evaluate performance:* The visit schedule for the first week provides more frequent visits to provide opportunities for you to review any difficulties that may be impeding the participant from completing the activities as scheduled. After that, at least once a week, the activities should be reviewed to determine if more challenge is needed (either within the same activity) or a new activity is needed, and whether more practice time is possible. It is important to vary the activities, every week so that the participant is challenged.

NOTE: The worksheets and activity logs attached for those participants who are literate. Pictorial representations of these concepts will be provided for participants who are not literate.

The UPPER Program is based on the work of the following:

Jones, F. (2006). Strategies to enhance chronic disease self-management: How can we apply this to stroke? Disability & Rehabilitation, 28(13), 841-847.

Kitago, T., & Krakauer, J. W. (2013). Motor learning principles for neurorehabilitation. In M. P. Barnes & D. C. Good (Eds.), Handbook of Clinical Neurology, Neurological Rehabilitation (Vol. 110, pp. 93-103).

Kleim, J. A., & Jones, T. A. (2008). Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. J Speech Lang Hear Res, 51(1), S225-239. doi: 10.1044/1092-4388(2008/018)

Korpershoek, C., van der Bijl, J., & Hafsteinsdottir, T. B. (2011). Self-efficacy and its influence on recovery of patients with stroke: a systematic review. Journal of Advanced Nursing, 67(9), 1876-1894. doi: 10.1111/j.1365-

Kwakkel, G. (2006). Impact of intensity of practice after stroke: Issues for consideration. Disability and Rehabilitation, 28(13-14), 823-830.

Schmidt, R. A., & Lee, T. D. (2014). Introduction to Motor Learning: Concepts and Methods in Research and Application Motor Learning and Performance (5th ed., pp. 175-196). Champaign, Illinois: Human Kinetics.

Activity List:
This list is meant to be a guide to the possible activities that can be negotiated i.e. it should not be considered exhaustive and you are encouraged be creative in both identifying and making activities more challenging! As more data are received in the study, we will be adding to this list and distributing. All activities should be practiced in sitting to avoid the potential for a fall (unless it is evident that the participant is safe to perform the activity in standing). Consider fatigue – the shoulder and elbow may fatigue but hand activities should still be encouraged.

Activity	To work on	Equipment need
Dressing		
Putting on shirt/coat	Shoulder movement ++ Elbow movement + Wrist movement+	Shirt or coat
Buttoning shirt	Elbow movement++ Wrist movement++ Pinch, grasp++	Shirt with buttons
Putting Items on a Shelf	Shoulder movement+++ Elbow movement + Wrist movement +	Start with light items (towel or clothing) move to heaving items
Pouring Water		
Glass to Glass	Shoulder movement+++ Elbow movement+++ Wrist movement++ Grasp+++	Two glasses, water Towel (just in case)
Jug to Glass	Shoulder movement+++ Elbow movement+++ Wrist movement++ Grasp+++	Jug, glass, water Towel (just in case)
Bottle to Glass	Shoulder movement +++ Elbow movement+++ Wrist movement+++ Grasp+++	Bottle, glass, water Towel (just in case)
Towel		
Wiping table top	Shoulder movement++ Elbow movement+ Wrist movement+	Towel (dry or wet; wet offering more resistance)
Wringing Out	Shoulder movement++	Towel (large or

Activity	To work on	Equipment need
	Elbow movement+++ Wrist movement+++ Grasp+++	small) Bowel or something to wring water in
Drying self after shower (including the back)	Shoulder movement+++ Elbow movement++ Wrist movement++ Grasp++	Towel – the participant does not necessarily need to shower
Opening Jar	Shoulder movement + Elbow movement++ Wrist movement +++	Jar with lids (jar and lid size can vary)
Drinking from a Cup	Shoulder movement+++ Elbow movement++ Wrist movement++ Grasp++	Cup, water
Cutting Food	Shoulder movement++ Elbow movement+++ Wrist movement+++ Grasp+++	Knife, fork, plate Food or plastercine (or something to cut)
Using a tooth brush	Shoulder movement++ Elbow movement+++ Wrist movement+++ Grasp+++	Toothbrush, toothpaste

+indicates the amount of the specified movement that the activity is likely to elicit. More +s means more movement

Appendix D: UPPER WORKSHEET

Participant ID ☐ ☐ ☐ ☐ ☐ ☐ ☐ Date:

1. What activity do you want to perform, but can't, because of how the stroke affected your arm? Please describe the activity and what you can't do.

2. Is it important to you that you are able to use arm to perform this activity?

   No ☐ Yes ☐

It is important that when you practice these activities your remember the following:

Use both hands to complete to do the activity and try to use your hand the same way you would have before the stroke. If you normally pick things up with your right hand, and your right hand has been affected by the stroke, try to pick things up with your right hand and use your left hand to help when needed.

Try to follow the practice schedule - this is really key!! Use your activity log to record how well you do!

If you start to feel any pain or swelling during practice please stop and contact your study coordinator as soon as possible

Here are the activities you should do on a daily basis, and when you should practice:

Activity	When	Hints/Tips
Date:	☐ morning _____ min ☐ afternoon	

Activity	When	Hints/Tips
	_____ min ☐ evening _____ min	
Date:	☐ morning _____ min ☐ afternoon _____ min ☐ evening _____ min	

Participant Weekly Activity Log: Pt ID ☐☐☐☐☐☐☐

Please record the number of minutes you spent each day performing each activity. If you experience any pain, write a P beside the time.

Activity		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	Morn							
	Aft							
	Even							
	Morn							
	Aft							
	Even							

Appendix E: Draft Case Report Forms

PROOF

Post-Stroke Recovery of Optimal Function (PROOF)

Study Case Report Forms

PROOF Instructions for Screening Log Page 1

A screening log should be completed for every patient admitted.

Participants are **eligible** if they:

- Have had a recent stroke (4-10 days)
- Can actively shrug their shoulders
- Have active finger extension (at least one)

Participants are **ineligible** if they have:

- A comorbid medical musculoskeletal or neurological condition that may preclude or make difficult their participation in a walking program (e.g. severe congestive heart failure, severe osteoarthritis of knees)

- Cognitive or communication deficits, that in the opinion of the attending therapist, would prevent the participant from understanding or implementing the intervention

PROOF Screening Log Page 1

PROOF Screening Log #001 Screening Visit #001

Participant ID# ☐ ☐☐☐ (Center # / Participant #) Initials ☐☐☐ (F/M/L)

Screening Date: 20☐☐ ☐☐ ☐☐ (year / month / day)

1. Eligibility

a) Confirmed Stroke: ☐ Yes ☐ No ⟶ **Exclude Participant**

b) Date of stroke: 20☐☐ ☐☐ ☐☐ (year / month / day)

Stroke location: ☐ Right Hemisphere ☐ Left Hemisphere ☐ Brain-stem

Hand Dominance: ☐ Right ☐ Left

	No	*Yes*
c) Actively shrug shoulders	☐	☐
d) Active finger extension (at least one)	☐	☐

☐ **Participant included if Yes to criteria b), c) and d)**

☐ **Participant excluded** *(check reasons for exclusion):*

☐ Cognitive & communication deficits ☐ Comorbid muscoskeletal, medical, or neurological condition

☐ Unwilling to sign consent ☐ Other:_____

Time taken to assess eligibility: ☐☐☐ minutes

Person completing report: _____ _____ 20☐☐ ☐☐ ☐☐
Last Name *(print)* First Initial *(year / month / day)*

Date: Please record the date that the consent form is signed. This is the date the study starts for that participant.

2. c) Ethnicity Codes: This question refers to ethnic origin (country of ancestral origin), and should not be confused with nationality or race. Ask the participant how she/he perceives her/his own ethnicity.

01 - Canadian of European Descent
02 - European/Caucasian (If Spanish descent, but living in another country, please check this category)
03 - South Asian (India, Sri Lanka, Pakistan, Nepal, Bangladesh)
04 - Chinese (China, Hong Kong, Taiwan or Chinese living in other countries)
05 - Japanese
06 - Malays
07 - Other Asian (Korea, Malaysia, Papua New Guinea,
Thailand, Philippines, Indonesia, Vietnam, Cambodia, Laos
Myanmar/Burma, Bhutan, Singapore)
08 - Persian
09 - Arab
10 - Black African
11 - Sub-Saharan African
12 - Native Latin (Brazil, Argentina, Mexico, Colombia)
13 - Native North American
14 - Australian Aboriginal
15 - Other (any other ethno-racial group not listed above.

PROOF Baseline #002 Baseline Visit #002

Participant ID# ☐ ☐☐☐ (*Center #* *Participant #*) Initials ☐☐☐ (*F/M/L*) Date: 20☐☐ (*year*) ☐☐ (*month*) ☐☐ (*day*)

1. **Consent** Did the participant sign the consent form? *No* ☐ ⟶ **Exclude Participant** *Yes* ☐

2. **Participant Information**

a) Date of Birth: ☐☐☐☐ (*year*) ☐☐ (*month*) ☐☐ (*day*) b) Gender: ☐ *M* ☐ *F* c) Ethnicity: ☐☐ *see instruction page for codes

b) Level of formal education completed *(check highest level only)*:

☐ None ☐ 1-8 ☐ 9-12 ☐ Trade School ☐ College/University

c) Marital Status *(select one only)*:

☐ Never Married ☐ Currently Married ☐ Common Law/Living Partner ☐ Widowed

☐ Separated ☐ Divorced

e) Occupation *(select one only)*:

☐ Professional ☐ Skilled Labor ☐ General Labor ☐ Housewife ☐ Farmer

☐ Police/Military ☐ Business ☐ Clerical ☐ Self-employed

☐ Retired ☐ On Disability Insurance ☐ Other *(specify)*_____

☐ Unemployed

3. **Social Support**

a) Does the participant live in a:

☐ House/Apartment ☐ Retirement Residence ☐ Long-Term Care Facility

b) Who does the participant live with:

☐ Spouse/Partner ☐ Other Family Members ☐ Another Person (not family) ☐ Alone

c) How often do family members/friends come to visit the participant on the unit:

☐ Daily ☐ 2x/week ☐ 3x/week ☐ 4x/week ☐ 5x/week ☐ 6x/week

d) Is there someone who can help the participant practice regularly? *No* ☐ *Yes* ☐

5. c) Stroke Type
If the primary diagnosis of stroke is Ischemic, please complete i) and ii)

i) OCSP: Select the most appropriate stroke subtype according to the Oxfordshire Community Stroke Project.
Check one box only:
- TACI: Total Anterior Circulation Infarct
- PACI: Partial Anterior Circulation Infarct
- POCI: Posterior Circulation Infarct
- LACI: Lacunar Infarct
- Other: If the stroke subtype data does not fall under any of the above categories, mark this box

ii) TOAST: Select the most appropriate stroke subtype according to the Trial Org 10172 in Acute Stroke Treatment.
Check all boxes that apply.
- Other: Select the most appropriate "Other" stroke subtype.
- CVST refers to Cerebral Venous Sinus Thrombosis

If the primary diagnosis of stroke is **ICH** (intracerebral hemorrhage): **Check all types that apply.**

If the primary diagnosis of stroke is **Subarachnoid hemorrhage, check this box.**

6. Medication at Baseline: Refer to this list for generic names of common medication categories.

ACE-I	ARB	CCB	Diuretics	B-Blockers	Statin	A-Diabetic	A-depress	NSAID
Benazepril	Cadesartan	Amlodipine	Amiloride	Acebutolol	Atorvastatin	Buformin	Citalopram	Aspirin
Captopril	Eprosartan	Diltiazem	Bumetanide	Atenolol	Cerivastatin	Glyburide	Duloxetine	Celecoxib
Enalapril	Irbesartan	Felodipine	Chlorothalidone	Betaxolol	Fluvastatin	Metformin	Lubazodone	Diclofenac
Fosinopril	Losartan	Isradipine	Furosemide	Bisoprolol	Lovastatin	Repaglinide	Reboxetine	Ibuprofen
Lisinopril	Olmesartan	Nicardipine	Hydrochlorothiazide	Carvedilol	Pitavastatin	Rosiglitazone	Trimipramine	Naproxen
Perindopril	Telmisartan	Nifedipine	Metolazone	Metoprolol	Pravastatin			Sulindac
Quinapril	Valsartan	Nisoldipine	Torsemide	Nadolol	Simvastatin			
Ramipril		Verapamil	Triamterene	Penbutolol				

6. h) Refer to this list for codes to the specific type of anti-coagulant or anti-platelet medication prescribed:

01	Acenocoumarol	06	Dipyridamole
02	Apixaban	07	Prasugrel
03	Aspirin	08	Ticlopidine
04	Clopidogrel	09	Rivaroxaban
05	Cilostazol	10	Warfarin

PROOF Baseline #003 Baseline Visit #002

Participant ID# ☐ ☐☐☐ (*Center # Participant #*) Initials ☐☐☐ (*F/M/L*) Date: 20☐☐ ☐☐ ☐☐ (*year month day*)

4. **Physical Activity**

a) What was the participant's activity level before the stroke?

At work: ☐ Mainly sedentary

☐ Mainly walking, including climbing stairs, or walking uphill

☐ Heavy physical labor e.g. lifting heavy objects

☐ Predominately walking on one level

☐ Did not work

During leisure time:

☐ Mainly Sedentary (reading, watching TV) ☐ Mild Exercise (gardening)

☐ Moderate Exercise (4 hours of activity/wk) ☐ Strenuous Exercise (sports)

5. **Stroke Information**

a) Hospital Admission Date: 20☐☐ ☐☐ ☐☐ (*year month day*) b) Rehab Admission Date: 20☐☐ ☐☐ ☐☐ (*year month day*)

c) Stroke Type *(see instructions page)*:

☐ **Ischemic**: i) **OCSP**: ☐ TACI ☐ PACI ☐ POCI ☐ LACI ☐ Other

ii) → **TOAST**: ☐ Cardioembolic ☐ Large Vessel ☐ Small Vessel ☐ Undetermined

→ **Other**: ☐ Dissection ☐ Vasculitis ☐ CVST ☐ Other_____

☐ **ICH**: ☐ Amyloid Angiopathy ☐ Trauma ☐ AVM ☐ Other_____

☐ **Subarachnoid hemorrhage**

6. **Medication at Baseline**

Is the participant currently taking or prescribed any of the following non-study medications?

	No	*Yes*		*No*	*Yes*	
a) ACE-I	☐	☐	f) Statin	☐	☐	
b) ARB	☐	☐	g) Anti-diabetic (A-diabetic)	☐	☐	Code
c) Calcium Channel Blockers (CCB)	☐	☐	h) Anti-coagulant/platelet (A-C/P)	☐	☐	→ ☐☐
d) Diuretics	☐	☐	j) Antidepressant (A-depress)	☐	☐	
e) Beta-Blockers (B-blocker)	☐	☐	k) NSAID	☐	☐	

For questions that don't specify the age or year of diagnosis, assume that there is no specific time frame required.

7. p) Arthritis: This question refers to the type and location of the participant's arthritis. Check the appropriate box for the type of arthritis (osteoarthritis, rheumatoid or other) and then use the codes below to specify the location.

01 - Neck
02 - Back
03 - Hip
04 - Knee(s)
06 - Hands
07 - Shoulder(s)
08 - Hands, Shoulders, Neck and Back (Upper Body)
09 - Knee(s) and Hip (Lower Body)
10 - All

PROOF Baseline #004 Baseline Visit #002

Participant ID# ☐ ☐☐☐ Initials ☐☐☐ Date: 20☐☐☐☐☐☐

Center # Participant # *F/M/L* *year month day*

7. **Medical History** *(taken from chart)*:

	No	*Yes*	
a) Previous Stroke	☐	☐ →	☐☐☐☐ *year*
b) TIA	☐	☐	
c) Carotid Endarterectomy/Stenting	☐	☐	
d) Myocardial Infarction	☐	☐	
e) Angina → *Stable*	☐	☐	
→ *Unstable*	☐	☐	
f) Heart Failure	☐	☐ →	☐ Class I ☐ Class II ☐ Class III ☐ Class IV
g) CABG Surgery	☐	☐	
h) Atrial Fibrillation	☐	☐ *Year Dx* →	☐☐☐☐ *year*
i) Coronary PTCA/PCI	☐	☐	
j) Aortic Aneurysm Repair	☐	☐	
k) Peripheral Artery Surgery	☐	☐	
l) Diabetes	☐	☐ *Age at Dx* →	☐☐ yrs old
m) Limb or Foot Amputation	☐	☐	
n) Fracture	☐	☐ →	☐ Upper Extremity ☐ Lower Extremity ☐ Other *specify:*_____
o) Joint Replacement	☐	☐ →	☐ Upper Extremity ☐ Lower Extremity ☐ Other *specify:*_____
p) Arthritis	☐	☐ →	☐ Osteoarthritis (*see facing page for codes*): ☐☐
			☐ Rheumatoid (*see facing page for codes*): ☐☐
q) Cancer	☐	☐ *Check all that apply* →	☐ Lung ☐ Breast ☐ Prostate ☐ Skin ☐ Colon ☐ Other *specify:*_____
r) Urinary Incontinence	☐	☐	

PROOF Baseline #005 Baseline Visit #002

Participant ID# ☐ ☐☐☐ (*Center #* *Participant #*) Initials ☐☐☐ (*F/M/L*) Date: 20☐☐☐☐☐☐ (*year* *month* *day*)

8. Will the participant receive rehabilitation services? *No* ☐ *Yes* ☐ → Inpatient *No* ☐ *Yes* ☐

9. What services will the participant receive:

	No	*Yes*		*No*	*Yes*		*No*	*Yes*
a) Physiotherapy	☐	☐	b) Occupational Therapy	☐	☐	c) PTA	☐	☐
d) OTA	☐	☐	e) SLP/CDA	☐	☐	f) Other	☐	☐

specify:_____

10. Blood Pressure Reading:

20☐☐☐☐☐☐ (*year* *month* *day*) ☐☐☐ (*systolic*) ☐☐☐ (*diastolic*) mm Hg

11. Current rating of pain: ☐☐

0 1 2 3 4 5 6 7 8 9 10

12. Modified Rankin Scale (mRS)

Date completed: 20☐☐☐☐☐☐ (*year* *month* *day*) Score: ☐☐

13. Functional Independence Measure (FIM) ☐ not available

Date completed: 20☐☐☐☐☐☐ (*year* *month* *day*) FIM Total: ☐☐☐

14. Action Research Arm Test

Date completed: 20☐☐☐☐☐☐ Score: ☐☐

15. Mini Mental States Exam Score

Date completed: 20☐☐☐☐☐☐ Score: ☐☐

Person completing report: _____ (Last Name *(print)*) _____ (First Initial) 20☐☐☐☐☐☐ (*year* *month* *day*)

PROOF Weekly Forms (to be completed at the end of each week)

PROOF Participant Activity Log #008 ☐ Week 1 ☐ Week 2 ☐ Week 3 ☐ Week 4

Participant ID# ☐ ☐☐☐ Initials ☐☐☐
Center # Participant # F/M/L

1. Was the participant seen for both study visits?
   - ☐ Yes → go to question 2
   - ☐ No → Did they miss: ☐ 1 visit ☐ 2 visits
     Reason: ☐ ill ☐ forgot ☐ couldn't get to visit ☐ other *(specify)*:_____

2. Did the participant take all of their study dopamine for the week?
   - ☐ Yes → go to question 3
   - ☐ No → Reason: ☐ too ill ☐ forgot ☐ side effect *(specify)*:_____ ☐ other *(specify)*:_____

3. Has the participant stopped the study drug permanently? Yes ☐ No ☐

4. Did the participant complete all activities as prescribed?
   - ☐ Yes → go to question 4
   - ☐ No → Reason: ☐ too ill ☐ forgot ☐ other *(specify)*:_____

5. Will the participant's activity list be revised?
   - ☐ No
   - ☐ Yes → ☐ more time or activities ☐ less time or activities

6. Will the activity log be submitted? Yes ☐ No ☐ → Explain:_____

7. Has accelerometer data been uploaded? Yes ☐ No ☐ → Explain:_____

Person completing report: _____ _____ 20☐☐☐☐☐☐
Last Name *(print)* First Initial *year month day*

Appendix F: Scoring Sheet for Action Research Arm Test

(downloaded from http://www.strokecenter.org/wp-content/uploads/2011/08/action_research_arm_test.pdf)

ACTION RESEARCH ARM TEST

Patient Name: _____
Rater Name: _____
Date: _____

Instructions

There are four subtests: Grasp, Grip, Pinch, Gross Movement. Items in each are ordered so that:

- if the subject passes the first, no more need to be administered and he scores top marks for that subtest;
- if the subject fails the first *and* fails the second, he scores zero, and again no more tests need to be performed in that subtest;
- otherwise he needs to complete all tasks within the subtest

Activity	Score
Grasp	
1. Block, wood, 10 cm cube (If score = 3, total = 18 and to Grip) Pick up a 10 cm block	_____
2. Block, wood, 2.5 cm cube (If score = 0, total = 0 and go to Grip) Pick up 2.5 cm block	_____
3. Block, wood, 5 cm cube	_____
4. Block, wood, 7.5 cm cube	_____
5. Ball (Cricket), 7.5 cm diameter	_____
6. Stone 10 x 2.5 x 1 cm	_____
Coefficient of reproducibility = 0.98	
Coefficient of scalability = 0.94	
Grip	
1. Pour water from glass to glass (If score = 3, total = 12, and go to Pinch)	_____
2. Tube 2.25 cm (If score = 0, total = 0 and go to Pinch)	_____
3. Tube 1 x 16 cm	_____
4. Washer (3.5 cm diameter) over bolt	_____
Coefficient of reproducibility = 0.99	
Coefficient of scalability = 0.98	
Pinch	
1. Ball bearing, 6 mm, 3rd finger and thumb (If score = 3, total = 18 and go to Grossmt)	_____
2. Marble, 1.5 cm, index finger and thumb (If score = 0, total = 0 and go to Grossmt)	_____
3. Ball bearing 2nd finger and thumb	_____
4. Ball bearing 1st finger and thumb	_____
5. Marble 3rd finger and thumb	_____
6. Marble 2nd finger and thumb	_____
Coefficient of reproducibility = 0.99	
Coefficient of scalability = 0.98	

Provided by the Internet Stroke Center — www.strokecenter.org

Appendix F (con't): Scoring Sheet for Action Research Arm Test

Grossmt (Gross Movement)

1. Place hand behind head (If score = 3, total = 9 and finish) _____
2. (If score = 0, total = 0 and finish _____
3. Place hand on top of head _____
4. Hand to mouth _____

Coefficient of reproducibility = 0.98

Coefficient of scalability = 0.97

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CHAPTER 5: CONCLUSION

Throughout the papers that comprise this dissertation, there is a clear and consistent message - disability after stroke is common and affects functional ability. While still a problem in high-income countries, post-stroke disability is now occurring more frequently in low and middle-income countries (Feigin et al., 2014), probably because more people are living after stroke. This makes post-stroke disability a global problem. A key contributor to post-stroke disability is motor impairment, and in particular upper extremity motor impairment (defined as a problem of body function or structure (World Health Organization, 2002)). Although common after stroke, we do not yet have simple, clearly effective interventions to improve post-stroke disability.

Working as a clinician in inpatient and outpatient neurological services, it became evident that patients' post-stroke needed interventions that they can start early, and do not require sustained, direct involvement of trained health care professionals (as patients spend very little time with therapists, even in resource rich countries). As a researcher, it became apparent that with the increase in post-stroke disability in low and middle-income countries, where structured post-stroke rehabilitation is limited, there is a further need for interventions that are simple to implement and sustain. Disability secondary to motor impairment can result because of impairment of the upper, lower or both extremities. Simple interventions

focussed on increasing the amount of walking practice have shown benefit (French et al., 2010; Veerbeek et al., 2014) however similar interventions to improve upper extremity motor impairment do not exist, even though upper extremity motor impairment has an equally devastating effect on functional ability. Based on this need, I embarked on a program of research to identify and test potentially effective, globally applicable, interventions to improve post-stroke activity limitation secondary to upper extremity motor impairment.

The need for globally applicable interventions was the starting point for my program of enquiry, and quickly two fundamental questions became evident. The first was whether upper extremity motor impairment post-stroke was truly a global problem, as the existence of post-stroke disability in all parts of the world is evident, but the extent has never been clearly described nor understood. The second was whether task-based practice, an intervention that could be initiated by health-care workers but then continued by the patients themselves, would be an effective intervention to include in a globally applicable upper extremity motor impairment intervention. Canadian guidelines indicate that there is good evidence for the effectiveness of task-based practice on motor impairment; there is weaker evidence in support of the actual amount of practice required (Dawson et al., 2013). Interventions that do exist to address activity limitation secondary to post-stroke upper extremity motor weakness are

not necessarily task-based, almost all lack evidence on effect (Foley, Mehta, Jutai, Staines, & Teasell, 2013) and all require rehabilitation professionals to develop, implement and carefully monitor patients' progress. For example Neurodevelopmental Therapy, Motor Relearning Program, virtual reality, Functional Electrical Stimulation and Constraint Induced Movement Therapy (CIMT) all require rehabilitation specialists to provide and in some cases require additional equipment. Thus the need for alternative, simple interventions is clear (Amosun, Nyante, & Wiredu, 2013; Lemogoum, Degaute, & Bovet, 2005).

To develop such interventions required an understanding of the global picture of post-stroke disability secondary to upper extremity motor impairment, and an understanding of the most appropriate "active ingredients" that could be used in simple, internationally applicable interventions. This was the purpose of my program of study, and resulted in the work contained in the previous chapters. In this final chapter, I will summarize the key results from each of the research activities and highlight some of the unique challenges discovered in the course of developing each of these sections. Finally, I will discuss this work in the context of my larger program of research.

Understanding the Global Profile of Post-Stroke Upper Extremity Weakness (Chapter 2)

Importance of Results

The purpose of these analyses was to determine the global profile of post-stroke upper extremity weakness and the related activity limitation. The data confirm that post-stroke upper extremity weakness and activity limitation is common throughout the world, persists at one month, and there is little if any formal rehabilitation available.

The INTERSTROKE Study, a large, international case-control study, provided a unique opportunity to study post-stroke activity limitation and upper extremity weakness across many countries. Ideally, to accurately understand the global profile of any condition, a consistent protocol is implemented in every country (e.g. ask the same questions, use the same procedures). INTERSTROKE used a consistent data collection protocol in 32 countries. While the majority of the information that was collected focussed on risk factors for stroke (the primary objective of the study), for each of the cases, data were collected on post-stroke sequela, as well as a measure of functional ability. These data provided the opportunity to consistently quantify the prevalence of arm weakness and functional ability in those with arm weakness, across 32 countries. These analyses demonstrated that post-stroke arm weakness is common in all parts of the world, with 77.9% of all patients reporting weakness, and is more common in middle and low-income countries. Post-stroke functional deficits are also very common in those with upper extremity weakness, ranging from about 25%-55% in the INTERSTROKE countries, indicating that those with

upper extremity weakness also have moderate to severe activity limitation, which persists at one month. These data demonstrate that although there are motor impairments and activity limitations, stroke patients are most often at home and experiencing some disability at one month post-stroke, especially in low and middle-income countries.

Unique Challenges Experienced when Analysing the Data

While these data are extremely helpful in understanding the scope of the problem, there are important considerations when interpreting the information, and many of these were raised in the discussion section of the paper. These include the potential for measurement error, as both the assessment of sequela and post-stroke activity limitation were obtained through patient report, and biases inherent in case control designs. The data were interpreted conservatively in light of these limitations, and efforts at over-interpretation, such as my original attempts at modeling change in activity limitation by region, were abandoned on the advice of my committee.

One area that deserves additional consideration that was not discussed in the paper is the quantification of rehabilitation service provision one month post-stroke. The specific question on the study case report form asks about discharge location from the initial hospitalization, and if not discharged, whether the patient remains on acute care, rehabilitation or long term-care or had died. The question actually focuses more on the

patients' discharge location, rather than the rehabilitation services that the patient is receiving, although the assumption is that those who are on an inpatient rehabilitation service are receiving rehabilitation. In hospitals were there is no organized rehabilitation care, patients may remain on an acute service or be admitted to a longer-term care facility for a chance to relearn certain skills before returning home; i.e. they receive rehabilitation, but not on a rehabilitation service. Those who return home could also receive homecare rehabilitation services. This could account for an under-representation of the amount of rehabilitation services provided at one month.

However although possible, under-representation is not likely to be large since very few patients remain in hospital at one month ((4.4%) or discharged to institutional care (1.0%)) and it is unlikely that all these patients would receive rehabilitation. In terms of those receiving rehabilitation in the home, based on data from 2012, 20% of patients received in home physiotherapy and 36% received occupational therapy (Hall et al., 2013). These data are from the Ontario system, that is well organized and fairly well funded (Black, Lewis, Monaghan, & Trypuc, 2003), and likely to provide more home rehabilitation than most places in the world. Even given this level of organization and funding, on average stroke patients in Ontario receive less than 4 visits in total (Hall et al., 2013). Therefore it is unlikely that home-based rehabilitation accounts for

a large amount of task-based practice opportunity, even if it is occurring. Based on these data, we can very conservatively estimate that at most, 10-15% of patients after stroke receive any amount of rehabilitation, still leaving a large percentage without any structured rehabilitation.

The INTERSTROKE investigators recognized the lack of specific information on the provision of post-stroke rehabilitation services and have collected additional data on the last 5,000 cases recruited. These data will be presented along with the main study results later this year, and will provide additional information to help understand the global profile of post-stroke rehabilitation throughout the world.

Summary

This manuscript provides evidence that upper extremity impairment is common worldwide after stroke, those with upper extremity impairment experience activity limitation and at one month, most patients are at home and unlikely to be receiving any rehabilitation therapy. Never before has there been data that provided a global profile of the burden of post-stroke upper extremity motor impairment and activity limitation. These data can be used to inform research that spans UMIC, LMIC and LIC, where post-stroke rehabilitation research has been scarce, as well as HIC.

Does Task-Based Practice Improve Activity Limitation Secondary to Upper Extremity Motor Impairment? (Chapter 3)

Importance of Results

The purpose of this systematic review was to determine the evidence for simple, task-based practice in improving upper extremity motor impairment and activity limitation. Due to the lack of evidence, the conclusions were that simple, task-based practice is promising, but further studies are warranted. This is the first review to attempt to quantify the effect of simple task-based practice and while not conclusive, these data do support the potential for effect.

Unique Challenges Experienced when Performing the Systematic Review

The key criterion for this review is the definition of simple as “not related to any specific approach or philosophical belief”. Instead the focus was on task-based practice that was built on the theoretical concepts of motor learning, using abundant and challenging practice. The move from “approaches” to theoretically based (and ideally evidence based) practices is supported by Pollock et al. (2014) in a recent systematic review of physical rehabilitation post-stroke. For our review, the “simple” criterion resulted in very few eligible studies and illustrated a key problem with many studies in stroke rehabilitation.

The paucity of articles that met the review criteria speaks to the key finding from this systematic review; unless there is a detailed explanation and quantification of the active ingredient of an intervention, in enough detail to allows others to replicate the intervention and obtain similar results, it is difficult to compare studies and impossible to implement the intervention,

even if the results are positive. Trying to determine the “active ingredient” in post-stroke motor impairment interventions is difficult because descriptions of the intervention are not readily available, and if used in a study, published results often lack the specific rationale and rarely provide the detail of the intervention, or how the maximal dose was achieved. Consideration was given to contacting authors for more detail about each intervention, but without the ability to quantify whether the described components of the intervention actually occurred as intended, it is difficult to know if the right dose of the active ingredient was provided, and therefore difficult to interpret the results. In future, studies in post-stroke rehabilitation research must not only identify the active ingredient, but also the methods for monitoring compliance to the components, so that an accurate estimate of dose (and subsequently effect) can be made.

There is a growing effort from stroke rehabilitation researchers to clearly define and publish intervention protocols. This began with the efforts of the first researchers who studied motor learning interventions and constraint induced movement therapy (Morris, Taub, & Mark, 2006; Winstein et al., 2004). Since then, researchers are publishing more details on interventions, recognizing that an open exchange of information is a fundamental requirement to move the field forward (Arya et al., 2012; Nijland et al., 2013; Winstein et al., 2013). Concurrently, information on critical steps in developing complex interventions was published by the

Medical Research Council in the UK (Craig et al., 2008), providing a structure for development, testing and implementation of interventions. The recently published TIDieR checklist and guide from the CONSORT group (Hoffmann et al., 2014) goes one step further in describing 12 explicit components of an intervention that should be reported when publishing on an intervention study, but really should be considered during the development of the intervention. If, similar to the CONSORT flow diagram, journals make the TIDieR reporting elements a requirement for publication, it will greatly facilitate the understanding of individual study results (as we will be able to quantify "dose") and the ability to determine which studies are appropriate to consider together in a systematic review. In turn this will enhance the ability to perform robust meta-analyses.

Summary

The systematic review on practice found some evidence to support the effect of simple, task-based practice but there were too few studies that met the inclusion criteria to be able to make any definitive conclusions. This review has highlighted the need for post-stroke rehabilitation studies to clearly describe the interventions used and quantify and maximize the "dose" of active ingredient that is being given, key considerations incorporated into the development of the UPPER intervention and the PROOF study.

Developing and Testing Globally Applicable Post-Stroke Motor Impairment Interventions (Chapter 4)

Importance of the Work

The Post-Stroke Recovery of Optimal Function (PROOF) protocol was developed to test whether a simple, task-based intervention or a safe, inexpensive pharmacological intervention could improve activity limitation secondary to post-stroke upper extremity motor impairment. In designing the PROOF protocol, careful consideration was given to every aspect of study design, combining novel methodology with my experience designing and running large, international, factorial design studies.

PROOF is the first of it's kind in many ways; i) The UPPER (Upper-extremity Practice Post-stroke in Early Recovery) intervention is designed to be globally applicable. Minimal health care provider training is required, which means implementation is possible even when there are limited stroke rehabilitation resources. Instructions for the task-based practice are simple, to reflect international variation in educational levels of stroke patients (Bosch et al., 2014) and experience of the healthcare professionals who will implement the intervention. Where therapy is available, UPPER can be used as an adjunct. ii) Intervention development follows the suggested plan described in the MRC and TIDieR guidelines (Craig et al., 2008; Hoffmann et al., 2014), namely careful consideration of the rationale, detailed information on how to implement, and feasibility and

pilot testing followed by formal evaluation of the intervention, iii) The combination of behavioural and pharmacological interventions in a factorial design that will provide an accurate estimate of the effect of each, as well as an exploratory analysis on the effectiveness of the combination, iv) The study methodology is unique as there are few clinical trials that use a factorial design, with both cluster and individual patient level randomization (the pros and cons of each have been discussed in the Chapter 4), and v) The vast majority of stroke rehabilitation trials are conducted in high income countries, therefore performing the study in high, upper middle, lower middle and low-income countries will be the first of it's kind. PROOF will provide clear answers that will be applicable throughout the world.

Creating the PROOF study required a considerable amount of thought on specific issues that is in not reflected in the protocol itself. These considerations are presented below.

Unique Considerations for the PROOF Study

A fundamental consideration that has resonated throughout this dissertation is how to ensure the intervention delivers a maximal "dose" of task-based practice to stimulate neuroplasticity. Several steps have been taken to increase the likelihood that a maximal dose will be achieved. First, one of the most important inclusion criteria for this study is the ability of the study participant to identify one activity goal that relates to improving

upper extremity motor impairment. This is a key step in ensuring the participant is engaged in the task-based practice process. Ideally, the participant will also be able to identify the activities that he or she would like to practice, further enhancing their motivation.

Although motivated, there may be other reasons why the patient is not able to practice and the pilot study will help to identify these issues. I am currently leading a similar development process for an intervention designed to increase the amount of walking related practice post-stroke (http://www.hhsresearchadmin.ca/wp-content/uploads/2013/09/2013-HPI-Award-Recipients.pdf). Based on experiences to date, early identification and negotiation of activities is key. By collecting participant activity logs each week, we will monitor the type and number of activities that are negotiated and completed. When needed, the study team will talk with the study staff at the site to discuss strategies for improving the amount of task-based practice. Additionally, as logs are received they will be scanned to identify new activities, which can constantly be added to a list of common activities, and provided to the UPPER healthcare workers through the PROOF website (this information would be restricted to UPPER sites only). Ensuring the maximal dose of task-based practice is provided will require a multi-faceted approach and constant review that will be implemented as soon as recruitment begins. Comparatively, compliance with the pharmacological intervention (carbidopa-levodopa)

will not be as difficult since it is easy take and well tolerated. However, adherence to this arm will also be carefully monitored from the start, and solutions to improve provided if issues arise.

Careful site selection will also be important, as site involvement will be an important determinant of study success. The use of both rehabilitation and pharmacological interventions means that the ideal study site will be co-led by a physician and rehabilitation specialist or health care worker. Site identification will occur through a variety of strategies including approaching INTERSTROKE sites, as well as using site data gathered in a recent global survey to identify sites for another post-stroke trial. Potential sites will be sent an invitation to determine initial interest, which will be followed by an extensive questionnaire to determine not only interest in the research question, but the plan to ensure adequate research infrastructure. Careful site selection will be useful not only for PROOF, but will hopefully be the start of an international network of sites for post-stroke rehabilitation studies. I have experience successfully using this model to create the network of sites that I work with on long-term primary and secondary cardiovascular disease preventions studies.

The next consideration in developing the protocol was the feasibility of obtaining funding for the study. Recognizing that it is unlikely that any one funding agency will provide all necessary funding, we will approach multiple funding bodies to obtain the overall amount required for the study.

I am familiar with this approach as I have been involved in similar strategies for many of the large clinical trials I have worked on (Bosch et al., 2006; Bosch et al., 2002; Mayosi et al., 2013), for which funding was obtained from a variety of sources. The structure of the PROOF study allows for investigators in each of the regions (high income, upper middle income, lower middle income and low income) to apply for local funding as a stand alone study, as the results have the potential to directly inform practice in their region, but will also benefit from being part of a larger program of research. Benefits include minimization of local costs as activities such as data management, study oversight (e.g. recruitment and adherence) and study materials will be provided centrally. Funding for central coordination will be sought from a variety of organizations including traditional governmental funding agencies, but also through existing clinical trial site networks. For example, Dr.'s Robert Hart and Mike Sharma, neurologists at the Population Health Research Institute, McMaster University, are in the process of establishing an international network of stroke centres, and we have been in discussion to determine whether PROOF could be one of the network projects, perhaps as a substudy to a pharmacological intervention trial.

Funding applications will be further supported by the related work currently underway on the Independent Mobility and Physical Activity Training (IMPACT) program. IMPACT relates to walking as PROOF relates to

upper extremity motor impairment and activity limitation, as the IMPACT intervention is designed to be globally applicable and improve patients' post-stroke walking ability (by addressing lower extremity motor impairment). The development study was completed last fall, and we have just started a pilot study to determine the dose of practice that can be achieved, as well as feasibility of recruitment. The study is being implemented by a multi-disciplinary team of experienced researchers that includes physiotherapists (Dr. Laurie Wishart, PhD Supervisor, Dr. Vince DePaul), doctors (Dr. Martin O'Donnell, committee member, Dr. Robert Hart, Dr. Wes Oczkowski), nurses (Harriett Draaistra) and occupational therapists (Michaela Ferguson and myself). I have taken a lead role in obtaining funding and implementing both studies. IMPACT has provided me first-hand experience with some of the unique difficulties implementing stroke rehabilitation trials, which were not present in other research programs that I have coordinated. These experiences will be used to improve activities in PROOF.

In addition, information gained from the results of currently ongoing studies with similar interventions will also be used to inform PROOF. The Interdisciplinary Comprehensive Arm Rehabilitation Evaluation (ICARE) Study is evaluating the effect of abundant task-based practice (the Accelerated Skill Acquisition Program (ASAP)) in those who had a stroke within the last 1 to 3 months, implemented over a 10 week period, with

therapy sessions scheduled 3 times a week (ICARE Study Team, 2014). ICARE study is recruiting 360 participants from 7 centres in the US (Winstein et al., 2013) and results should be available by the end of 2014. ICARE results will be important in terms of understanding the primary outcome, as well as providing valuable information on the implementation of the ASAP intervention.

The EXplaining PLastICITy after stroke (EXPLICIT) trial is also testing an intervention to improve post-stroke upper extremity motor impairment (Nijland et al., 2013), using modified constraint induced movement therapy implemented within two weeks of stroke. Participants receive one hour of direct training and are asked to wear the constraint on the affected extremity an additional three hours outside of therapy time; this intervention is provided for 15 days. 60 participants have been recruited from four centres in the Netherlands (Kwakkel et al., 2008), and published results of the study should be available shortly. Although the EXPLICIT results will not be directly applicable to PROOF, as they are using a constraint induced movement protocol,. EXPLICIT is one of the few studies to implement an upper extremity motor impairment intervention within the first two weeks of stroke, and will provide insights into issues of implementation in this early phase.

Finally, the ATTEND study (http://www.georgeinstitute.org/projects/family-led-rehabilitation-after-stroke-in-india-the-attend-trial) plans to recruit 1200

stroke patients from multiple sites in India to determine if family led care, compared to usual care, can improve functional outcomes for stroke patients who are discharged home. Results are not expected for many years, but the investigators will be contacted to determine if strategies for training family members and protocols can be shared.

There is also one ongoing study of dopamine in combination with occupational and physical therapy, however the primary outcome is walking related (Bhakta et al., 2010). This multi-centre trial recruited 572 participants and is now in follow-up, with results expected either late 2014 or early 2015. The primary outcome of this trial will be of interest, however not directly extrapolatable to the upper extremity. Tolerability, as well as adherence, will be key considerations that are directly related to the PROOF study.

The amount of ongoing research demonstrates the interest in the area, and the focus on task-based practice further supports the choice to use task-based practice as the key active ingredient in UPPER. The use of self-efficacy strategies combined with careful oversight in terms of adherence and most importantly maximal dose, coupled with the lessons learned from other ongoing investigations will form the basis for the multi-strategy approach to maximizing dose throughout the study.

Summary

The PROOF study design is a novel study in the area of stroke rehabilitation interventions and will address two clinically important questions in an efficient design. My experience conducting large, multi-centre, multi-national trials in various parts of the world, provides me with a unique skill set in terms of trial conduct, that will help to ensure key study parameters are closely monitored and solutions implemented when needed. The issues of adherence to intervention, development of the network of sites as well as securing study funding are challenging but have been carefully considered, and viable solutions provided. Publication of the PROOF protocol will change the way in which post-stroke rehabilitation interventions and trials are designed.

Conclusion

These three bodies of work have addressed important questions in terms of post-stroke activity limitation secondary to upper extremity motor impairment. They have provided information and ideas that have never before been presented, and will hopefully change thinking in terms of post-stroke upper extremity rehabilitation. Using my unique skill set developed through 20 years of conducting large, simple clinical trials along with my clinical interest in stroke rehabilitation, I am excited about continuing to develop my program of research on effective, globally applicable, upper extremity motor impairment interventions.

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