THE USE OF ACTION OBSERVATION AND IMITATION IN THE TREATMENT OF UPPER LIMB PARESIS EARLY AFTER STROKE

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ABSTRACT

Background: Evidence suggests that repetitive functional training might improve upper limb (UL) recovery following a stroke however, individuals with more severe paresis often find participating in such training difficult. There is therefore a need for new therapies that can "prime" the central nervous system for movement before commencing repetitive training.

Primary Aim: To ascertain if a new therapy called "Observation with intent To Imitate" (OTI)+Motor Practice (MP) sufficiently enhanced UL recovery in individuals with moderate/severe paresis early after stroke to justify proceeding to subsequent dose finding (phase I) and efficacy (phase II) trials.

Methods: Seventeen individuals with moderate/severe UL limb paresis 3 to 31 days following ischaemic/haemorrhagic stroke were recruited. Those who were able to imitate an action were randomly assigned to receive either OTI+MP in addition to conventional physical therapy (CPT) or CPT alone. Those appointed to the OTI+MP group received up to an hour of OTI+MP once a day, for 15 consecutive working days. The outcome measures used were the Motricity Index (MI) to ascertain the ability to voluntarily contract paretic muscle (strength), the Action Research Arm Test (ARAT) to assess function and adverse event monitoring.

Results: Both groups significantly improved in UL strength and function but the addition of OTI+MP did not result in better outcomes than CPT alone ($P=0.425$, MI), ($P=0.520$, ARAT). No adverse events were recorded.

Conclusion: The addition of OTI+MP to CPT did not significantly improve UL strength and function compared to CPT alone. There were however, more clinically important changes with a general trend to greater improvement witnessed within the OTI+MP group, indicating that some individuals may have benefited from the additional therapy. More studies are required to establish which stroke survivors are most likely to benefit from OTI+MP early after stroke before progressing to dose finding and efficacy trials.

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OUTLINE STRUCTURE

Chapter One

This chapter provides the reader with background information on the impact of stroke at both an individual and societal level. Some of the latest theories regarding brain reorganisation and motor recovery following stroke and how these are set to change the face of traditional rehabilitation practice are also briefly discussed. A potential new therapy to assist individuals with more severe paresis, "Observation with intent To Imitate plus Motor Practice" (OTI+MP) is then introduced. The concepts on which this therapy is based, action observation and imitation are then discussed, specifically in relation to how they might provide this population of individuals with an alternative way of accessing the motor execution system in the absence of little or no voluntary movement which may assist in recovery. Finally the focus of the research project, primary aim, objectives and perceived value of this research project are presented.

Chapter Two

This chapter provides the reader with a critical review of previous research studies that have investigated the use of action observation and imitation as a rehabilitative therapy following stroke. Written in the style of a Cochrane Systematic review, it focuses on two areas: a) the use of action observation and imitation to enhance the recovery of the upper limb and b) the effects of action observation and imitation on neurological activity within the brain and/or associated tracts. The results retrieved are presented and discussed in relation to previous research and methodological quality. Gaps within current research are then identified with recommendations made for further research.

Chapter Three

This chapter presents the methods used to conduct an original piece of empirical research investigating OTI+MP as a rehabilitative therapy for the upper limb early after stroke. The aims of the study are presented followed by a description of the overall design along with justification for its use. Information regarding the procedures adopted in relation to the screening and recruitment of participants, the application of the intervention and the statistical model employed to analyse the data captured are then depicted.

OUTLINE STRUCTURE

Chapter Four

This chapter provides the reader with information following the analysis of the data collected from the empirical research study. Details are initially provided regarding the characteristics of the participants at the start of the study along with information pertaining to individuals who were unable to complete the intervention. The efficacy of the intervention is then discussed and comments are made in relation to the estimated sample size required for future studies, treatment dose/response, the amount and type of conventional physical therapy delivered and participant compliance with the intervention. Tables, figures and graphs are used to enhance the presentation of the analysis throughout this chapter.

Chapter Five

This chapter provides the reader with an interpretation of the results presented following the analysis of the data. It commences with a discussion around some of the reasons why the results obtained may have come to fruition, incorporating previous research on the same subject. Issues such as dosage, initial severity and neurophysiological parameters including lesion location and corticospinal tract integrity are discussed. The perceived strengths and weaknesses of the research design employed are then given.

Chapter Six

The final chapter within this research thesis commences with a brief reminder of the aims of the study and then provides a synopsis of why a new therapy such as OTI+MP is required within the field of stroke rehabilitation. It then goes on to conclude the findings made from the empirical research study before discussing potential future directions in which further research should consider proceeding. Finally an overall summary is presented.

References

Full details of the references used throughout this research thesis are depicted within this section.

Appendices

Fundamental documents pertaining to the empirical research study conducted as part of this project are presented within this section.

CHAPTER ONE – INTRODUCTION

1.1 BACKGROUND

1.1.1   Stroke

Stroke is the second leading cause of death in the world behind cancer, being responsible for approximately 5.7 million each year (Di Carlo, 2009). It is estimated that around 110,000 of these deaths occur within England (National Audit Office, 2005) and that stroke accounts for 1 in 18 deaths (5.6%) within the United States of America (Lloyd-Jones *et al*, 2010). As well as being a leading cause of death, it is also responsible for the largest single cause of residual disability with an annual economic cost to society of approximately £8.9 billion in the United Kingdom (5% of the total National Health Service cost) (Saka *et al* 2009) and $65.5 billion in the United States of America (Di Carlo, 2009). Various deficits can be experienced after a stroke within a number of neurological domains however, the most common arise within the motor system resulting in motor impairment (Rathore *et al*, 2002). It is estimated that around 80% of stroke survivors experience some form of motor impairment following their stroke (Langhorne *et al*, 2009) which can be described as a loss or limitation in function and/or mobility (Wade, 1992).

A form of motor impairment that is frequently experienced by stroke survivors is upper limb paresis (Department of Health, 2006). More than 80% of individuals have some form of upper limb deficit immediately following their stroke (Murphy *et al*, 2011) with an estimated 30-65% continuing to experience motor disabilities 12 months after the event (Kwakkel *et al*, 2003; Lloyd-Jones *et al*, 2010). These impairments can have a devastating effect on the lives of stroke survivors by preventing them from independently performing daily activities such as washing, dressing, feeding and other aspects of personal care which can subsequently lead to a reduction in social participation (Langhorne *et al*, 2009) and ultimately in quality of life (Hackett *et al*, 2005).

Conventional physical therapy (CPT) has been shown to assist stroke survivors in adapting to these residual impairments however, it is estimated that over 50% of individuals continue to experience a deficit (Calautti *et al*, 2003) even after completing standard therapy (Hendricks *et al*, 2002).   This indicates that there is a need for new therapies which are designed specifically to maximise upper limb

recovery. One area that may assist with this process is the increase in knowledge surrounding the neuroscience of brain reorganisation following a stroke. This subject has received increasing attention over the past decade with the introduction of sophisticated technology such as functional magnetic resonance imaging, transcranial magnetic stimulation, positron emission tomography and diffusion tensor imaging, enabling some of the mechanisms that occur to be analysed in greater detail. Although not yet clearly elucidated (Cramer & Riley, 2008), research into this area has provided a general insight into what happens within the brain immediately after a stroke and subsequently as recovery progresses and this will now be discussed briefly below.

1.1.2   Brain Reorganisation After Stroke

After a stroke a level of spontaneous repair occurs as the brain tries to recover from the insult (Cramer & Riley, 2008). This manifests as a number of biological changes including an increase in growth factors, inflammatory markers, sprouting from surviving neurons and synaptogenesis (Nudo, 2007; Mintzopoulos *et al*, 2009), leading to a general increase in brain activity across multiple spheres including the primary and associative motor areas (Buma *et al*, 2010). This can include raised activity levels within the contralesional hemisphere (Cramer *et al*, 1997; Tombari *et al*, 2004; Richards *et al*, 2008; Stoeckel & Binkofski, 2010) which is believed to occur as a result of decreased inter-hemispheric inhibition (Feydy *et al*, 2002; Shimizu *et al*, 2002; Murase *et al*, 2004; Butefisch *et al*, 2008). In the weeks to months following the event brain reorganisation continues, with in some cases the increased activity levels declining and returning to normal. In others however, the levels remain high particularly within the contralesional hemisphere even into the chronic phase of stroke (Richards *et al*, 2008a). The reasons for this continued high level of activation in some stroke survivors are not well understood, although it has been directly correlated with reduced upper limb recovery compared to those with near normal levels (Hendricks *et al*, 2002; Stinear, 2010), which has led some authors to purport it as being maladaptive (Ward *et al*, 2003; Cramer *et al*, 2006; Calautti *et al*, 2007).

As prolonged high levels of activation particularly within the contralesional hemisphere have been linked to poor recovery, it has been suggested that therapies encouraging the recruitment of neurons from within the lesioned hemisphere and/or that facilitate a general decrease in activation, may be beneficial in promoting more efficacious reorganisation within the brain and subsequent upper limb recovery

(Marshall *et al* 2000; Calautti *et al*, 2001; Jang, 2007). This theory has been supported by a number of studies that have demonstrated an increase in functional performance when such brain reorganization has occurred (Cramer *et al*, 2000; Kim *et al*, 2004; Jang *et al*, 2005) or when the intact motor cortex has been inhibited using such modalities as transcranial magnetic stimulation (Nowak *et al*, 2009). In studies of rats, this type of recruitment has also been associated with the largest level of growth-related molecular changes which may additionally contribute to a more successful recovery (Cramer, 2008).

In terms of upper limb therapy, direct and increased engagement of the lesioned hemisphere has been found to occur with activity-based upper limb interventions (Calutti *et al* 2001; Sharma *et al*, 2006), with an increase in brain reorganisation and recovery being demonstrated when it has been repetitive, intensive, challenging, highly motivating and functionally task orientated (Kwakkel *et al*, 1997; Feys *et al*, 1998; Cramer *et al*, 2002; Hallett *et al*, 2002; Barreca *et al*, 2003; Steultjens *et al*, 2003; Schaechter, 2004; Van Peppen *et al*, 2004; Pomeroy *et al*, 2005; Teasell *et al*, 2009). These findings suggest that the spontaneous brain reorganisation witnessed following a stroke could potentially be augmented by physical therapies based on these principles. In view of these findings, a number of new therapies that can be termed as "repetitive based interventions" such as constraint-induced movement therapy and robotics have been developed which have in general, demonstrated early efficacy in terms of promoting brain reorganisation (Liepert *et al*, 2000; Levy *et al*, 2001; Wittenberg *et al*, 2003; Liepert, 2006; Szaflarski *et al*, 2006; Sheng and Lin, 2009) and upper limb recovery in stroke survivors (Page *et al*, 2002; Page *et al*, 2004; Taub *et al*, 2006; Wolf *et al*, 2006; Kwakkel *et al*, 2008; Mehrholz *et al* 2009).

Although these therapies show promise in promoting recovery within the paretic upper limb after stroke, they do come with pre-requisites that render them inappropriate for approximately 25% of the stroke survivor population who experience more severe paresis (Blanton *et al*, 2008). For example, to participate in constraint-induced movement therapy individuals must be able to demonstrate some active voluntary movement such as 20 degrees of wrist extension, 10 degrees of thumb adduction/extension and 10 degrees of extension in two other additional digits (Winstein *et al*, 2003). Robotics may provide an attractive plausible alternative as it could be used by this population however, robots are expensive and space consuming and studies have found that the individual participating must be actively engaged in attempting to move their paretic upper limb to enhance recovery

(Krebs *et al*, 2009). There is therefore a need for further repetitive based interventions to be developed for this specific population of stroke survivors, who are commonly excluded from active rehabilitation (Hayward *et al*, 2010), to facilitate sufficient activation within their upper limb to enable them to progress to more repetitive, high-intensity therapies such as constraint-induced movement therapy. One such therapy that has been purported as possibly providing an answer is Observation with intent To Imitate (OTI) as suggested by Pomeroy *et al*, (2005), which is based on the concepts of action observation and imitation which will now be introduced below.

1.1.3 Action Observation and Imitation

Action observation and imitation can be defined as the observation of another's actions and the copying of body movements that are observed (Brass and Heyes, 2005). In 1992 whilst conducting an experiment of single-cell recordings within the Macaque monkey brain, di Pellergrino *et al* made an important discovery regarding their neurophysiological behaviour when observing another's actions. They found that certain individual neurons within the ventral premotor cortex (area F5) and the inferior parietal cortex were activated when the monkey not only performed a goal-directed movement (movement execution), but also when it observed the scientist performing the same action (action observation). Many other studies later corroborated these findings (Gallese *et al*, 1996; Rizzolatti *et al*, 1996; Rizzolatti and Craighero, 2004; Fogassi *et al*, 2005) leading to these neurons being termed "mirror neurons". Since this discovery, numerous neuroimaging and neurophysiological studies have been conducted to ascertain if there are similar neurons within the human brain that behave in the same manner.

The concept of mirror neurons residing within the human brain is still under debate as no direct evidence via single cell recordings has been completed (Turella *et al*, 2009) however, studies in healthy subjects have obtained indirect evidence for their existence during the observation (Grafton *et al*, 1996; Rizzolatti *et al*, 1996a; Decety *et al*, 1997; Buccino *et al*, 2001; Iacoboni 2005; Molnar-Szakacs *et al*, 2006; Filimon *et al*, 2007; Gazzola *et al*, 2007) and subsequent imitation (Buccino *et al*, 2004; Chaminade *et al*, 2005; Jackson *et al*, 2006; Jonas *et al*, 2007) of motor acts. Traditionally it has been purported that these mirror neurons reside within a parietalfrontal mirror neuron system that contains the ventral premotor cortex specifically areas BA44 and BA45 (Brocas area which is believed to be the equivalent of the Macaque brain area F5) (Pomeroy *et al* 2005; Baumgaertner *et al*.

2007; Molenbergs *et al*, 2009), plus the caudal part of the inferior frontal gyrus (Cattaneo and Rizzolatti, 2009). A recent systematic review of 159 functional magnetic resonance imaging and positron emission tomography studies in healthy humans by Caspers *et al* (2010), confirmed the existence of this parietalfrontal mirror neuron system although other areas of the brain were also found to contain mirror neurons including the dorsal pre-motor cortex (area BA6), the supplementary motor area (area BA6), the posterior middle temporal gyrus and the extrastriate visual area indicating that a much wider mirror neuron system possibly exists.

In terms of the purpose of the mirror neuron system, it has been suggested that it plays an important part in a number of human social interactions (Iacaboni, 2009) including: i) the understanding of actions and intentions of others (Nishitani *et al*, 2005; Rizzolatti 2005; Fabbro-Destro and Rizzolatti, 2008); ii) object recognition (Helbig *et al*, 2006; Helbig *et al*, 2010); iii) demonstrating empathy (Leslie *et al*, 2004; Yuan and Hoff, 2008); iv) awareness of self and v) in social understanding (Holmes and Ewan, 2007). Also, as several areas of the brain responsible for motor execution share common neural substrates with action observation and imitation (Buccino *et al*, 2004; Gazzola and Keyers 2009; Bach *et al*, 2010; Caspers *et al*, 2010), it has additionally been advocated that the mirror neuron system plays a significant role in the motor learning process (Craighero *et al*, 2002; Vogt *et al*, 2003) which is of particular interest in neurorehabilitation.

According to Magill (2011, p.249), motor learning can be described as "a change in the capability of a person to perform a skill that must be inferred from a relatively permanent improvement in performance as a result of practice or experience". Indeed, it is believed that learning through observation and imitation commences in childhood and is a common way to acquire new skills (Hetu *et al*, 2010). When humans learn new motor skills, it is postulated that they first observe another's movement and then unconsciously map it to their own motor repertoire. This movement is then recombined and created into an internal motor representation enabling them to accurately prepare their body to imitate the new motor sequence observed (Rizzolatti and Craighero, 2004; Iacoboni, 2005; Iacoboni and Dapretto, 2006; Sakamoto *et al*, 2009). This process is believed to be performed by the mirror neuron system and transcranial magnetic stimulation studies in healthy subjects have confirmed this "body priming", recording increases in evoked potentials within corresponding muscles during the observation of a motor task (Brighina *et al*, 2000; Maeda *et al*, 2002; Clark *et al*, 2004; Fadiga *et al*, 2005; Montagna *et al*, 2005;

Avenanti *et al*, 2007; Liepert and Neveling, 2009) which are further enhanced during observation with the intention to imitate (Decety *et al*, 1997; Buccino *et al*, 2004; Zentgraf *et al*, 2005; Frey *et al*, 2006; Suchan *et al*, 2008; Roosink and Zijdewind, 2010).

As well as potentially priming the body for movement, further evidence for the involvement of the mirror neuron system in motor learning comes from studies of healthy individuals that have found mirror neuron activity within the cerebellum (Calvo-Merino *et al*, 2006; Sokolov *et al*, 2010) and the primary motor cortex, both of which are believed to be critical in facilitating this process (Celnik, 2010). The involvement of the primary motor cortex is more uncertain, having been refuted in the past (Iacoboni *et al*, 1999) although supported more recently in monkey (Raos *et al*, 2004; Tkach *et al*, 2007; Dushanova and Donoghue, 2010) and human studies (Montagna *et al*, 2005; Lago *et al*, 2010), with some recording increases in neurological activity (plasticity) within this area, which is believed to represent the encoding of motor memories (Stefan *et al*, 2005; Celnik *et al*, 2006; Stefan *et al*, 2008). In these particular studies, it was found that in healthy older adults the encoding of a motor memory only occurred when action observation and physical motor practice were combined, suggesting that this may be the most efficacious method of facilitating motor learning and enhancing training effects within this population.

1.2 RESEARCH PROJECT FOCUS

In summary, stroke is an immense burden to both society and the individuals who experience the event, with upper limb motor deficits being common which can leave a number of individuals dependent and with a reduced quality of life. Global demographic data suggests that the number of surviving older adults will continue to increase from an estimated 488 million in 1990 to 1,363 million in 2030 (Di Carlo, 2009). Therefore, as age is one of the key risk factors for stroke it would seem reasonable to surmise that there will be a growing number of people at risk.

As previously discussed, the understanding of the neurophysiological changes that drive brain reorganisation and recovery after stroke is increasing, although the exact mechanisms are not currently understood. Subsequently, various new physical therapies which are repetitive and intensive in nature such as constraint-induced

movement therapy have been introduced and have shown early efficacy in promoting upper limb recovery. However, many of them are not suitable for or accessible by those with a more severely paretic upper limb which accounts for around 25% of the stroke population (Blanton *et al*, 2008). This indicates that there is clearly a need for new therapies accessible by this population that facilitate enough recovery of voluntary movement to enable these individuals to participate within more intensive and repetitive rehabilitation. Having such therapies will lead to an increase in recovery, reduce residual disability, improve quality of life and decrease the overall societal burden of stroke.

One such therapy based on the concepts of action observation and imitation termed Observation with intent To Imitate (OTI) as suggested by Pomeroy *et al* (2005), may provide an answer particularly when combined with physical motor practice (MP). The evidence presented suggests that OTI (action observation) + MP (imitation) could furnish those with insufficient voluntary movement an alternative method of accessing the motor system, thus "priming" the appropriate muscles for movement whilst also enhancing the potential for motor learning, enabling them to participate in sufficient repetitive motor training to maximise upper limb recovery. This research project therefore focused on the use of such a therapy within upper limb rehabilitation after stroke.

1.3 RESEARCH PROJECT AIM AND OBJECTIVES

The ***overall aim*** of this research project was to increase/add to the current knowledge base surrounding the use of action observation and imitation as a potential therapy within stroke rehabilitation by completing the following ***objectives***:

Objective One
Through the conduction of a literature review, to understand the current knowledge base surrounding the use of therapies based on action observation and imitation in stroke rehabilitation (chapter two), specifically in relation to studies investigating:

> a) The effectiveness of action observation and imitation as a rehabilitation intervention to improve recovery in the upper limb after stroke;

b) Changes in neurological activity within the lesioned brain and/or associated tracts, in response to action observation and imitation after stroke.

Objective Two

Through the conduction of an empirical research study, explore the use of OTI+MP as a rehabilitative intervention for the moderate to severe paretic upper limb early after stroke (chapter three: Research methods; chapter four: Results and chapter five: Discussion).

Objective Three

To formulate recommendations (if applicable) for the clinical use/future studies of OTI+MP as a therapy in stroke rehabilitation (chapter six: Conclusion).

1.4 VALUE OF THIS RESEARCH PROJECT

It is anticipated that this research project will enhance knowledge surrounding the possible use of action observation and imitation within stroke rehabilitation. As previously discussed, there is a need for new therapies that will enable stroke survivors with more severe paresis to participate in repetitive functional training and therefore maximise their upper limb recovery. It is hoped that the empirical data retrieved from this study will help to inform whether or not OTI+MP has the potential to be such a therapy and if future studies should be pursued.

CHAPTER TWO – LITERATURE REVIEW

The format of this literature review has been produced in line with the Cochrane Handbook for Systematic Reviews (Higgins and Green, 2009). Whilst it is acknowledged that this may slightly differ from the approach traditionally used when presenting a literature review within a thesis, it was felt that this was the most appropriate way to demonstrate that a thorough, systematic and critical approach had been taken in reviewing the existing literature regarding the use of action observation and imitation within stroke rehabilitation.

2.1 INTRODUCTION

Chapter one of this research project addressed the immense burden that stroke places on society and individuals in terms of cost and quality of life due to the high levels of residual disability experienced. As already discussed, the population is ageing exponentially potentially increasing this overall burden. Although various therapies are in place to assist stroke survivors in adapting to this disability, a large number of them remain functionally impaired suggesting that new therapies are needed. As depicted in chapter one section 1.1.3, therapies based on the concepts of action observation and imitation such as Observation with intent To Imitate combined with Motor Practice (OTI+MP) may help, as it could furnish those with insufficient voluntary movement an alternative method of accessing the motor system, thus "priming" the appropriate muscles for movement whilst also enhancing the potential for motor learning, enabling them to participate in sufficient repetitive motor training to maximise upper limb recovery. To ascertain whether the use of action observation and imitation had been explored in previous research studies, it was necessary to complete ***objective one*** as presented in chapter one, section 1.3 which was:

> *To understand the current knowledge base surrounding the use of therapies based on action observation and imitation in stroke rehabilitation, specifically in relation to studies investigating:*
>
> > *a) The effectiveness of action observation and imitation as a rehabilitation intervention to improve recovery in the upper limb after stroke;*

b) *Changes in neurological activity within the lesioned brain and/or associated tracts, in response to action observation and imitation after stroke.*

2.2 METHODS

2.2.1 Inclusion Criteria

Types of Studies

Studies investigating upper limb recovery – Any study of an analytical (quantitative) design investigating the effects of action observation and imitation on upper limb recovery including: i) Randomised controlled trials including cross-over and cluster trials and ii) Non-randomised trials ie; cohort studies, case controlled studies and single case studies. Qualitative studies and surveys were specifically excluded as these are descriptive rather than analytical in nature.

Studies investigating changes in neurological activity - Observational studies of an analytical (quantitative) design using either: i) functional magnetic resonance imaging; ii) transcranial magnetic stimulation; iii) positron emission tomography or iv) diffusion-tensor imaging as the investigative medium.

All publications had to be: i) available in full to enable a full critique of the methods and reporting of results to be conducted and ii) written in the English language only due to translation facilities being unavailable.

Types of Participants

Studies were included of adults (18 years and older), with a clinical diagnosis of stroke (all types, severity and phases of stroke) and who were experiencing paresis of the upper limb due to a motor deficit. It is acknowledged that action observation and imitation may have been investigated in other fields of rehabilitation however, it was felt appropriate to conduct this literature review within the specific area of interest only (ie stroke) to ensure that a focused view of the current literature base was gained.

Types of Interventions

Studies investigating upper limb recovery only – Studies investigating any type of intervention that involved participants being treated either individually or as a group, where they observed and imitated an action that was demonstrated either by a live human being or via electronic media such as video/dvd in either the 1st person (as if looking through one's own eyes) or the 3rd person (watching oneself or others), were included to maximise publication involvement. Mirror therapy was excluded due to the observer watching their own limb rather than observing and imitating that of another human being.

Types of Outcome Measures

Studies investigating upper limb recovery – To ensure that a comprehensive view of the potential effects of action observation and imitation on upper limb recovery was accomplished, measures at both the impairment (ie measures that are not related directly to the accomplishment of a task but that measure motor aspects that may impede such accomplishment ie muscle strength, muscle tone and joint range of movement) and functional (ie measures that quantify the actual amount of task success) levels using validated outcome measures (Levin *et al*, 2009) were included.

Studies investigating changes in neurological activity – To ensure that a comprehensive view of the potential effects of action observation and imitation on neurological activity was accomplished, any studies that included the examination of changes in brain/central nervous system activity or muscle evoked potentials were included.

2.2.2   Search Strategy

Electronic Search

The following electronic databases were searched: Allied and Complementary Medicine Database (AMED); Cumulative Index to Nursing and Allied Health Literature (CINAHL); European Medical Database (EMBASE); US National Library of Medicine Database (MEDLINE/Pubmed, http://www.ncbi.nlm.nih/gov/pubmed) and the Cochrane Central Register of Controlled Trials (CENTRAL). The search was conducted from the inception of the databases to December 2010. The keywords and various combinations applied during this process are shown in table 2.1. MESH terms were utilized where the database allowed. The Physiotherapy

Evidence Database (PEDro, http://www.pedro.org.au/) and the Occupational Therapy Systematic Evaluation of Evidence Database (http://otseeker.com) were also searched from their inception to December 2010 using the terms "stroke and upper limb" only as they were unable to accommodate the combinations depicted in table 2.1.

Combination → Key Words ↓	ONE	TWO	THREE	FOUR	FIVE	SIX
Action Observation	X				X	
Imitation		X				
Imitative Behaviour			X			
Mirror Neuron				X		X
Stroke	X	X	X	X	X	X
Upper limb	X	X	X	X		

Table 2.1: Keywords and Various Combinations used in the Literature Search

Hand Search

A hand search of the specialist journals, Topics in Stroke Rehabilitation (2008 to December 2010); Neurorehabilitation and Neural Repair (2008 to December 2010); Neurorehabilitation (2008 to December 2010) and Restorative Neurology and Neuroscience (2008 to December 2010) also took place. These journals were chosen because of their specialist interest within the specific areas of neurological rehabilitation, neuroscience and stroke.

Citation Search

All studies identified for inclusion from the electronic and hand search were subject to a citation search using the Web of Knowledge (http://isiwebofknowledge.com) and Scopus (http://www.scopus.com) databases.

Unpublished Literature Search

In an attempt to include any unpublished literature on the subject, the following national and international trial registers were searched using the terms "stroke and

upper limb": United States Institute of health clinical trials
(http://www.clinicaltrials.gov); Current controlled trials (http://www.controlled-trials.com/mrct) and the Stroke trials registry (http://strokecentre.org/trials/).

Reference List Search
Finally the reference lists of the retrieved articles were also scanned for any further relevant literature.

2.2.3   Selection Criteria

The articles retrieved from the searches were initially tabulated to facilitate the identification of duplicates which were subsequently removed. An assessment of the remaining articles was then undertaken by a reviewer who scanned the titles in relation to the review objectives, with those not relating directly being rejected. The abstracts for the remaining articles were then consulted and were again rejected if they did not pertain to the review objectives. Those that remained were then assessed for inclusion using the established criteria. Where uncertainly occurred, the full text was recovered and read. Once again if the study did not meet the inclusion criteria it was rejected.

2.2.4   Assessment of Risk of Bias in Included Studies

The methodological quality of the included studies was assessed using the criteria recommended in section 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2009). This includes an assessment over six domains: i) sequence generation; ii) allocation concealment; iii) blinding of participants (personnel and outcome assessors); iv) incomplete outcome data; v) selective reporting and vi) other plausible sources of bias. Although this method is more commonly used for the assessment of randomised controlled trials only, it was felt appropriate to utilise it for all other studies included within this review to ascertain an overall picture of the current quality of the available evidence.

2.3 RESULTS

2.3.1   Literature Search

A total of 1049 potential studies were identified following the electronic, hand, citation, unpublished literature and reference list search. No systematic or literature reviews were retrieved during this process in direct relation to the review objectives.

Figure 2.1 illustrates a flow chart of this process. Six full text articles were assessed with three meeting the inclusion criteria, the characteristics of which are detailed within section 2.3.2. Three studies were excluded and these are listed in table 2.2 along with reasons for their omission.
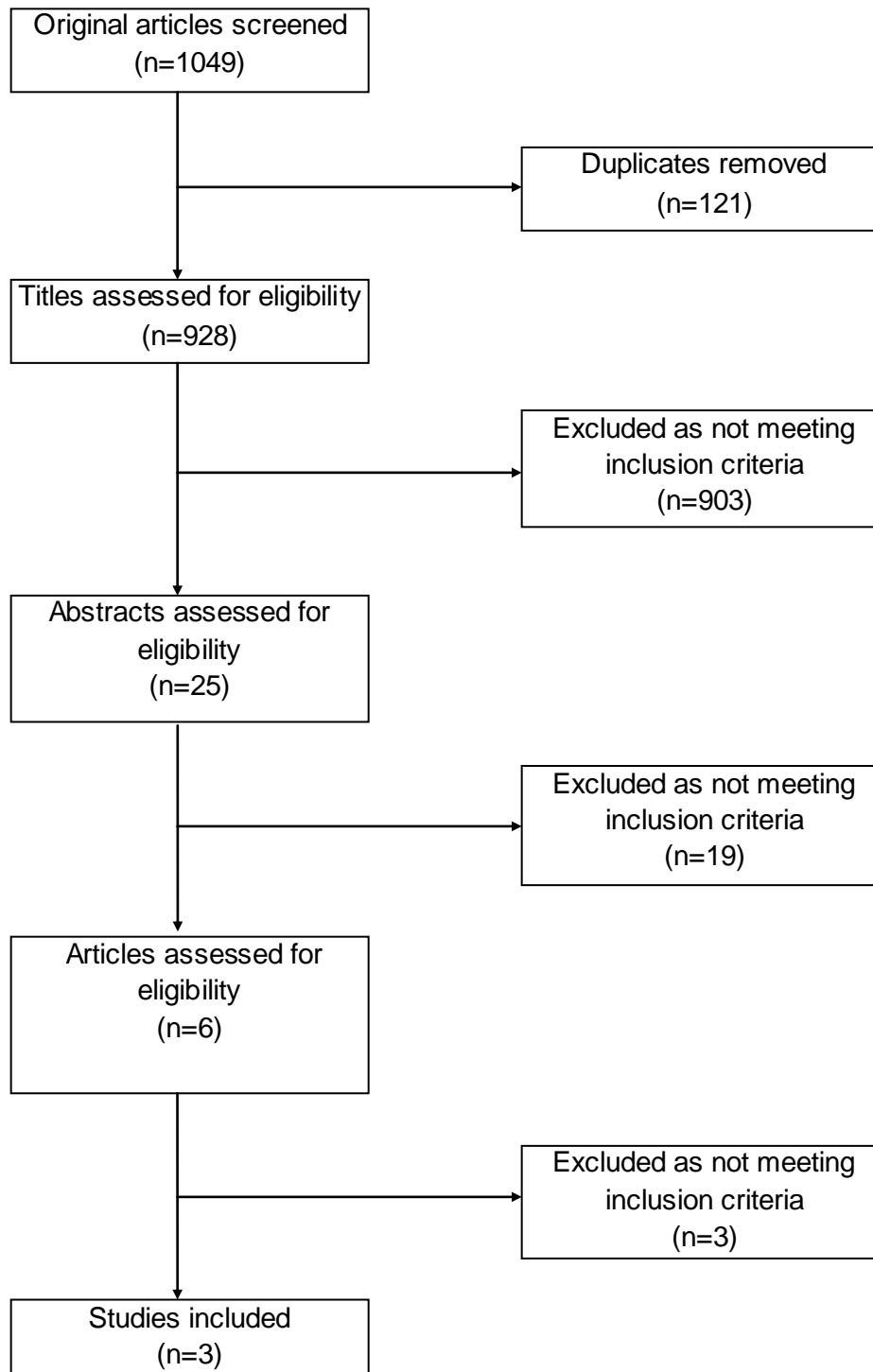
Figure 2.1 : Flow Chart depicting Literature Search Results

Study	Reason for Exclusion
Ewan *et al*, 2010 (upper limb recovery)	Qualitative study
Wenkeler *et al*, 2009 (neurological activity)	Conference poster - Not full publication
Chatterton *et al*, 2008 (upper limb recovery)	Single case study, not exclusively upper limb focused

Table 2.2: Studies Excluded from Review with Reasons

2.3.2 Characteristics of Included Studies

The characteristics pertaining to each individual study will now be presented.

Ertelt *et al* 2007	
Study Aim	To investigate if the activation of motor areas by action observation became reinforced by the concomitant active execution of observed actions and to investigate whether reorganization occurred within the motor areas of the brain following the intervention.
Methods	Parallel group randomised controlled trial with embedded functional magnetic resonance imaging.
Participants	**Functional magnetic resonance imaging** = 13 participants (7 intervention, 6 control.) **Rehabilitation intervention** = 16 participants (8 in each group, 5 female) with moderate paresis; age < 76; first ever ischaemic stroke in the middle cerebral artery territory; not experiencing neglect, depression, anosognosia, amnesia, dementia or moderate to severe aphasia. Post Stroke > 6 months mean 1098.9 days; not receiving active therapy during study.
Interventions	**Experimental:** Video sequences of hand and/or arm actions viewed from three different perspectives for 6 minutes and then performed for 6 minutes as directed by a therapist. Three different actions presented in each session which were performed twice. Actions presented commenced with simple tasks that increased in complexity. Each session lasted 90 minutes and was performed for 18 consecutive working days (54 different videos in total per participant). **Control:** As per the experimental group however, the 6 minute videos contained geometric symbols rather than hand and/or arm actions.
Outcomes	**Functional magnetic resonance imaging** = Observation of brain activity during the manual exploration of objects using functional magnetic resonance imaging before (baseline) and soon after the end of the intervention (outcome). **Rehabilitation intervention** = Frenchay arm test; Wolf motor function test; Stroke impact scale at baseline one and two (14 days apart) to rule out spontaneous recovery then after treatment at 4 weeks (both groups) and at 8 weeks (intervention group only).

Celnik *et al* 2008	
Study Aim	To investigate if action observation could enhance the beneficial effects of physical training on motor memory formation in patients with chronic stroke.
Methods	Crossover randomised controlled trial.
Participants	8 participants (5 women) aged 40 to 74 with single cortical or subcortical lesions with partial paresis of the hand.
Interventions	Each participant took part in 3 testing sessions separated by at least 7 days. Transcranial magnetic stimulation was delivered over the primary motor cortex to evoke contralateral thumb movements where electromyographic activity was recorded from the extensor and flexor pollicis brevis muscles. Each session commenced with the recording of 60 transcranial magnetic stimulated evoked thumb movements (baseline) followed by one of the following 30 minute interventions in each separate session performed in random order: a) Motor practice only consisting of voluntary thumb movements performed in a direction opposite to baseline for 3 blocks of 10 minutes each separated by a 2 minute rest. b) Motor practice (imitation) and congruent action observation, consisting of performing voluntary thumb movements whilst watching a video displaying the hand (1st person) of a healthy volunteer simultaneously in the same direction for 3 blocks of 10 minutes separated by a 2 minute rest. c) Motor practice and incongruent action observation. As b) but participant observed thumb movements in the opposite direction to those being physically practiced.
Outcomes	Percentage of transcranial magnetic stimulation evoked thumb movements that fell within the training target zone defined as a window of +/- 20° centred on the mean training direction; Effects of each training intervention on motor cortical excitability; Consistency of motor training and attention and fatigue levels at baseline and outcome.

Franceschini *et al* 2010	
Aim	To investigate whether action observation treatment improved upper limb motor impairment in chronic stroke patients.
Methods	Observational Study
Participants	28 chronic stroke patients; 18-75; first ever stroke of any type within middle cerebral artery territory; no previous neurological pathologies; normal visual and auditory acuity; no neglect; mini mental state examiniation of 24; no depression; no apraxia; absence of total deficit of tactile sensibility; > 6 months after stroke.
Interventions	20 daily activities involving use of an object were viewed on a video (one activity per session). Each activity was subdivided into 3 or 4 constituent motor acts. Each motor act was presented for 3 minutes followed later by their imitation for 2 minutes. Each activity was repeated twice = total duration 30-40 minutes, 5 days per week over 4 weeks. Different actions were presented in fixed order according to level of increasing complexity as judged by the experimenter. Encouraged to pay attention to video and during imitation of task.
Outcomes	Fugl-Meyer; Ashworth scale; Frenchay arm test; Modified barthel index and Functional independence measure. Baseline one and two (30 days apart) to rule out spontaneous recovery then after treatment at 4 weeks and at 2 months.

2.3.3 Summary of Included Studies

Upper Limb Recovery

Two studies investigated the use of action observation and imitation as a potential therapy to increase recovery in the upper limb after stroke. These studies were published in 2007 and 2010 and were conducted in Italy (Franceschini *et al*, 2010) and the other unknown (Ertelt *et al*, 2007). All participants were recruited from local rehabilitation centres.

Study Design

One was a randomised controlled trial (Ertelt *et al*, 2007) and the other an observational study (Franceschini *et al*, 2010) with sample sizes of 16 and 28 respectively.

Participants

A total of 44 adults (30 male, 14 female) with first ever stroke of any type within the middle cerebral artery territory with reported mean age ranges of 56.3 (Ertelt *et al*, 2007) and 58.5 years (Franceschini *et al*, 2010) were included. Both studies investigated participants in the chronic phase of stroke ranging from a mean of 817.6 (Franceschini *et al*, 2010) to 1098.9 days (Ertelt *et al*, 2007) after the event. Only Ertelt *et al* (2007) specified the stroke severity of the upper limb as being "moderate" as assessed by the Frenchay arm test and the Wolf motor function test.

Interventions

Both studies delivered their intervention by video which contained various goal-directed hand and/or arm movements filmed from different perspectives, with each movement being imitated (motor practice) after its observation. Dose and duration differed with the action observation component ranging in total from 36 minutes (Ertelt *et al*, 2007) to 24 minutes (Franceschini *et al*, 2010) and the imitation (motor practice) component ranging from 36 minutes (Ertelt *et al*, 2007) to 16 minutes (Franceschini *et al*, 2010). Total session times were 90 minutes over 18 days (27 hours) (Ertelt *et al*, 2007) and 40 minutes over 20 days (13 hours) (Franceschini *et al*, 2010) respectively.

Changes in Neurological Activity

Two studies investigated the effects of action observation and imitation on neurological activity within the lesioned brain and/or associated tracts after stroke.

These studies were published in 2007 and 2008 and were conducted in the United States using transcranial magnetic stimulation (Celnik *et al*, 2008) and the other unknown using functional magnetic resonance imaging (Ertelt *et al*, 2007).

Study Design

One was a randomised cross-over design and the other an observational study.

Participants

A total of 21 individuals with first every stroke within the middle cerebral artery (Ertelt *et al*, 2007) or single unilateral cortical or subcortical strokes (Celnik *et al*, 2008) were included. All participants were within the chronic phase of stroke. The study conducted by Celnik *et al* (2008) included right handed individuals only, with an average age of 58.9 (4 male, 4 female). Four had a lesion within the left hemisphere and four within the right with the mean post stroke time being 2.3 years. No details regarding participant age or their stroke (ie location/time since stroke etc) was made available by Ertelt *et al* (2007). Severity of the upper limb was moderate (Ertelt *et al*, 2007) to mild (Celnik *et al*, 2008).

Interventions

The study by Ertelt *et al* (2007) used functional magnetic resonance imaging to measure changes in neurological activity within the brain following the application of action observation and imitation as a rehabilitative intervention. Celnik *et al* (2008) used transcranial magnetic stimulation to determine changes within the primary motor cortex following motor training by either i) motor practice only; ii) action observation of a movement in the same direction as being practiced (imitation) or iii) action observation of a movement in the opposite direction as being practiced.

2.3.4 Methodological Quality Summary

A summary of the risk of bias for all included studies and at an individual level are depicted in figures 2.2 and 2.3 respectfully. In view of these findings the overall risk of bias was assessed to be high. The categories assessed will now be presented.

Sequence Generation and Allocation Concealment

Two studies were randomised controlled trials but were unclear regarding the randomisation and allocation concealment procedures used (Ertelt *et al*, 2007; Celnik *et al*, 2008) with the other not applying randomisation or allocation concealment due to the study design chosen (Franceschini *et al*, 2010). This subjected all studies to the potential of selection bias which could have been

avoided by applying robust randomisation and allocation concealment procedures by evenly distributing the patient characteristics between groups (Roberts and Torgerson, 1999) and by shielding the study's group assignment from both the participants and the researchers (Forder *et al*, 2005). If selection bias were to occur then there is a risk that any outcome realized could find in favour of the intervention giving misleading results (Helewa and Walker, 2000).

Blinding

Only Celnik *et al* (2008) reported that the outcome assessor was blinded to group allocation. Neither of the other two studies annotated whether any of the personnel involved in the conduction of the research were blinded leaving them potentially at risk of both performance and measurement bias which can manifest as a change in behaviour either consciously or subconsciously that can affect the overall outcome (Glasziou *et al*, 2008).

Incomplete outcome data

It is usual for some participants to be lost during a trial yet, unless it is a random event then attrition can lead to selection bias as the patient characteristics within the groups previously allocated through randomisation change (Torgerson and Torgerson, 2003). This can be avoided by ensuring that an "intention to treat" analysis is used when calculating the final results (Centre for Reviews and Dissemination, 2001).

None of the studies included within this review reported incomplete outcome data and therefore no risk of bias was identified for this category.

Selective reporting

The instruments used to measure the variables were identified in all cases. Two studies reported the outcomes of all included measures (Celnik *et al*, 2008; Franceschini *et al*, 2010). Ertelt *et al* (2007) however, only chose to follow up the intervention group and not the control group at 8 weeks, the reasons for which were unclear.

Other bias

All of the studies were subject to other potential sources of bias including small sample sizes (Ertelt *et al*, 2007; Celnik *et al*, 2008) or inadequate study design (Franceschini *et al*, 2010), leading to the possibility that they all failed to detect important differences or obtained false results by chance (Blowers *et al*, 2006).
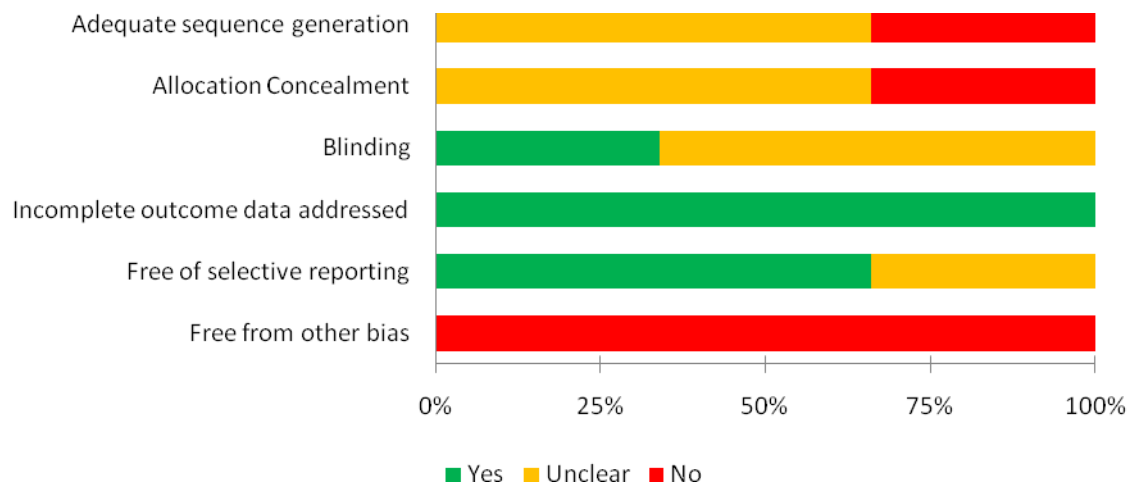
Figure 2.2: Methodological Quality Graph: Review Author's Judgement regarding Potential Bias occurring as a Percentage across all Included Studies
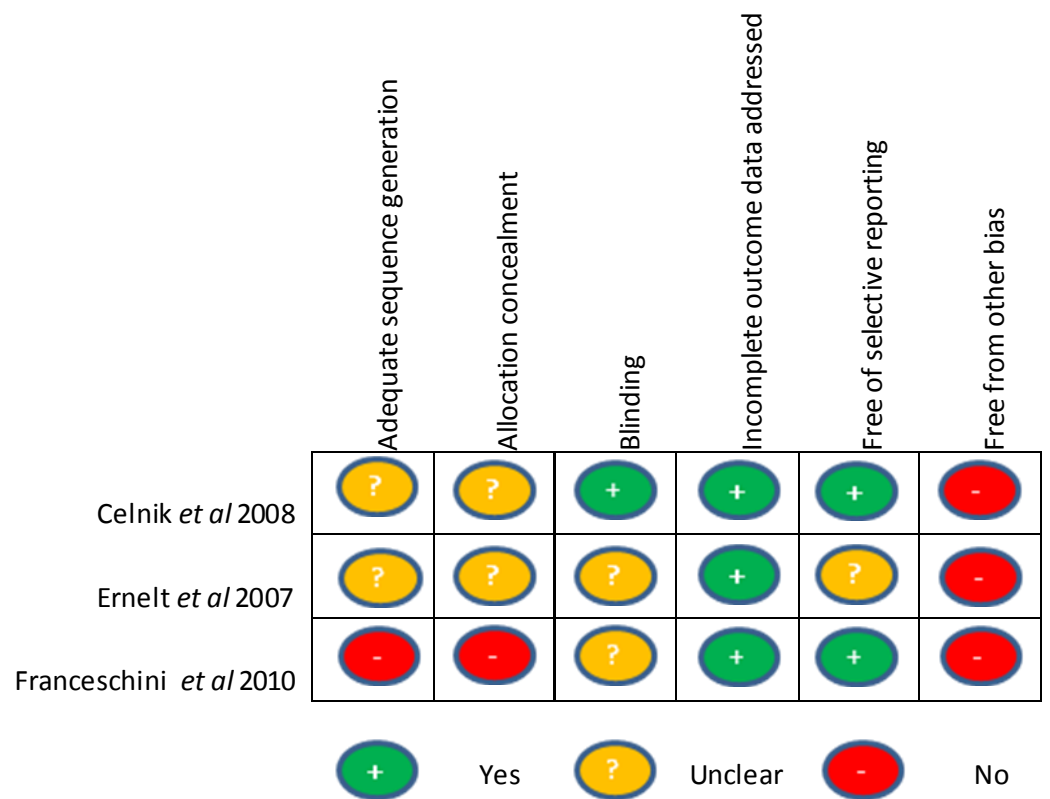
Figure 2.3: Methodological Quality Summary: Review Author's Judgement of potential Risk of Bias occurring in Each Individual Study

2.3.5 Effects of Action Observation and Imitation

Upper Limb Recovery

The studies were in the main heterogeneous in terms of the types of outcome measures used with the exception of the Frenchay arm test which was applied in both. No analysis was possible in relation to this outcome due to a lack of data reporting in one study (Franceschini *et al*, 2010) and therefore the results from each study are presented as reported in table 2.3. All figures quoted are the mean unless otherwise stated and statistically significant findings (P≤0.05) are highlighted in *italics.* Essentially, significant increases were seen in recovery within each group including the Frenchay arm test (mean 2.625 to 4.375, *P=0.007,* (Ertelt *et al,* 2007; median 1.0 to 2.0, *P=0.005,* (Franceschini *et al*, 2010)) and the Fugel-Meyer (median 38.5 to 39, *P=0.001,* (Franceschini *et al,* 2010)) with a decrease in time taken to complete the Wolf motor function test (mean of 10.88 to 7.04, *P=0.008,* (Ertelt et al, 2007)) and in spasticity (Median 7.5 to 5.5, *P=0.044*, (Franceschini *et al*, 2010). Ertelt *et al*, 2007 also reported a significant increase in upper limb recovery (*P=0.0005*) and a decrease in time taken to complete tasks within the Wolf motor function test (*P=0.525*) in favour of the intervention group compared to the control group.

	Intervention					Control			
Outcome Measure	Base line*	Out come*	Within Group P-Value	Follow-Up	Follow Up P-Value	Base line*	Out come*	Within Group P-Value	Between Group P-Value
AS Median (Fran)	7.5	5.5	*0.044*	N/R	N/R	N/A	N/A	N/A	N/A
FAT (Ertelt)	2.625	4.375	*0.007*	4.43	1.00	2.250	2.125	0.158	*0.0005*
FAT Median (Fran)	1.0	2.0	*0.005*	N/R	N/R	N/A	N/A	N/A	N/A
FM Median (Fran)	38.5	49	*0.001*	N/R	N/R	N/A	N/A	N/A	N/A
WMFT (Ertelt)	10.88	7.04	*0.008*	9.32	0.63	16.67	16.97	0.287	0.0525

AS = Ashworth Scale ; FAT = Frenchay Arm Test; FM = Fugel-Meyer : N/A = Not Applicable; N/R = Not Reported; WMFT = Wolf Motor Function Test; *Figures quoted are the mean unless otherwise stated.

Table 2.3: Results for the Outcomes of Interest

No studies annotated specifically if any participants experienced any adverse events during their conduction.

Changes in Neurological Activity

Increases in brain activity were detected by functional magnetic resonance imaging throughout the motor execution network including within the: supplementary motor area; bilateral ventral premotor cortex; bilateral cerebellum and bilateral superior and inferior parietal areas when manipulating complex items in the affected hand. Smaller increases within the inferior and superior parietal lobule and cerebellum in the non-affected hemisphere and the ventral premotor cortex and cerebellum in the affected hemisphere were witnessed during the manipulation of the same objects in the unaffected hand. Significant differences in the levels of activity between the intervention and control groups were found bilaterally in the ventral premotor cortex and the superior temporal gyrus and unilaterally within the supplementary motor area and the insula within the non-affected hemisphere and the supramarginal gyrus in the affected hemisphere during the manipulation of objects with the affected hand (Ertelt *et al*, 2007).

Examination of excitability within the corticospinal pathways by transcranial magnetic stimulation, found that muscle-evoked potentials within the extensor and flexor pollicis brevis muscles within the thumb were greater when the action being observed was imitated simultaneously in the same direction (congruent) compared to the action observed being performed in the opposite direction to that being practiced simultaneously (incongruent) (*P<0.04*) or by motor practice alone (*P<0.02*) (Celnik *et al*, 2008).

Adverse Events

Only Celnik *et al* (2008) reported any adverse events, with one of their participants being withdrawn after experiencing a transcranial magnetic stimulation induced headache.

2.4 DISCUSSION

The aim of this review was to investigate the effects of action observation and imitation on upper limb recovery and changes in neurological activity within the brain and/or associated tracts following a stroke. In terms of upper limb recovery, early results indicate that it could potentially be a promising adjunct to conventional physical therapy. The studies included all combined action observation with some form of imitation (physical motor practice) and found significant changes in a number of outcome measures investigating changes in function and impairment including a decrease in the time taken to complete tasks, an increase in proximal control and dexterity and a decrease in spasticity. These improvements were maintained at four weeks after the cessation of the intervention, suggesting that it might possibly have a long term benefit. Neither of the studies included directly reported whether any adverse events occurred, although no individuals were lost to follow up indicating that no participants withdrew due to the intervention.

In respect of potential changes that occurred in relation to neurological activity following the application of action observation and imitation, increases were found within areas within the brain responsible for movement execution, including those implicated as being part of the mirror neuron system such as the ventral premotor cortex, supplementary motor area and the cerebellum, with a number of changes being recorded within the ipsilesional hemisphere which is associated with more beneficial recovery (Marshall *et al* 2000; Calautti *et al*, 2001; Jang, 2007). Increases in muscle evoked potentials were also recorded when action observation was applied, with the largest increases being found when it was combined with the simultaneous imitation of the observed action (Motor Practice) in the same direction, which according to the authors inferred the encoding of a motor memory within the primary motor cortex. This finding was similar to previous studies investigating the same training regime in healthy older adults (Stefan *et al*, 2005; Celnik *et al*, 2006; Stefan *et al*, 2008) further supporting the notion that this area of the brain may form part of the mirror neuron system (Montagna *et al*, 2005; Lago *et al*, 2010).

In the study by Ertelt *et al* (2007), the effects of action observation and imitation on neurological activity and recovery were being measured concurrently suggesting that the increases witnessed within the upper limb might have been associated with the changes in neurological activation. As these neurological changes were found to be greater following the application of action observation and imitation compared to motor practice alone, it is postulated that the observation component may have

acted as a cue to imitation thus priming the execution system for movement through the increased recruitment of motor areas, resulting in enhanced recovery. Support for this theory comes from studies of healthy individuals that have demonstrated improvements in functional skills where the movement has been initially observed. For example, in a study conducted by Brass *et al* (2000), finger movement initiation times were found to be faster in response to an imitative cue compared to a spatial or symbolic one. More recent evidence within the fields of general and neuro-rehabilitation has emerged also supporting this theory. In terms of general rehabilitation, Tia *et al* (2010) found that walking velocity and the time taken to move from stand to sit were reduced in elderly adults following observational practice and Bellelli *et al* (2010) found that action observation and imitation training combined with conventional therapy improved functional outcomes more than conventional therapy alone following orthopaedic surgery. In the field of neuro-rehabilitation, the application of this intervention has resulted in a positive effect on the recovery of walking ability within individuals who experienced freezing of gait due to Parkinsons disease (Pelosin *et al* 2010) and in the treatment of aphasia (Lee *et al*, 2010).

Another area that may have had an impact on these positive findings was the use of familiar movements when applying the intervention. During motor learning, viewing such motor patterns that have previously been learnt and that are present within the observer's motor repertoire have been found to modulate the mirror neuron system. For example, Buccino *et al* (2004a) found that the mirror neuron system was only activated within healthy individuals when observing a human performing silent speech or a monkey smacking its lips compared to watching a dog bark which resulted in no activation. Pianists observing finger movements of other pianists compared to non-pianists have been found to facilitate higher mirror neuron system levels (Haslinger *et al*, 2005), as have ballet dancers observing other ballet dancers compared to observing capoeira dancers (Calvo-Merino *et al*, 2005).

As discussed so far, the findings from this review indicate that the use of action observation and imitation may be a potentially beneficial adjunct to conventional therapy however, a number of areas concerning the applicability and completeness of the available evidence need to be highlighted. All of the participants included in the studies within this review were in the chronic phase of stroke (average 2-3 years), where spontaneous recovery is believed to have either stopped or slowed down dramatically (Page *et al*, 2007; Cramer *et al*, 2008a). Accordingly, the results cannot be generalised to the acute or subacute phases of stroke in which varying levels of spontaneous recovery continue to occur (Cramer, 2008a). Their mean

ages were between 56.3 and 58.9 years of age which is relatively young in relation to experiencing a stroke which is more likely to occur over the age of 75 (The Stroke Association, 2006). Only two of the studies described the severity of upper limb paresis as moderate (Ertelt *et al*, 2007) or mild (Celnik *et al*, 2008) and therefore the results cannot currently be applied to those with more severe paresis who arguably are the population for whom new innovative therapies are required as denoted in chapter one of this thesis.

In terms of the rehabilitation studies (Ertelt *et al*, 2007; Franceschini *et al*, 2010) the population was heterogeneous in respect of gender, type of stroke and its hemispheric location, although they were homogenous with regards to the location of the ictus which had to be within the middle cerebral artery territory and the modality used to deliver the intervention (video). Restricting strokes to the middle cerebral artery territory however, does preclude the results from being applied to individuals who have experienced strokes within the anterior or posterior cerebral artery territory. Participants were also excluded if they had apraxia, inattention/neglect and/or depression, again reducing the generalisability of the findings. The dose and duration of therapy additionally differed between the two studies with Franceschini *et al* (2010) applying 33% less observation and 56% less motor practice (52% less therapy in terms of total time overall) than Ertelt *et al* (2007) whilst still obtaining beneficial results. These results are of interest as they indicate that potentially around 40 minutes of therapy would be sufficient to increase upper limb recovery, virtually meeting the current daily requirements for therapy within the United Kingdom (45 minutes) laid down by the Royal College of Physicians (Royal College of Physicians, 2008). Franceschini *et al* (2010) also used a lower ratio of motor practice compared to action observation than Ertelt *et al* (2007) (0.7:1 v 1:1) which may assist when using the therapy with individuals who find participating in motor practice difficult however, as Franceschini *et al* (2010) did not specify the paretic severity of the participants (ie they may have had mild paresis and therefore made a more significant recovery) or include a control group within their study, it is difficult to quantify the effectiveness of their results.

With regards to the studies investigating changes in neurological activity, only two studies met this reviews inclusion criteria (Ertelt *et al*, 2007; Celnik *et al*, 2008) both of which used different modalities (functional magnetic resonance imaging and transcranial magnetic stimulation). There was heterogeneity in participants in relation to gender, stroke type, hemispheric and ictus locations. Participants were excluded from the study conducted by Ertelt *et al*, 2007 if they had apraxia,

inattention/neglect and/or depression again precluding these results from being applied to such a population as stated above. No exclusion criteria was annotated by Celnik *et al* (2008). The reason for this may have been that no exclusion criteria was applied however, this is unlikely in a study using such a modality as transcranial magnetic stimulation and therefore it would be unwise to assume that this method could be applied to a wide variety of stroke survivors.

2.4.1 Quality of Evidence

The overall quality of the evidence was assessed as being medium to low. This was in the main due to the methods applied being either unclear through poor explanation or no annotation at all, the use of small sample sizes and in some cases the study design applied. It should be noted however, that the study by Ertelt *et al* (2007) was dose-matched with a sham control applied for the observation component and no other form of therapy being received. These factors strengthen the argument that the beneficial results witnessed were solely due to the addition of the action observation and not the motor practice.

2.4.2 Limitations of this Review

There are some limitations to this review that now need to be acknowledged. The author endeavoured to be as systematic and comprehensive as possible in their search strategy however, elements of publication bias occurred when two studies relating to the areas of interest were rejected due to them not being full articles. For a more accurate answer to be obtained it may be prudent for future reviews if possible, to obtain the results from the authors of these studies to facilitate their inclusion. Also, only one author conducted this review and therefore it is feasible that the view taken in relation to the studies quality and findings was not always an impartial one. Having a second reviewer may have averted this potential risk. Finally, due to some studies failing to adequately report their outcome data, no analysis could be performed to determine the overall effect sizes or confidence intervals and therefore the clinical significance of the combined results could not be determined.

2.4.3 Future Research

Upper Limb Recovery

Whilst there is proof of concept for the use of action observation and imitation in people with chronic stroke, there is no evidence for its use within the acute or subacute phases. This indicates the need for high quality early phase trials to explore proof of concept within these populations, with further additional studies

across all phases to increase the knowledge surrounding the effectiveness of the intervention. These studies should also investigate differential effects such as stroke severity, clinical presentation ie apraxia/ inattention, age, location of the stroke ictus and the dose and duration of the therapy.

Changes in Neurological Activity

Early phase studies have shown that in chronic stroke, activation within the brain and/or associated tracts can increase following the application of action observation and imitation however, again as discussed above there is no evidence of its effects in the acute or subacute populations. High quality trials are therefore required using modalities such as functional magnetic resonance imaging, transcranial magnetic stimulation, positron emission tomography or diffusion tensor imaging to ascertain the changes in neurological activity within early stroke with further additional studies across all phases to investigate differential effects such as stroke severity, location of stroke ictus, clinical presentation and age.

2.5 CONCLUSION

Early phase studies indicate potential benefit for the use of action observation and imitation to increase neurological activity within the lesioned brain/associated tracts and to improve upper limb recovery after stroke. Current research is however limited, due to the small samples sizes investigated and the inclusion of individuals restricted to those within the later stages of stroke. Further research is therefore required to ascertain if similar findings in relation to upper limb recovery occur within the stroke population early after the event, which was the subject of the empirical research study conducted during this research project.

CHAPTER THREE – RESEARCH METHODS

3.1 INTRODUCTION

Through the conduction of a literature review, chapter two synthesized the latest published research findings regarding the effects of action observation and imitation in stroke rehabilitation. It was concluded that proof of concept exists for the use of a therapy based on these concepts in people late after stroke however, there was insufficient evidence to advocate its use early after stroke, hence there was a need for a clinical trial to investigate whether action observation and imitation could enhance upper limb recovery within this population. It is widely accepted that patients achieve more beneficial functional outcomes with early rehabilitation (Musicco *et al*, 2003; Salter *et al*, 2006) and the need for the development of evidence based interventions during this time is further warranted from findings purporting that the spontaneous recovery witnessed after stroke is most prolific within the first three months, particularly in relation to functional recovery (Kwakkel *et al*, 2006; Cramer, 2008). The empirical study conducted as part of this research project was therefore conducted within the first month after stroke (3-31 days) with the therapy under investigation being termed "Observation with the intent To Imitate" (action observation) plus Motor Practice (imitation) (OTI+MP). This chapter will now introduce the methods used to meet *objective two* of this research project as presented in chapter one, section 1.3 which was:

To explore the use of OTI+MP as a rehabilitative intervention for the moderate to severe paretic upper limb early after stroke.

3.1.1 Study Aims
The aims of the study were specifically to find out:

1. If there was sufficient proof of concept to justify the use of OTI+MP as an adjunct to conventional physical therapy (CPT) in subsequent dose-finding (Phase I) and efficacy (Phase II) trials;

2. If OTI+MP produced more adverse events than CPT in the paretic upper limb in people post stroke.

3.2 STUDY DESIGN

Before undertaking large clinical trials in which stroke survivors are exposed to an intervention that may be ineffective or harmful, it was important to establish whether there was sufficient evidence of benefit for OTI+MP. This ethical consideration shaped the research approach of first undertaking a small, early phase study. Employing such a method permitted preliminary testing in a specific subset of individuals who were believed to most likely benefit from OTI+MP, thus allowing any potential methodological problems to be identified which could assist in the design and conduction of a future phase II study (Teijlingen *et al*, 2001; Tarling and Crofts, 2002) which according to Hayward *et al* (2007), strengthens the prospect of gaining funding. The gold standard for analysing the effectiveness of an intervention is the randomised controlled trial which due to its design, is the most effective at mitigating the risk of bias (Evans, 2003; Akobeng, 2005; Rothwell, 2005) and therefore this method was employed in the conduction of this study. The overall trial design is depicted in figure 3.1 below.
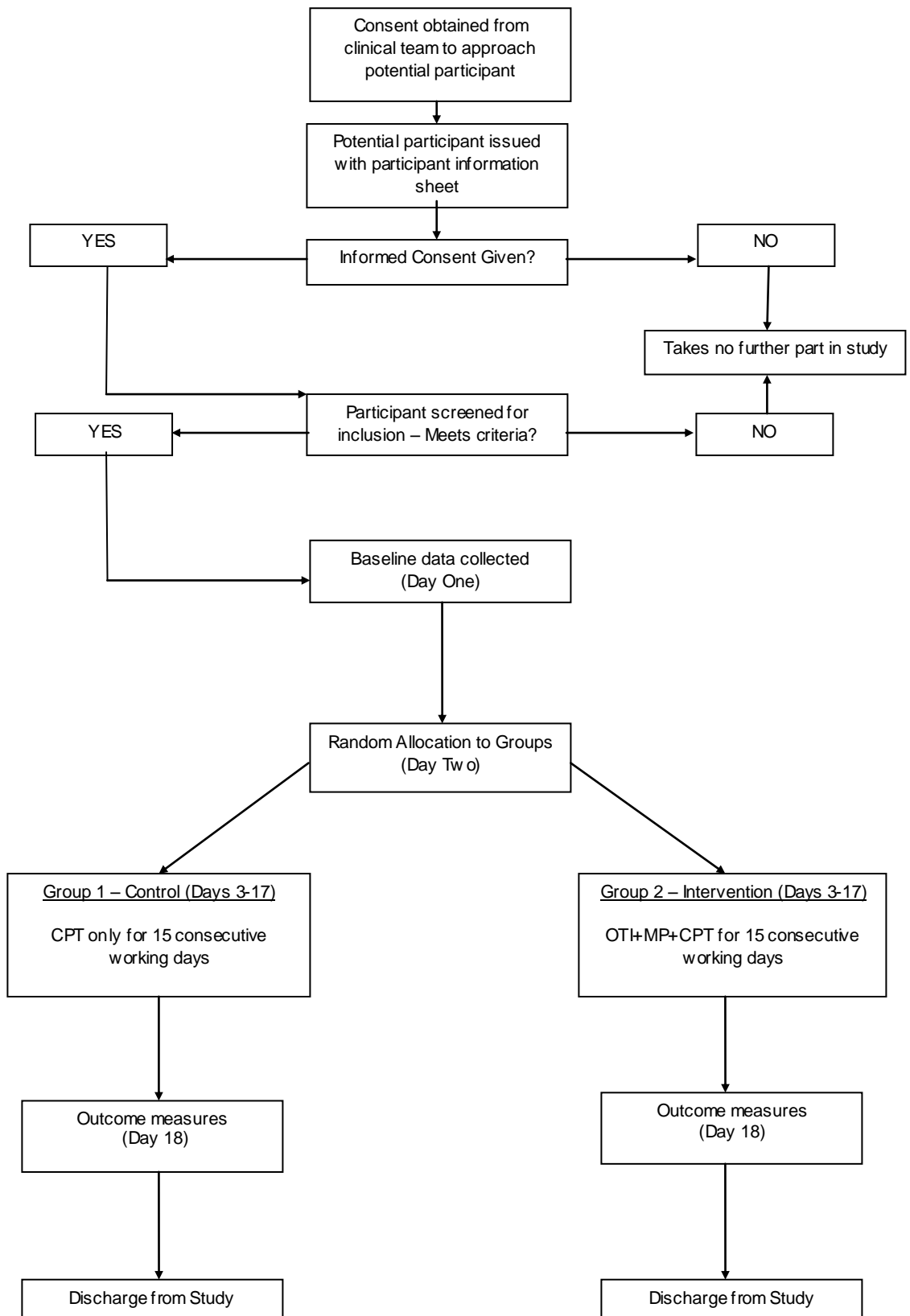
CPT = Conventional Physical Therapy; OTI = Observation with intent To Imitate; MP = Motor Practice

Figure 3.1 : A Flowchart showing the Design of the Early Phase Study

3.3 ELIGIBILITY CRITERIA

It is necessary to specify the eligibility criteria to enable the reader to judge the extent of a trial's generalisability and relevance within the clinical setting (Rothwell, 2005). The eligibility criteria applied in this study along with the relevant justification relating to each individual criterion is depicted in table 3.1 below:

Eligibility Criteria
1. Adults aged 18+ who suffered a stroke between 3 and 31 days before recruitment.   **Justification**   The majority of strokes occur within the adult population (75% over the age of 65 with approximately 1000 per annum in the under 30's) (Different Strokes, 2010) and it was therefore felt appropriate to target this particular demographic. No upper age limit was applied to increase the generalisability of the study. The time parameter of 3-31 days was specifically chosen as participants needed to be medically stable and were required to have sufficient sitting balance to enable them to participate within the study (clinical decision). Research has also confirmed that recovery within a rehabilitative setting is most rapid within the first month (Schaechter, 2004), when the brain is believed to be most amenable to interventions designed to aid recovery. Therefore this time period was deemed the most appropriate to investigate the use of OTI+MP in early stroke.
2. Had an intact pre-motor area (location of mirror neurons – Brodmann area 44/45) as confirmed by routine clinical neuro-imaging.   **Justification**   Early evidence from neuroscience indicates that the ability to imitate requires the use of mirror neurons (Pomeroy *et al*, 2005). A number of these neurons are believed to exist within the pre-motor area within the brain (specifically Brodmann areas 44 and 45) (Caspers *et al*, 2010) and therefore individuals with lesions within this area were excluded. It is possible however, that these individuals could have benefited from OTI+MP but as this was an early phase study the rationale for their inclusion was based on the strongest evidence available. This meant that if no improvement in motor function was found within the stroke survivors most likely to benefit, then there would be little chance of improvement in those believed to benefit the least.

3. **Had a moderate to severe paretic upper limb as measured by:**

   o **A grip force of less than 65% of that of the non-paretic limb**

   o **Unable to complete the 9 hole peg test in 50 seconds or less (this measure was only used if unable to compare grip force as described above with non-paretic limb. Eg: due to amputation or other pathology rendering an accurate comparison unobtainable)**

   o **A score of 18 or more on the Motricity Index.**

<u>**Justification**</u>

Many stroke survivors with moderate to severe paresis are unable to complete repetitive, intensive and challenging activities that have been shown to stimulate the most beneficial changes in upper limb recovery (Kwakkel *et al*, 1997; Cramer *et al*, 2002; Hallett *et al*, 2002; Barreca *et al*, 2003; Steultjens *et al*, 2003; Teasell *et al*, 2003; Schaechter, 2004; Van Peppen *et al*, 2004; Pomeroy *et al*, 2005). The parameters above were therefore included to ensure that those individuals who fell within this category were screened for their eligibility to take part within this study.

4. **Had no observable upper limb movement deficits attributable to pathology other than stroke.**

<u>**Justification**</u>

To enable the efficacy of the therapy to be exclusively measured in terms of paresis following stroke, it was important to ensure that no other factors were contributing to the weakness that could impact on the outcome eg: shoulder pain, previous shoulder surgery with residual functional limitation, osteoarthritis, previous residual weakness.

5. **Be able to imitate actions with their non-paretic limb (ie no severe visual, communication or cognitive deficits precluding participation in OTI+MP) and be deemed medically fit to partake within the research study.**

<u>**Justification**</u>

The justification from neuroscience in terms of the ability to imitate was discussed in section one above however, it was also important to ensure that individuals had sufficient visual and cognitive capacity to participate ie be able to see the actions being performed and to be able to attend/concentrate sufficiently.

Table 3.1: Eligibility Criteria and Relevant Justification for Inclusion

3.4 SAMPLE SIZE

It is recognised that if a study is too small that it may fail to detect important differences or obtain a false result by chance (Blowers *et al*, 2006) however, as this was the first study to investigate the use of OTI+MP in the treatment of the moderate to substantially paretic upper limb early after stroke, there were no other studies to provide information regarding a suitable sample size. Practical reasoning was therefore used to calculate the required sample size for this study. As the research project was being conducted over a period of 15 months, a reasonable estimate for recruitment was two participants per month over 9 months enabling a total of 18 participants to be recruited into this study. This allowed three months for initial training and preparation and three months for data analysis and writing of the thesis and associated journal papers.

3.5 ETHICAL CONSIDERATIONS

3.5.1 Conflict of Interest

No clinical staff members were involved in any key aspects of the study including: i) the provision of information; ii) recruiting participants; iii) taking informed consent; iv) providing the intervention or v) undertaking any of the blinded measurements. All of these tasks were conducted by the research team ensuring that routine clinical and research treatment were kept distinct. No researcher provided clinical treatment and no clinician provided research treatment.

3.5.2 Confidentiality

Only the master list of participants and the consent forms contained sensitive data. All consent forms were stored in lockable filing cabinets in a research laboratory that was accessible by a key code. The master list was encrypted and stored on a password protected computer. This data was only accessible by the research team for the duration of the study. Participant anonymity was therefore protected with all other data collection material being identifiable through the use of a participant number.

Any information deemed unnecessary was shredded in line with the local trust's confidentiality policy or deleted from computer hard drives when no longer required (ie video screening for ability to imitate once independently assessed). Participants

were made aware of their rights to confidentiality through the participant information sheet (appendix three) and this was also re-iterated during enrolment. All members of the research team were aware of their responsibility to confidentiality, with the primary researcher being a member of the Health Professions Council, therefore binding them to the same rules of professional conduct as the clinical team including the NHS Code of Confidentiality.

3.5.3 Consent

The flowchart depicted in figure 3.2 shows the process employed for obtaining informed consent.
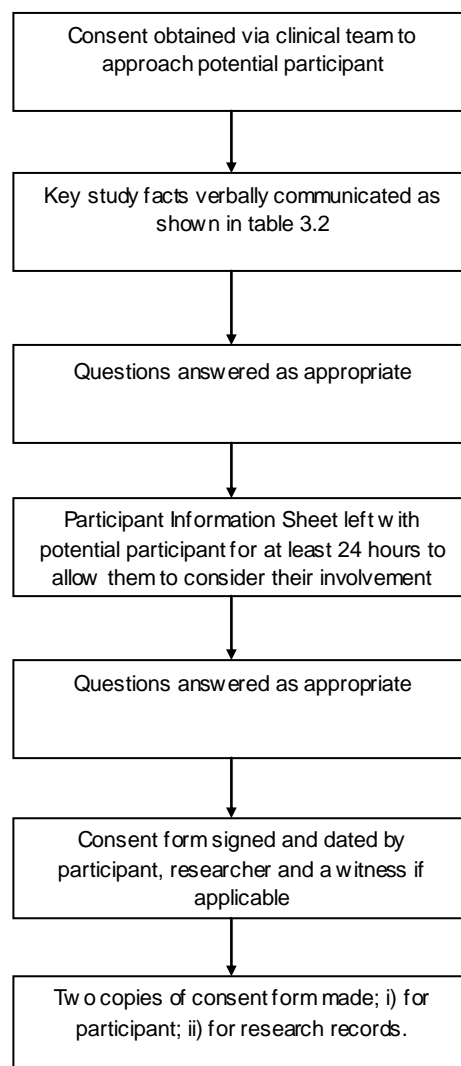
Figure 3.2: The Consent Process

All documentation that was presented to the participant was designed so that the information could be given both verbally and pictorially so that the participant was able to consult and understand the information when the researcher was not

present. In terms of communication, every effort was made to include individuals with aphasia as this condition affects approximately one third of stroke survivors (Engelter *et al*, 2006) and therefore their inclusion was important to ensure that the sample was representative. If aphasia was present then enhanced communication strategies were employed as necessary including the use of picture cards, diagrams, pencil and paper, short sentences, repetition, responding to cues, gesturing and using closed questions to check understanding.

If the potential participant had difficulty with reading or was unable to sign the consent form (appendix four) with their full signature (ie could only make a mark), the researcher involved an individual chosen by the potential participant such as a friend, family or clinical staff member who countersigned the consent form to confirm their agreement to participate.

3.5.4   Ethical Approval

Ethical approval to conduct this trial was received from the Cambridgeshire 3 Research Ethics Committee (appendix one). Research and development approval was also obtained from the Norfolk and Norwich University Hospital and NHS Norfolk to enable the research study to be conducted within their premises (appendix two). The researchers involved within the study had research passports and honorary contracts in place and were registered with the Health Professions Council where appropriate. Good clinical practice guidelines were followed at all times.

3.5.5   Funding and Trial Registration

Funding for the research project was provided by the Dunhill Medical Trust. The project was registered on the United Kingdom Clinical Research Network Portfolio (UKCRN), ISRCTN number: 51553998.

3.6 SCREENING AND RECRUITMENT

3.6.1   Initial Screening and Recruitment

Potential participants were screened for inclusion during their inpatient stay from either an acute stroke unit (Norfolk and Norwich University hospital) or a stroke rehabilitation unit (Norfolk Community Health and Care – NHS Norfolk). They were identified for potential inclusion by the clinical staff in conjunction with the researcher. If there were important clinical reasons for the potential participants not

to be approached ie they were distressed, medically unfit to participate or had severe cognitive or communication difficulties which rendered them unable to give informed consent, then they were not approached. Those who were deemed appropriate were asked for their consent by the clinical team to be seen by the researcher. After introducing themselves, their place of work and giving a brief overview of the study, the researcher advised the key factors of the study as depicted in table 3.2 in conjunction with the participant information sheet:

Key Study Factors Communicated to Potential Participants
An explanation of the purpose of the study;
Who had provided ethical approval for the study;
Why they were being asked to participate;
The potential benefits and risks of taking part;
That there was no obligation to participate and that if they withdrew, their usual therapy would not be compromised;
The screening process, making it clear that consent had to be obtained prior to performing this and that they would not be eligible to take part if they did not pass this screening;
The measurements that would be taken and when;
The randomisation process, particularly concerning the potential for not being within the intervention group;
The nature of the intervention;
The duration of the study and the commitment required from the participant;
That all information would be kept confidential and that they would only be identified by a study number;
Who to contact during the study if they had a problem or complaint;
What would happen to the results of the research study;
That they had at least 24 hours to consider if they wanted to be included within the study;
That they could discuss their potential participation with others ie family or clinical staff.

Table 3.2: Key Study Factors Communicated to Potential Participants

Any questions that the potential participant had during this initial session were answered and they were left with the participant information sheet and given at least 24 hours to consider their inclusion. After this period of time, the researcher returned and answered any further questions that the potential participant had. Family members were included if requested by the potential participant or when the researcher felt it was appropriate (with the potential participant's permission). If the potential participant did not wish to be included within the study then they were thanked for their time. If however they wanted to proceed to the next stage of the study they were asked to sign and date a consent form, a copy of which was retained by the participant with the original placed within their medical file. The researcher also retained a copy.

3.6.2 Screening following Recruitment

Once informed consent had been obtained, permission was sought from the participant to assess their upper limb to ensure that they met the eligibility criteria. For those that had sufficient voluntary movement within their hand, a myometer was used to measure their grip strength. A myometer is an instrumented measure of ability to produce composite voluntary muscle contraction with the strength being measured in Newtons. The use of the myometer was initially demonstrated by the researcher and then the participant was asked to grip the myometer three times in succession, first with the non-paretic hand and then with the paretic. The following instructions were given:

"I want you to hold the handle like this and squeeze as hard as you can, when I say squeeze"

"Are you ready? Squeeze", As the patient begins to squeeze say,
"*Harder!....Harder!.....Relax*".

The highest score achieved for the non-paretic and paretic hand were compared and a percentage calculated. Standardization of grip position was achieved by placing a marker (tape) on the myometer and ensuring that the participant placed their hand in the same position during each grip testing. If a comparison with the non-paretic hand was not possible ie due to amputation or pathology, then the 9 hole peg test was used to determine the level of weakness.

The 9 hole peg test is a measure of hand dexterity. Participants picked up from a container 9 wooden dowels (9mm diameter by 32mm long) and then placed them in holes (10mm diameter by 15mm deep) placed 15mm apart in three rows of three holes in a wooden base. The maximum time allowed to complete the test was 50 seconds as most healthy adults complete the test in 18 seconds (Wade, 1992).

For those that had insufficient voluntary movement within their hand precluding an assessment of grip strength to take place, the motricity index (full description within section 3.10.2) was used to assess the paretic and non-paretic upper limbs.

If the participant met the relevant eligibility criteria at this stage (table 3.1), the researcher then progressed to screening for the ability to imitate.

3.6.3 Screening for Ability to Imitate

This took place in a quiet room away from the ward to ensure that concentration and attention could be maximised. The session was videotaped for independent assessment and the participant sat at a table, hips, knees and ankles at approximately 90 degrees, with the head held directly over the pelvis and spine erect (pillows were used to maintain this position if necessary). The forearms were resting comfortably on the table without depression or elevation of the shoulder girdle. The researcher sat alongside the participant on their non-paretic side so that the movement demonstration was performed within the same plane. Prior to commencing the video recording, the researcher allowed a practice demonstration in order to ensure that the participant understood the purpose of the task. The action used in this demonstration did not include those completed during the video recording.

The researcher then explained what was going to happen in the following terms:

"I am going to perform a pantomime action. I will show you three times. I want you to watch me carefully and then copy the action as accurately as you can"

The researcher then demonstrated the pantomime action three times whilst the participant observed with the intent to imitate. Each action lasted for at least five seconds and was separated by a brief gap. The participant then performed the action once with their non-paretic limb. Five different actions were completed as shown in table 3.3. These were chosen as they represent a number of variable upper limb movements that are required to complete every day activities and were

sufficiently different to ensure that robust testing of the ability to imitate was conducted.

List of Pantomime Action
Drawing a vertical line
Bringing a cup to the mouth
Hammering a nail
Turning a page
Unscrewing a lid

Table 3.3: List of Pantomime Actions performed in Video Screening for Ability to Imitate

When the five actions had been completed the videotape was assessed by the primary researcher and an independent assessor not involved in the recruitment of the participant. This was completed using a 3 point scale: 2 = correctly reproduced the action; 1 = incorrectly reproduced the action and 0 = not reproduced (Decety *et al*, 1997). Those who scored a mean of 8/10 or above were considered to have the ability to imitate and proceeded to baseline measures. No discrepancies in scores between the researcher and assessor occurred.

3.7 RANDOMISATION AND ALLOCATION CONCEALMENT

Randomisation gives each participant an equal chance of being assigned to either group. Using a robust randomisation and allocation concealment procedure can decrease the risk of selection bias from occurring (Roberts and Torgerson, 1999). If selection bias were to occur then there is a risk that any outcome realized could find in favour of the intervention giving misleading results (Forder *et al*, 2005).

The randomisation allocation sequence used in the study was computer generated and prepared by a statistician within the university and was held by a third party throughout. The randomisation method used was block randomisation. It is acknowledged that this form of randomisation would not fully conceal all group allocation from the researchers involved in recruitment (up to 50% of group allocation was known to the researcher) and that other methods such as simple

randomisation are more preferable to prevent this potential form of bias from occurring (Schulz, 1995) however, the rationale behind adopting this approach was to ensure that the groups were equal after randomisation, thus maximising the statistical power which was compromised due to the small sample size used within this study.

After obtaining informed consent and baseline measures, a telephone call was made to the third party who held the allocation sequence. On receipt of this telephone call an opaque sealed envelope was opened and the researcher advised of the group allocation which was then reported to the participant. The allocation was concealed from the researcher who was involved in the enrolment and recruitment of participants until the interventions were assigned. Using this method ensured that the researcher who enrolled the participants could not be influenced by such knowledge therefore preventing the potential for bias to occur (Saks and Allsop, 2007).

3.8 BLINDING

Blinding is the term used to describe how various individuals are kept unaware of the allocated intervention throughout a study and ideally the patient, treatment provider and outcome assessor should all be exposed to this procedure (Saks and Allsop, 2007). If blinding does not occur then the research is left open to both performance and measurement bias. This can manifest as a change in behaviour either consciously or subconsciously that can affect the overall outcome (Glasziou *et al*, 2003). The blinding of the participants and researcher within this study was not possible due to the nature of the intervention. All baseline and outcome measures were however, made by an assessor blinded to treatment allocation. This was therefore a single-blinded study.

3.9 THE INTERVENTION

A clear explanation of the interventions applied is necessary to enable the reader to ascertain their appropriateness and to facilitate their replication (Mayer *et al*, 2004). After randomisation occurred, the intervention period commenced. All participants

included within the study received their usual CPT as deemed appropriate by the clinicians. Participants who were discharged from the in-patient unit before the end of the intervention period were followed up at home until they had completed the study.

3.9.1 The Intervention Group

Duration and Dose

Those allocated to the intervention group received OTI+MP therapy for up to one hour per day in addition to their usual CPT, for 15 consecutive working days. This time period was chosen as it was deemed to be achievable within the allocated time-scale for the completion of this research project and sufficient to provide an acceptable level of data to ascertain the potential efficacy of OTI+MP as an adjunct to CPT. The plan was to deliver each treatment session in two 30 minute sessions consisting 6-8 minutes of treatment divided by 2-4 minutes of rest. This time period was chosen through the combination of experimental evidence that found: i) 30 minutes of action observation and motor practice encodes a motor memory in the primary motor cortex of healthy older adults (Celnik *et al*, 2006) and that ii) beneficial effects were found following the use of OTI+MP late after stroke from provision of 90 minutes a day for 18 days (Ertelt *et al*, 2007) and 30 minutes on one day (Celnik *et al*, 2008). Although dose finding was not a pre-requisite of this study, informal opinion was requested regularly from the participant regarding the dose and spacing of OTI+MP. This enabled the daily intensity of the therapy to be adjusted in response to this feedback by adapting it to each participant's ability, whilst striving to maintain a total of one hour per day.

Activities

A minimum of two activities were chosen in conjunction with the participant to be practised during the treatment session. The researcher was able to review these regularly and change them if: i) the participant was able to complete them easily for the full duration of a treatment session; or ii) if the participant showed signs of decreased motivation or requested to change the activity. The specific experimental activities used for the duration of the study are shown in table 3.4. These were chosen as they represent a number of common functional movements that are used in everyday life and which could be tailored to each individual participant's needs based on what functional activities they wanted to re-learn and that they could complete with difficulty, ie cleaning the table requires more gross upper limb movement than transferring money from the table into a pot. This approach also

ensured that each session was meaningful rather than meaningless and represented a goal-directed activity that had been previously learnt, all of which have been shown to increase the accuracy of imitation and stimulation of the mirror neuron system (Grezes *et al*, 1998 and 1999; Buccino *et al*, 2004a; Jarvelainen *et al*, 2004) and result in an increase in corticospinal excitability (Lago *et al*, 2010).

List of Activities
1. **Bringing telephone to ear**
2. **Transferring money/pasta from the table to a pot/pot to table**
3. **Cleaning a table**
4. **Taking a glass/bottle/pot from/placing on a shelf**
5. **Pushing buttons on a telephone**
6. **Bringing cup to mouth**
7. **Turning cards/pages in a newspaper/magazine**
8. **Placing pegs on a washing line**
9. **Pouring water**
10. **Unscrewing/screwing lids from jars/bottles**

Table 3.4: List of Activities used for the Intervention

Delivery of the Intervention

Previous studies have obtained proof of concept for the use of action observation and imitation in stroke survivors late after the event. In these studies the medium used to deliver the action observation was via video film or pictures. This approach was considered however, evidence suggests that this type of presentation may not be as effective as viewing a live human hand which has been found to produce higher levels of activity within the primary motor cortex than watching video films (Jarvelainen *et al*, 2001). Also rehabilitation studies investigating the use of other therapies in early stroke such as constraint-induced movement therapy have suggested that high levels of intensive, repetitive stimulation at this stage may not have the desired effect on brain reorganisation and subsequent upper limb recovery (Dromerick *et al*, 2009). As this was an early phase study aiming to provide

sufficient proof of concept for OTI+MP as a potential adjunct to CPT, it was felt more appropriate to deliver the intervention as described subsequently.

Each participant sat at a table with hips, knees and ankles at approximately 90 degrees, with the head held directly over the pelvis and spine erect (pillows were used to maintain this position if necessary). The forearms were resting comfortably on the table without depression or elevation of the shoulder girdle. The researcher sat alongside the participant on their paretic side so that the movement demonstration was performed within the same plane. This method was chosen to avoid potential confusion that could have arisen if the researcher had sat opposite the participant (ie mirror image) and because the greatest increase in corticospinal excitability has been recorded when the action observed is performed in the same plane as the observer (Maeda *et al*, 2002). The researcher advised the participant to "***watch the movement being performed and to think about copying***" and then demonstrated the activity to be practiced for 1-2 minutes with the participant watching with the intention to imitate. After this time, the participant performed the activity with their paretic limb concurrently with the researcher to the best of their ability for up to 6 minutes. During this period, the researcher adapted their own performance to emphasize the components of the movements that the participant had particular difficulty with. For example, if the participant was attempting to pick up a bottle with the goal of pouring water, but was only able to perform the movement in part (ie only able to supinate their forearm but not extend their fingers sufficiently to grasp the bottle), the researcher would emphasize finger extension and grasping the bottle until the participant was able to accomplish this movement sufficiently to complete the task. This procedure was adopted because research has shown that physically training whilst simultaneously continuing to observe the same movement in the same direction, enhances the encoding of motor memories (Celnik *et al*, 2006; 2008). In terms of fatigue, this was monitored throughout the session with rest periods being taken between activities as deemed necessary either by the participant or the researcher. An example of the delivery of the intervention is shown in Figure 3.3.

a) Participant watches researcher perform the task   b) Participant joins in to the best of their ability

Figure 3.3: Example of the Intervention. Pouring water.

3.9.2 The Control Group

Those allocated to the control group continued to receive their usual CPT only.

3.10 DATA COLLECTION

3.10.1 Baseline Data

Baseline characteristics of participants should be provided to allow the reader to judge how comparable the groups are at the outset of the study and how clinically relevant the results may be in relation to a particular patient (Roberts and Torgerson, 1999).

The following baseline data regarding the population characteristics included within the study were captured; age, gender, days since stroke, paretic side, stroke type and stroke classification (Bamford Scale).

3.10.2 Measurement Battery

It is important that the outcome measures used within a study are clearly described so that they can be replicated in other research studies (Glasziou *et al*, 2008). Using validated instruments increases the quality of a study and also enables the reader to compare their use in similar studies (Clark, 2007).

All participants undertook the measurement battery twice, at baseline and again after the 15 day intervention period. Both of these were performed by an independent assessor who was blinded to group allocation. The outcome measures were:

The Motricity Index (appendix five). The motricity index is a clinical measure of the ability to produce voluntary paretic muscle (strength) (Colin and Wade, 1990). It is an ordinal scale with six levels of measurement within three categories of upper limb function: i) pinch grip (maximum score 33); ii) elbow flexion (maximum score 33) and iii) shoulder abduction (maximum score 33), with a total possible score of 100. A higher score indicates higher levels of strength. It has been widely used in clinical research and is reliable, valid and sensitive to any changes after stroke (Bohannon, 1999; Kwakkel *et al*, 1999). Figure 3.4 depicts two of the voluntary movements performed during the assessment.

Figure 3.4: Components of the Motricity Index Outcome Measure

The Action Research Arm Test (appendix six). This is a test for upper limb function which consists of 19 items, divided into 4 subsections covering: i) grasp (maximum score 18); ii) grip (maximum score 12); iii) pinch (maximum score 18) and iv) gross movement (maximum score 9), with each item graded on a 4-point ordinal scale (0=can perform no part of the test; 1 = performs test partially; 2 = completes test but takes abnormally long time or has great difficulty; 3 = performs test normally) with a total possible score of 57. The test is hierarchical in that if the patient is able to perform the most difficult item in each section, then they need not perform all of the subsequent items within that section. A higher score indicates better function. The action research arm test has high intrarater (*r=0.99*) and retest (*r=0.98*) reliability and validity (Van der Lee *et al*, 2001; Platz *et al*, 2005; Yozbatiran *et al*, 2008) and is widely used within clinical research. Figure 3.5 depicts two functional components tested during the action research arm test.
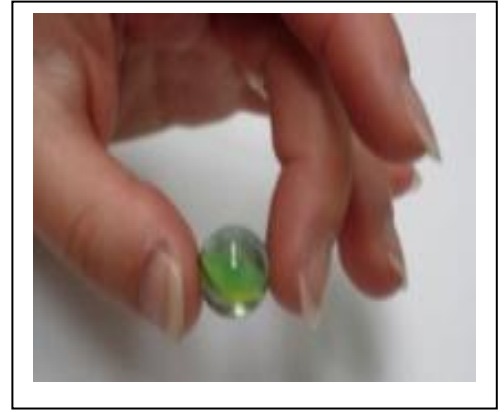
Figure 3.5: Two Components Tested in the Action Research Arm Test Outcome Measure

Also measured were:

Adverse Events (appendix seven). It is important to record adverse events so that the reader can make an informed decision about the impact of the intervention and whether or not it is of an acceptable level (Moher *et al*, 2010). There was a small risk that for some people OTI+MP may have led to an "overuse" syndrome, resulting in upper limb pain and discomfort. This was monitored regularly either verbally or behaviourally (e.g grimacing, postural guarding). If an adverse event was suspected, the participant was re-assessed using the motricity index. If a decrease of at least two measurement levels was detected every day for three days then an adverse event was deemed to have occurred.

CPT Treatment (appendix eight). A flaw in previous published rehabilitation research is that treatment pertaining to CPT is lacking in detail, inhibiting replication and the potential for implementation into clinical practice. All CPT delivered to participants pertaining to upper limb therapy was therefore notated on a treatment schedule by the clinical therapists, who received training regarding its completion from the researcher. The treatment schedule was developed iteratively with clinical therapists (Donaldson *et al*, 2009).

3.11 DATA ANALYSIS

According to Moher *et al*, (2001), it is important that the statistical procedures used within a study are reported fully to enable the reader to analyse whether or not they were suitable and therefore a full description of the statistical procedures applied along with the appropriate justification for their use is detailed below.

The statistical model applied to test the data collected within this study was as follows:

- One participant who was lost to follow up due to a completely random event out of the researcher's control (See results section 4.4 for full details) was excluded from the analysis. This exclusion was deemed acceptable as according to Howell (2009), although this may result in the overall power of the design being reduced, no bias was incurred due to the absence of the data. No other participants were lost to follow up and therefore 16 were included within the analysis.

- An intention-to-treat analysis was applied to all those participants who were randomised in terms of non-adherence to intervention completion. This was used to prevent bias such as an overestimation of clinical effectiveness, which could have occurred if those who had not completed all of the scheduled treatment sessions had been excluded from the final analysis (Lachin JL, 2000; Montori and Guyatt. 2001; Torgerson and Torgerson, 2003).

- Participant characteristics at baseline were depicted using descriptive statistics in the forms of the mean and standard deviation for continuous variables (age and time post stroke) and as a percentage for binary and nominal categorical variables (gender, paretic side, stroke type and stroke classification). No statistical testing of any differences between the groups was performed as according to Moher *et al* (2010), any that occur are the result of chance alone rather than bias and therefore statistically testing to see if the differences occurred by chance, although not incorrect is illogical.

- Inferential statistics were used to test for statistical significance with the significance level being set at ≤*0.05*. The main analysis consisted of two parts; the first a comparison of the test scores before and after treatment (within group change) and the second a comparison of the rehabilitative gain (between group change) which was defined as the difference between the

baseline and outcome scores at the end of the study. The decision to use the change score as a measure of recovery rather than that of the final score was based on past studies that have determined this approach to be a better reflection of the biological recovery process (Prabhakaran *et al*, 2008; Marshal *et al*, 2009). Two-tailed tests were applied to analyse if there was an increase or decrease in outcome measurement scores.

- The inferential statistics of choice were parametric tests in the form of a paired two-tailed t-test (within group) and an independent two-tailed t-test (between group) as these have more power to detect significant changes (Machin *et al*, 2007) however, these make a number of assumptions including that:

  a) the data is normally distributed. This is important as it represents the true population mean, therefore inferring that predictions made from the sample data represent the wider population more accurately than that of asymmetric data;

  b) any variances witnessed are the same throughout the data (homogeneity of variance);

  c) the variables being measured are continuous variables that are at least interval in nature;

  d) the data collected from participants is independent (ie not influenced by the behaviour of other participants) (Field, 2009).

  As the data collected within this study violated assumptions a) (see results section 4.5.1) and c) as the measurement scales used to collect the data were ordinal, it was more appropriate to apply non-parametric tests and therefore the Wilcoxon signed rank two-tailed exact test (within group) and the Mann-Whitney U independent samples two-tailed exact test (between group) were employed.

- Descriptive statistics were also applied to describe the differences found within and between the groups. Due to the use of ordinal measurement scales and non-parametric tests, the most appropriate form of central tendency was the median and the inter-quartile range (Bland, 2000) as the mean and standard deviations should usually only be applied to continuous data (Scott and Mazhindu, 2005). It is acknowledged however, that the mean is the most commonly used form of central tendency and has the advantage of including all data collected (Batavia, 2001) and that it is commonly displayed in the stroke rehabilitation research literature in conjunction with non-parametric testing and the use of ordinal measurement

scales (Page *et al*, 2007; Simmons *et al*, 2008; Dromerick *et al*, 2009; Page *et al*, 2009 etc). Therefore, the primary form of central tendency and variance annotated were the median/interquartile range, with the mean/standard deviation quoted for information only.

- To allow the clinical relevance of the intervention to be judged, effect sizes were calculated (Critical Appraisal Skills Programme, 2002). The effect size was estimated using the following equation (Field, 2009): Effect Size = Z score (taken from the test statistic) divided by the square root of the total number of observations ie r = Z/√N.
The actual size of the effect was then based on the interpretation made by Cohen (1988, 1992) as quoted by Field (2009, p.57) which was as follows:
    a) *r = .10* (small effect)
    b) *r = .30* (medium effect)
    c) *r = .50* (large effect)

- Adverse events were calculated as a percentage of participants within each group who were deemed to have experienced an adverse event as defined in section 3.10.2.

- PASW statistics 18 (SPSS) was used to conduct the statistical analysis of the data collected within this study.

CHAPTER FOUR – THE RESULTS

4.1 INTRODUCTION

Chapter three annotated the methods used to obtain and analyse the data collected during the conduction of this research project, the aims of which were to find out:

1. If there was sufficient proof of concept to justify the use of Observation with intent To Imitate (OTI) + Motor Practice (MP) as an adjunct to conventional physical therapy (CPT) in subsequent dose-finding (Phase I) and efficacy (Phase II) trials;

2. If OTI+MP produced more adverse events than CPT in the paretic upper limb post stroke.

This chapter will now present the results following the analysis of the collected data.

4.2 SCREENING AND RECRUITMENT

Participants were recruited into the study from baseline to outcome (18 consecutive working days) from February 2010 to October 2010 during their inpatient stay from either an acute stroke unit (Norfolk and Norwich University hospital) or a stroke rehabilitation unit (Norfolk Community Health and Care – NHS Norfolk) in Norwich, Norfolk, United Kingdom. Recruitment ceased once the planned timeframe for this phase of the study had been reached (9 months) to allow sufficient time for data analysis and thesis production. Figure 4.1 depicts the Consolidated Standards of Reporting Trials (CONSORT) participant flowchart for the study.

 A total of 255 stroke patients were screened for eligibility with 30 (12%) meeting the criteria. Of those, 17 (57%) gave written informed consent to be included within the study and three (10%) were discharged to either a residential home (n=2) (for which ethical approval was not in place to conduct the study) or to their place of residence outside of the Norfolk area (n=1) before consent could be sought, therefore rendering them "out of area" and unable to participate. The remaining 10 (33%) who were eligible to take part within the study refused to give consent. Although the reason for this refusal was not directly sought, the majority of individuals voluntarily

gave this information, with the main concern being in respect of the potential amount of physical effort required to participate. A total of 17 (57%) were therefore randomised to either the control group (CPT) (n=08) or the intervention group OTI+ MP (n=09).

4.3 PARTICIPANT CHARACTERISTICS AT BASELINE

The baseline characteristics of all participants are shown in table 4.1. In summary, the mean age of the participants was 77.88 (SD 11.72; range 48 to 95 years) with 9 being male and 8 being female. Mean time since stroke onset was 21.35 days (SD 6.20; range 12 to 31 days). In relation to Bamford stroke classification, 10 were partial anterior circulation strokes (PACS), 5 were lacunar strokes (LACS) and two were total anterior circulation strokes (TACS).   In terms of the type of stroke, 11 had experienced ischaemic stroke, four a cerebral haemorrhage and two were undetermined from diagnostic imaging (5 left hemisphere: 12 right hemisphere). Although a lesion could not be detected for these two participants during their routine diagnostic imaging, they were included following confirmation from the stroke physicians that they had experienced a stroke (clinical presentation) and had an intact pre-motor area (Brodmann area 44/45). On average participants within both groups had severe paresis (Based on the motricity score being ≤ 61 points, (Hunter *et al*, 2011)). The only obvious difference between the groups was that there was an imbalance in terms of paretic side within the intervention group.
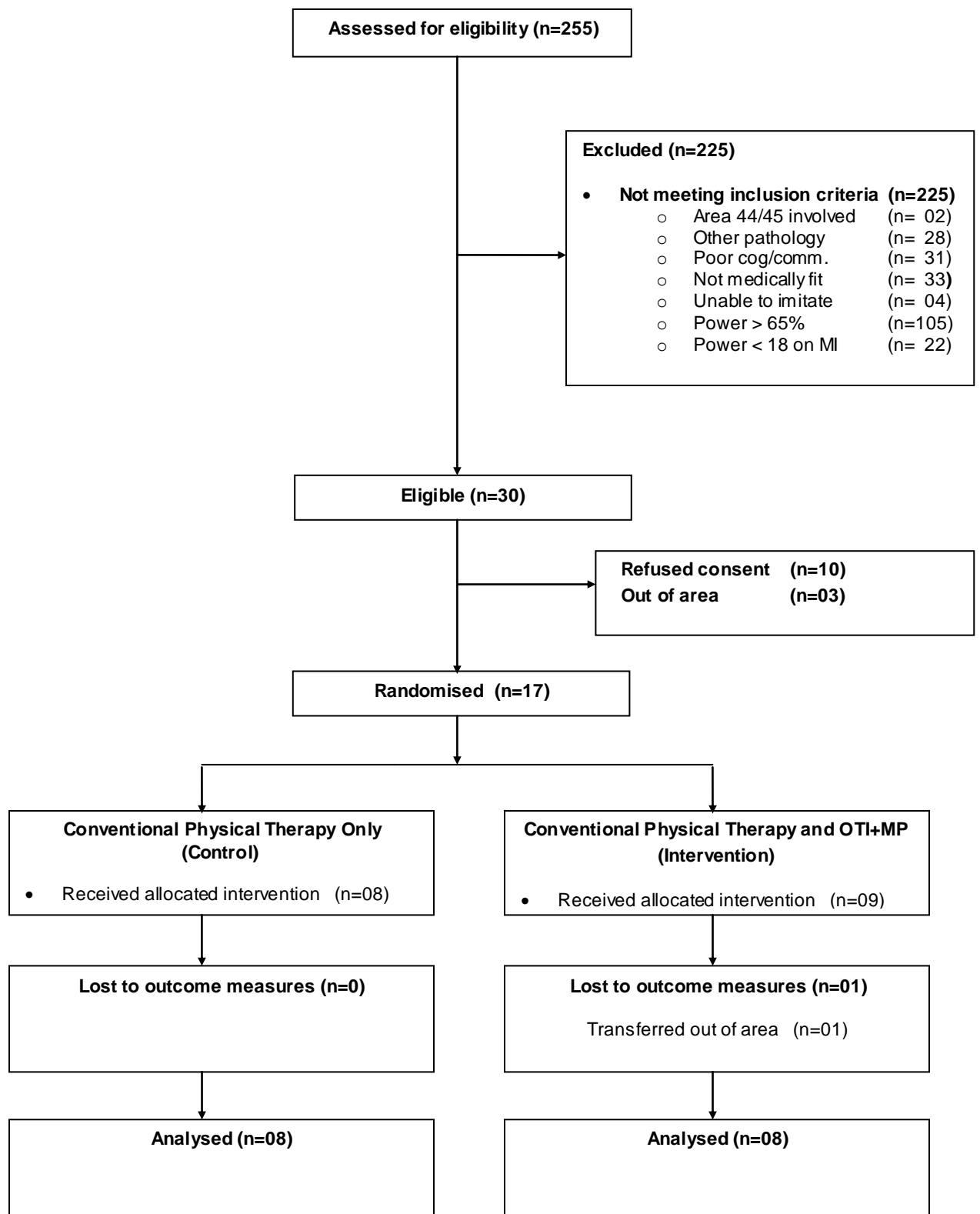
Figure 4.1 : Consolidated Standards of Reporting Trials (CONSORT) Flowchart

	CPT Only (n=08) (Control)	OTI+MP+CPT (n=09) (Intervention)	Total
Age (years) Mean (SD)	75.9 (14.06)	79.07 (9.71)	77.88 (11.72)
Gender (%)			
Male	5 (63%)	4 (44%)	9 (53%)
Female	3 (37%)	5 (66%)	8 (47%)
Days post stroke Mean (SD)	20.25 (5.28)	22.33 (7.09)	21.35 (6.20)
Paretic Side (%)			
Left	4 (50%)	8 (89%)	12 (71%)
Right	4 (50%)	1 (11%)	5 (29%)
Stroke Type (%)			
Ischemic	5 (63%)	6 (66%)	11 (65%)
Hemorrhagic	2 (25%)	2 (22%)	4 (24%)
Unknown	1 (12%)	1 (12%)	2 (11%)
Stroke Classification (%) (Bamford Scale)			
PACS	4 (50%)	6 (66%)	10 (59%)
LACS	3 (37%)	2 (22%)	5 (29%)
TACS	1 (13%)	1 (12%)	2 (12%)
ARAT Baseline Median (IQR)	12.50 (3.00-28.00)	7.00 (3.00-30.75)	7.00 (3.00-28.00)
Mean (SD)	17.38 (17.21)	14.25 (14.50)	15.81 (15.46)
Motricity Baseline Median (IQR)	56.00 (35.25-73.00)	53.50 (47.25-64.75)	53.50 (47.25-71.25)
Mean (SD)	55.13 (20.11)	54.63 (14.29)	54.87 (16.86)

Table 4.1: Participant Characteristics for Each Group at Baseline

4.4 ATTRITION

During the study one participant from the intervention group was unable to complete the outcome measures. This was due to them being discharged to a care home for which ethical approval to administer the intervention was not in place and accordingly the attrition rate for the study was 6%. As this was not due to the intervention, the data for this participant was excluded from the analysis which according to Howell (2009) is an acceptable course of action, thus 16 participants (n=8 control; n=8 intervention) were analysed on an intention to treat basis.

4.5 OUTCOMES

4.5.1 Distribution of Data

As discussed in section 3.11 "Data Analysis" within chapter three, the preferred methods for the testing of statistical significance was to use parametric tests however, a number of assumptions are made regarding the collected data including that of a normal distribution. Before commencing any statistical testing, it was therefore appropriate to assess the distribution of the data collected within this study to ascertain if this assumption was or was not met. This was achieved by assessing the change from baseline to outcome scores for each outcome measure in box plot diagrams as shown in figures 4.2 to 4.3. These clearly show that the data for both measures was skewed and as a consequence, violated the assumption of normality rendering the use of parametric test inappropriate. Non-parametric tests were consequently employed.

4.5.2 Efficacy of the Intervention

Table 4.2 and figures 4.2 and 4.3 illustrate the analysed data for each outcome measure which will now be explained separately.

Effect on Upper Limb Strength

Between baseline and outcome, 7 of the 8 (88%) participants within the control group increased in motricity index scores (range 4 to 21) and one (12%) showed no change. The median net gain between scores was 5.50 points within the group which was statistically significant ($z= -2.371$, *p=0.016*) with a large effect size (*r = 0.59*). In the intervention group, 6 of the 8 (75%) participants increased in motricity

index scores (range 5 to 26) and two (50%) showed no change. The median net gain between scores was 10.50 points within the group which was also statistically significant (z= -2.207, *p=0.031*) with a large effect size (*r = 0.55*) as stated above. In terms of clinically important changes which have been defined as a change of 10 points or more (Simmons *et al*, 2008), 63% (n=5) of participants within the intervention group achieved this compared to 37% (n=3) in the control group. Between the groups however, the median increase in the change scores was 5 points which was not statistically (U = 24.00, z= -0.845, *p=0.425*) or clinically significant, although a small to medium effect size (*r = 0.15*) was evident.
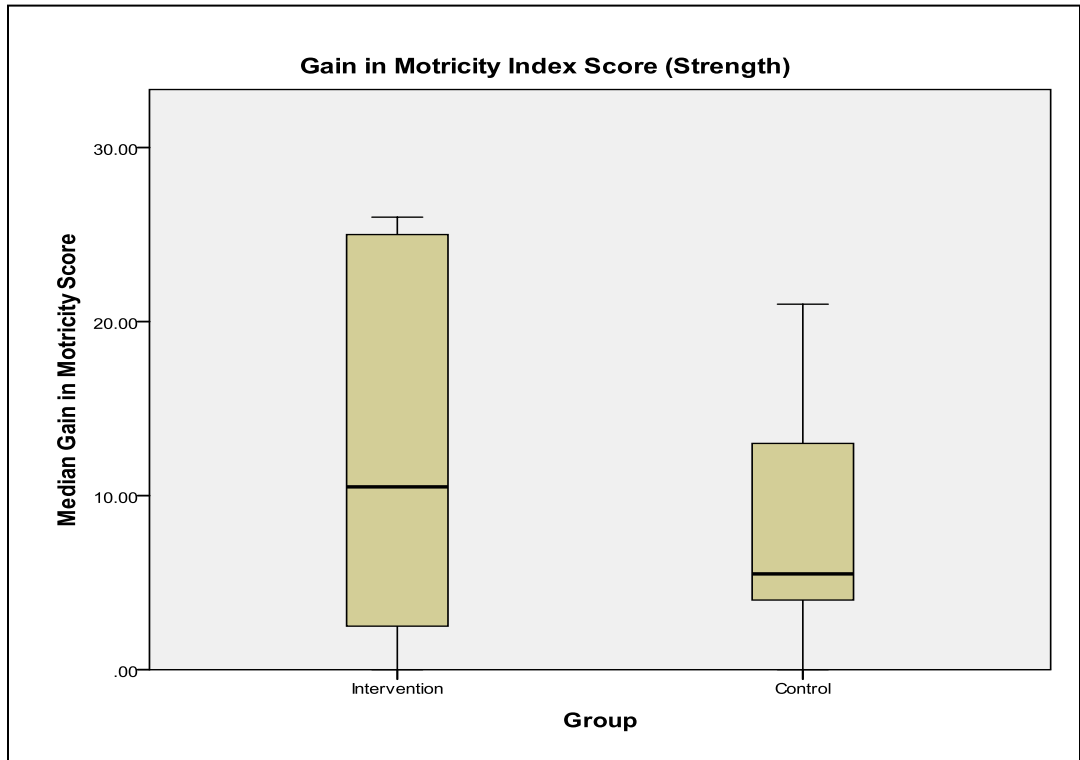
Effect on Upper Limb Function

Between baseline and outcome, 6 of the 8 (75%) participants within the control group increased in action research arm test scores (range 2 to 27) and two (25%) showed no change. The median net gain between scores was 6 points within the group which was statistically significant (z= -2.201, *p=0.031*) with a large effect size (*r = 0.55*). In the intervention group, all 8 (100%) of the participants increased in action research arm test scores (range 1 to 38). The median net gain between scores was 7.50 points within the group which was also statistically significant (z= -2.521, *p=0.008*) with a large effect size (*r = 0.63*). In terms of clinically important changes which have been defined as a change of 5.7 to 6 points or more (Van der Lee *et al*, 2001; Kwakkel *et al*, 2008a; van Delden *et al*, 2009), 63% (n=5) of participants within the intervention group achieved this compared to 50% (n=4) in the control group with both groups witnessing 37% (n=3) of their participants increasing their scores by ≥ 9 points which represents increases in some hand function (Yozbariran *et al*, 2008; Nijland *et al*, 2010). Between the groups however, the median increase in change scores was only 1.5 points which was not statistically (U= 25.50, z= -0.686, *p=0.520*) or clinically significant although a small to medium effect size (*r = 0.12*) was evident.

### 4.5.3 Adverse Events

No adverse events occurred in either group as defined in Chapter 3 "Research Methods" section 3.10.2. One participant in the intervention group was withdrawn from the study early after being deemed medically unfit to continue with the intervention by the clinical team however, as this was not in relation to the intervention itself it was not deemed to be an adverse event.

	CPT Only (Control) (n=08) Within Group Analysis					OTI+MP+CPT (Intervention) (n=08) Within Group Analysis					Between Group Analysis		
	Baseline	Outcome	Within Group Avg Gain	P Value	Effect Size (r)	Baseline	Outcome	Within Group Avg Gain	P Value	Effect Size (r)	Betwn Group Avg Gain	P Value	Effect Size (r)
MI													
Median (IQR)	56.00 (35.25-73.00)	69.00 (51.00-77.00)	+05.50 (04.00-14.50)	0.016	0.59	53.50 (47.25-64.75)	71.50 (55.00-77.00)	+10.50 (01.25-25.50)	0.031	0.55	+05.00	0.425	0.15
Mean (SD)	55.13 (20.11)	63.38 (18.81)	+08.25 (07.03)			54.63 (14.29)	67.38 (11.26)	+12.75 (11.17)			+04.50		
ARAT													
Median (IQR)	12.50 (03.00 - 28.00)	20.50 (03.50-52.50)	+06.00 (0.50-15.75)	0.031	0.55	07.00 (03.00-30.75)	28.50 (06.25-44.50)	+07.50 (03.50-17.75)	0.008	0.63	+01.50	0.520	0.12
Mean (SD)	17.38 (17.21)	26.12 (24.16)	+08.75 (09.51)			14.25 (14.50)	26.38 (18.47)	+12.13 (12.12)			+03.38		

Table 4.2: Outcomes and Estimation for the Motricity Index (MI) and Action Research Arm Test (ARAT)

Figure 4.2: Box Plot Showing the Gain in Upper Limb Strength in the Intervention and Control Groups
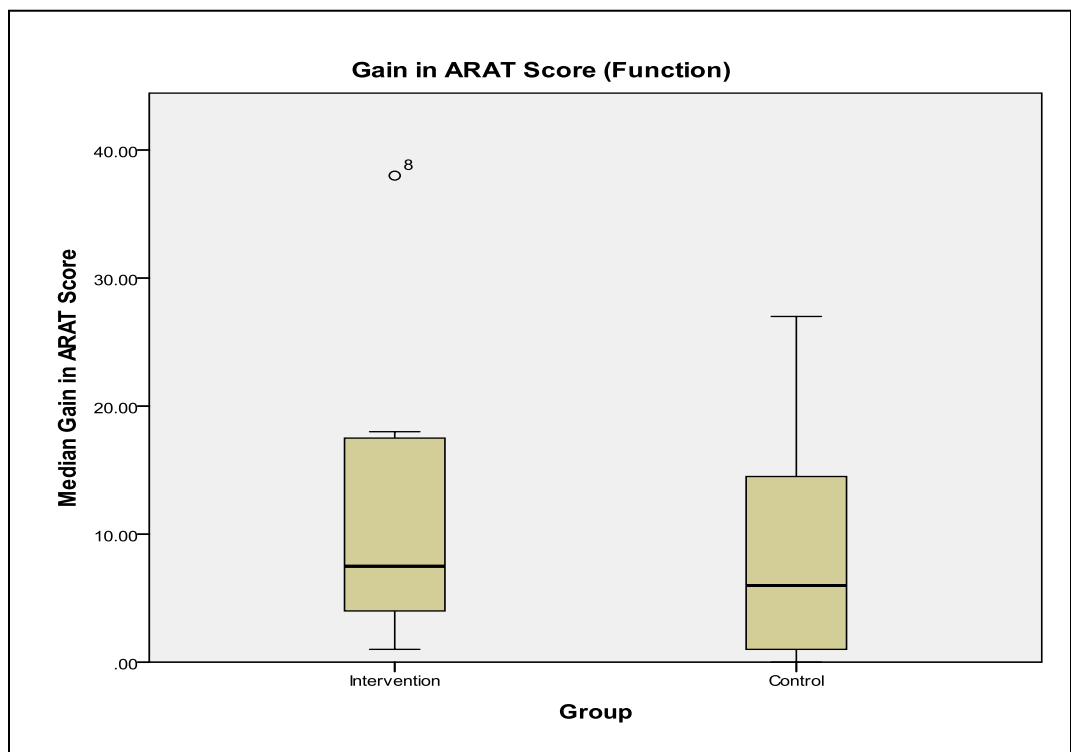
Figure 4.3: Box Plot Showing the Gain in Upper Limb Function in the Intervention and Control Groups

4.5.4 Sample Size for Future Trial

Based on the data collected during this study, the likely sample size required in a future trial to detect a statistically significant difference between the groups is 265 participants per group. This was calculated as follows: The standard deviation of the final Action Research Arm Test score was 21.32. To have 80% power to detect a difference of 5.7 on the Action Research Arm Test (deemed as a clinically significant change (Van der Lee *et al*, 2001)), a sample size of 221 participants per group would be required. As non-parametric tests would be used to analyse the statistical significance due to the Action Research Arm Test being an ordinal scale, it would be pertinent to increase this number by 20% to compensate for the decreased power of such a test to detect a difference (Machin *et al*, 2007). Therefore the final sample size required would be 265 participants per group.

4.6 TREATMENT DOSE AND COMPLIANCE

Although dose finding was not a pre-requisite of this study, it was felt pertinent to present findings regarding the following: i) the amount of therapy delivered within each group and the heterogeneity of response; ii) the type of CPT administered and iii) as this was the first study of its kind to be conducted within stroke patients early after the event, compliance with the intervention.

4.6.1 Dose and Response to Upper Limb Therapy

Table 4.3 shows the amount of therapy administered (hours) and the subsequent response made by each individual in the study. In terms of dose, over the course of the study each participant within the intervention group received a mean of 14.36 hours of therapy involving the upper limb (10.94 hours in respect of OTI+MP only) compared to 3.94 hours in the control group, which equates to a total therapy time per day of 57.3 minutes (43.6 minutes OTI+MP only) and 15.7 minutes respectfully. There was no significant difference in the amount of CPT treatment given to both groups (p = *0.667*), with those in the intervention group receiving a mean of 13.7 minutes per day compared to 15.7 minutes in the control group. In respect of the duration of each intervention session, the original plan of delivering the treatment in two 30 minute parts with a 10 minute rest was not tolerated early on in the study, leading to it being amended to two 20 minute sessions, each separated by a 10 minute rest. Once again however, a number of participants were not able to adhere to these times, requiring more rest ie after each individual activity although others required less rest ie after two activities only. The delivery of the therapy was

therefore ultimately dictated by each participant's own capacity to complete it (determined by the participant in conjunction with the researcher), with the primary aim being to complete at least one hour of therapy (including rest periods) each day. In relation to response to therapy, this was heterogeneous in nature with gains in motricity index scores ranging from 0 to 26 in the intervention group and 0 to 21 in the control group. This heterogeneity was also evident in respect of the action research arm test scores ranging from 1 to 38 in the intervention group and 0 to 27 in the control group.

4.6.2 Type of Conventional Physical Therapy Administered

As stated in the chapter three (Research methods) section 3.10.2, a flaw in previous published rehabilitation research is that treatment pertaining to CPT is lacking in detail, inhibiting replication and the potential for implementation into clinical practice. All of the CPT delivered to participants that involved an element of upper limb treatment was therefore recorded, the results of which are shown in figure 4.4. The four main types of CPT delivered most frequently in both groups consisted of: i) incorporating the upper limb into mobility and balance 23% (control 23%, intervention 22%); ii) facilitation of muscle activity 17% (control 16%, intervention 18%); iii) performing upper limb tasks 14% (control 14%, intervention 15%) and iv) providing education to patient/carer 13% (control 10%, intervention 17%). The types of CPT that were delivered with the least frequency were: i) soft tissue mobilisation 4% (control 5%, intervention 3%); ii) specific sensory input such as tactile or electrical stimulation 3% (control 4%, intervention 2%) and iii) splinting 1% (control 2%, intervention 0%).

4.6.3 Intervention Compliance

The total number of planned treatment sessions for 8 participants was 120 (15 each) however, only 98 (82%) were completed. Six of these were due to no therapist being available due to illness or other absence and consequently are not deemed to be in direct relation to compliance with the intervention. Taking this into account the actual number of completed sessions was 104 (87%) with the number of missed sessions that were either participant or clinically instigated being 16 (13%). The reasons for not participating in these sessions were: i) 13 (81%) due to the participant being unwell and therefore not wishing to complete the intervention and ii) 3 (19%) following a clinical decision not to administer the intervention due to the participant experiencing pain within their upper limb.

Participant Number	Group Allocation	Baseline		Type of Stroke	Amount of Therapy (hours)			Outcome		Post Treatment Gain	
		Motricity	ARAT		CPT	OTI+MP	Total	Motricity	ARAT	Motricity	ARAT
1	Control	24	3	Ischaemic	2.72	N/A	2.72	29	3	5	0
2	Control	30	3	Ischaemic	2.67	N/A	2.67	51	3	21	0
3	Control	78	49	Ischaemic	8.75	N/A	8.75	84	57	6	8
4	Control	51	3	Ischaemic	5.67	N/A	5.67	51	7	0	4
5	Control	73	28	Ischaemic	2.75	N/A	2.75	77	55	4	27
6	Control	73	22	Unknown	1.75	N/A	1.75	77	34	4	12
7	Control	61	28	Haemorrhagic	5.17	N/A	5.17	77	45	16	17
8	Control	51	3	Haemorrhagic	2.00	N/A	2.00	61	5	10	2
Median (IQR)		56 (35.25-73.00)	12.50 (03.00-28.00)		*3.94 (2.41)	N/A	*3.94 (2.41)	69.00 (51.00-77.00)	20.50 (03.50-52.50)	05.50 (04.00-14.50)	06.00 (00.50-15.75)
1	Intervention	29	3	Ischaemic	2.83	13.38	16.21	53	4	24	1
2	Intervention	51	3	Ischaemic	4.58	13.17	17.75	77	20	26	17
3	Intervention	56	32	Ischaemic	2.00	3.57	5.57	66	37	10	5
4	Intervention	46	0	Haemorrhagic	4.50	12.58	17.08	51	3	5	3
5	Intervention	66	35	Ischaemic	2.9	10.22	13.12	77	43	11	8
6	Intervention	77	27	Haemorrhagic	3.75	9.38	13.13	77	45	0	18
7	Intervention	61	6	Ischaemic	3.50	13.82	17.32	61	13	0	7
8	Intervention	51	8	Unknown	3.3	11.42	14.72	77	46	26	38
Median (IQR)		53.50 (47.25-64.75)	07.00 (03.00-30.75)		*3.42 (0.87)	*10.94 (3.37)	*14.36 (3.99)	71.50 (55.00-77.00)	28.50 (06.25-44.50)	10.50 (01.25-25.50)	07.50 (03.50-17.75)

*Mean (Standard Deviation)

Table 4.3: Total Amount of Therapy Administered and Individual Response within the Control and Intervention Groups.
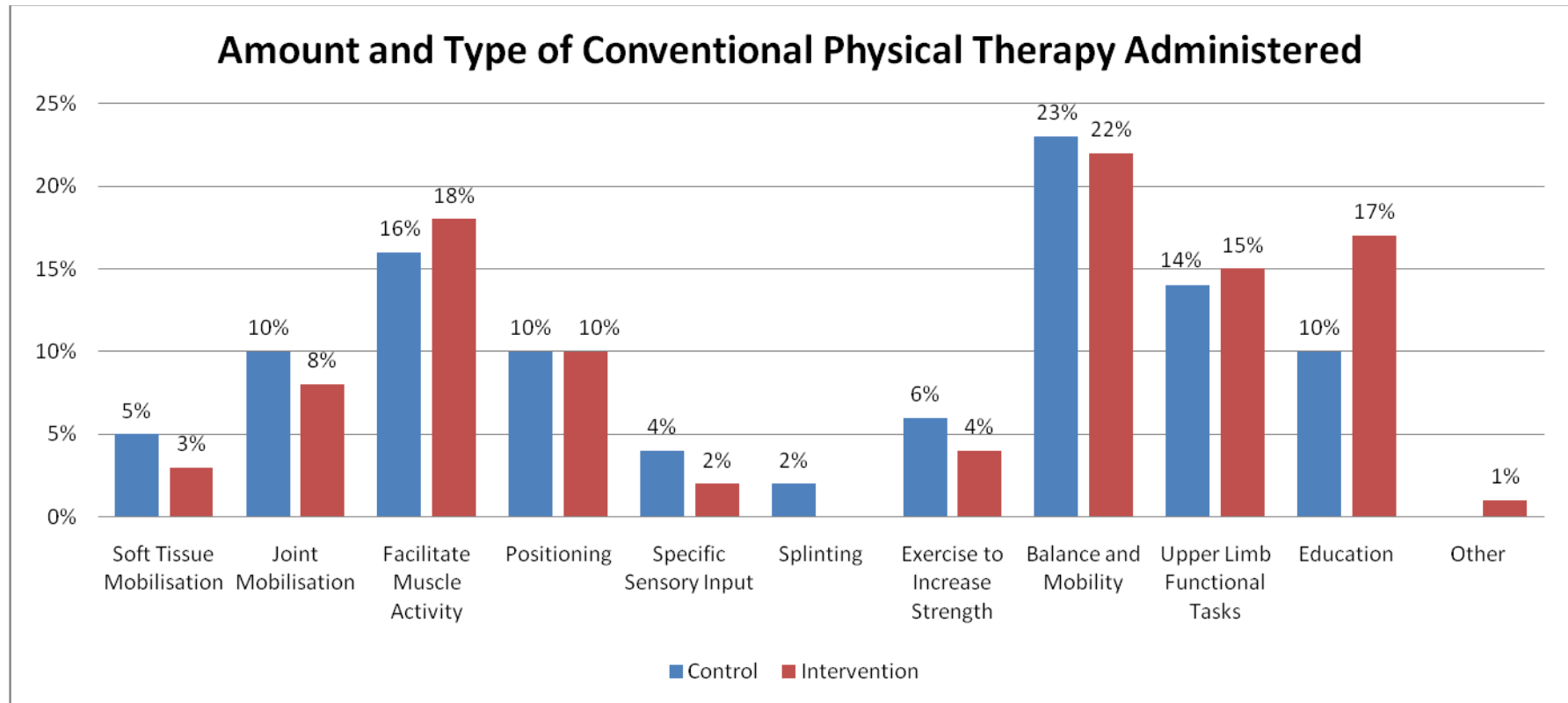
Table 4.4: Amount and Type (percentage of total) of Conventional Physical Therapy Administered to Both Groups during the Study

CHAPTER FIVE – DISCUSSION

5.1 INTRODUCTION

Chapter four of this research thesis described the findings from the data that was collected during the conduction of this research project. This chapter will now present an interpretation of these results in relation to the study aims which were to find out:

1. If there was sufficient proof of concept to justify the use of Observation with intent To Imitate (OTI) + Motor Practice (MP) as an adjunct to conventional physical therapy (CPT) in subsequent dose-finding (Phase I) and efficacy (Phase II) trials;

2. If OTI+MP produced more adverse events than CPT in the paretic upper limb post stroke.

5.2 INTERPRETATION OF THE RESULTS

Over the study period, both the intervention and control groups improved significantly in upper limb strength and function. The addition of OTI+MP to CPT however, did not result in statistically significance improvements compared to CPT alone, although there were more clinically important changes within the intervention group along with a general trend to a greater overall improvement, particularly in terms of gains made in upper limb strength. The treatment received during the intervention appeared to be acceptable to participants with on average 87% of the therapy sessions being completed, with no adverse events being reported in either group. These results differ from those obtained within the chronic stroke population which found statistically significant improvements in favour of such a therapy to improve upper limb recovery (Ertelt *et al*, 2007; Franceschini *et al*, 2010) however, fundamentally these studies did not compare the intervention to CPT and it is possible that had they done so, they would have achieved similar results as have been observed within this study.

The finding that those who received OTI+MP in addition to CPT did not improve in strength and upper limb function significantly more than those receiving CPT alone was surprising. During the study, both groups received similar amounts of CPT per day (13.7 minutes intervention group; 15.7 minutes control group) with those participants within the intervention group receiving on average an extra 44 minutes of therapy (around three times more) per day (10.9 hours over the course of the study) engaging in specific upper limb tasks than those receiving CPT alone. So why didn't those who received more therapy show much greater improvements? One explanation may be that the OTI+MP therapy was too intensive for those within the early stage of stroke. It is acknowledged that this study did not explore directly the effects of intensity on the outcomes of interest however, it is felt pertinent to examine the possible effects that applying OTI+MP, which could be construed as being an intensive repetitive based intervention due to the number of repetitive observations and movements/attempted movements required, had on this population.

Previous research has indicated that the most efficacious changes in brain reorganisation and recovery are witnessed when the therapy received is of an intense, repetitive and meaningful nature (Kwakkel *et al*, 1997; Feys *et al*, 1998; Cramer *et al*, 2002; Hallett *et al*, 2002; Barreca *et al*, 2003; Steultjens *et al*, 2003; Teasell *et al*, 2003; Schaechter, 2004; Van Peppen *et al*, 2004; Pomeroy *et al*, 2005; Buma *et al*, 2010) however, evidence is beginning to emerge within stroke rehabilitation to suggest that the beneficial results witnessed from applying such therapies in chronic stroke are not necessarily replicated in early stroke. In a recent study investigating the application of constraint-induced movement therapy on upper limb function early after stroke (mean post stroke time 9.7 days), Dromerick *et al*, (2009) found that applying a higher intensity of therapy (3 hours of shaping therapy and wearing the constraint mitten for 90% of waking hours) resulted in poorer outcomes at 90 days compared to a lower dose of constraint-induced movement therapy (2 hours of shaping therapy and wearing the constraint mitten for 6 hours) or the equivalent amount of usual standard care. Another study conducted early after stroke (mean post stroke time 14.6 days) that looked at a programme of intense motor training to improve balance found no significant changes compared to those receiving CPT, even though the intervention group received 7.5 hours more physical therapy over the 12 week study period (Askim *et al*, 2010). In a recent systematic review, Cooke *et al*, (2010) concluded that there is currently little

evidence to support the use of increased intensity of therapy, even in those during the early stage of stroke.

The reasons why more significant changes are not seen with extra therapy or on occasions, appear to have a detrimental effect are poorly understood. Studies in rats administered within this period have found that lesion size can increase with intense upper limb therapy resulting in poor recovery (Sharma *et al*, 2006) although no such increase was found in the human brain in the study conducted by Dromerick *et al* (2009). It is known however, that early after stroke during spontaneous recovery a number of changes occur within the brain such as: i) the alleviation of diaschisis due to cerebral shock, where activity gradually returns to uninjured areas of the brain that have connections with the area of injury; ii) the salvation of surrounding penumbral tissue and iii) the commencement of cortical reorganisation (Buccino *et al*, 2006; Buma *et al*, 2010). These changes are believed to be time dependent (Kwakkel *et al*, 2004; Buma *et al*, 2010) and it may therefore be that the biological effects induced by an intensive therapy such as OTI+MP are either negated by/or interfere with the brains spontaneous recovery "healing" process, potentially rendering such a therapy more appropriate for those in the more chronic stage of stroke when this form of recovery has slowed or stopped (Page *et al*, 2007; Cramer, 2008a).

Conversely however, other studies that have been conducted within early stroke have experienced significant improvements in outcomes in response to the use of repetitive based interventions. For example, Winstein *et al* (2004) (mean post stroke time 16.1 days) found large improvements in upper limb function following the administration of 20 hours of task specific repetitive therapy over four - six weeks in comparison to standard care, with Masiero *et al* (2009) having similar findings after the application of 20 hours of Robotic therapy (post stroke time ≤ 1 week). Other studies using therapies based on the same principles have also found either improvements in upper limb recovery or no detrimental effects from their application (Dromerick et al, 2000, Masiero *et al*, 2007; Hesse *et al*, 2008; Kwakkel *et al*, 2008; Harris *et al*, 2009). These results perhaps negate the argument previously presented regarding the potential negative or innate effects that such a therapy may have on spontaneous recovery in early stroke, suggesting that other factors perhaps impacted on the outcomes of this study. One such factor could have been in relation to the level of initial upper limb paresis which in this study on average, was classified as severe.

Severe paresis commonly results in a much slower and poorer recovery of function than those with mild paresis (Kwakkel *et al*, 2003; Cramer, 2008; Jeng *et al*, 2008; Chen *et al*, 2009; Hayward *et al*, 2010; Kwakkel *et al*, 2010). In the same study conducted by Winstein *et al* (2004) as described previously, little change in upper limb function was detected following the application of extra therapy when specifically analysing those with severe paresis, with this finding being concurred in a number of other studies using various therapies based on repetitive based intevention principles (Thrasher *et al*, 2008; Hayward *et al*, 2010). Evidence from a study of rats has shown that brain reorganisation and subsequent upper limb recovery are only induced when around 400 repetitions of an activity are completed in one session (Kleim et al, 2001), which is substantially more than participants within this study would have been able to complete due to a number of them not having the voluntary capacity to do so. Also, in the study by Ertelt *et al* (2007) (the most methodologically robust study investigating the use of action observation and imitation conducted to date) that obtained proof of concept for the use of such a therapy in those with moderate paresis in chronic stroke, a total of 90 minutes of therapy was administered per day over 18 days with the action observation component being a total of 36 minutes. In comparison, the participants in this study who had more severe paresis completed on average 57 minutes of therapy with only 16 minutes being in relation to the action observation of varying activities over 15 days. Evidence suggests that the most dramatic improvements seen after stroke can occur for up to 90 days in those with initially a higher level of paresis (Cramer, 2008) and it may be therefore, that had the participants within this study been subjected to more OTI+MP, possibly in a different format (ie longer durations of action observation before imitation may have primed the motor execution system substantially more, increasing the potential for motor learning) over a longer duration, then more significant gains may have been achieved. This statement is supported by the fact that there were more clinically important changes, along with a general trend to improvement witnessed within the intervention group compared to the control group, with no hindrance or ceasing of recovery being apparent.

The discussion above offers a number of possible reasons why the participants within the intervention group did not experience significantly more upper limb recovery than those within the control group, even though they received a much higher dose of therapy. The exact reasons for this occurrence currently remain unknown rendering future investigation regarding the most appropriate dose,

duration and format of the intervention relevant within this population of stroke survivors.

Although dose, duration and the format of the intervention along with initial severity may have impacted on the results of this study, these may not fully explain the variability in recovery that was witnessed across individuals. Here, large differences in strength and functional gains were made, even in those with very similar scores at baseline indicating that some participants may have benefited more than others following the administration of OTI+MP. Three fundamental reasons for this variance that may be of particular importance to the application of OTI+MP as a therapy are: i) lesion location, ii) corticospinal tract integrity and iii) the instructions used during the delivery of the therapy. These will now be presented below.

As discussed within the introduction section of this thesis, OTI is based on the concepts of action observation and imitation which may rely on the mirror neuron system to facilitate an alternative way of internally accessing the motor execution system, by mapping the observed movement within the observer's motor repetoire, thus priming the body for movement. If the lesion is located within an area in which mirror neurons are believed to reside, then it is logical to assume that the required neuronal outputs postulated to occur during OTI may not be generated. For example, as suggested by Garrison *et al*, (2009) an individual with a subcortical lesion within the internal capsule without motor cortex involvement may benefit more from the application of a therapy based on OTI than an individual with a lesion affecting Brodmann areas 44/45 (an area of the brain thought to contain mirror neurons (Pomeroy *et al*, 2005, Caspers *et al*, 2010). Although this study attempted to control this potential confounder in terms of lesion location by excluding those who did not have an intact Brodmann area 44/45, it has recently been suggested that other areas of the brain involved in motor execution such as the supplementary motor area, cerebellum and dorsal premotor cortex may also contain mirror neurons (Caspers *et al*, 2010). If participants within this study had lesions within these specific areas, then it is perhaps possible that they did not respond to the application of OTI as one may have expected.

The second reason that may explain some of the variance in response to OTI+MP is integrity of the corticospinal tract. The corticospinal tract is the most important neural pathway in the control of voluntary movement (Jang *et al*, 2009; Riley, 2011).

Complete injury to the lateral corticospinal tract results in individuals being unable to perform fine distal activities, with partial injury resulting in weakness and poor precision (Jankowska and Edgley, 2006). Research is beginning to emerge to suggest that corticospinal tract integrity (Stinear *et al*, 2007; Carter *et al*, 2010; Lindenberg *et al*, 2010) may be a primary reason for the variance in treatment outcomes commonly seen in stroke rehabilitation studies investigating physical therapy interventions (Marshall *et al*, 2009: Zhu *et al*, 2010). Studies in both the chronic (Stinear *et al*, 2007; Sterr *et al*, 2010; Stinear, 2010; Zhu *et al*, 2010) and acute (Jang *et al*, 2008; Radlinska *et al*, 2010) phases of stroke have confirmed that this may be a more important predictor for recovery than initial behavioural status alone (such as initial upper limb severity) which is only believed to account for approximately 30-50% of the variance seen (Marshall *et al*, 2009). As with other physical therapies, OTI+MP relies on sufficient corticospinal tract integrity to facilitate functional recovery and this may be why some individuals recovered better than others.

The third area that could be important in the delivery of a therapy using OTI+MP is in respect of the instructions given. In a recent transcranial magnetic stimulation study conducted in healthy adults, Hetu *et al* (2010) concluded that attention might be a significant factor in determining how an individual produces muscle-specific motor patterns (believed to preferentially modify excitability within the primary motor cortex) within their upper limb during the action observation of complex everyday movements, having found significant variability between participants. Here it was suggested that the ability to map the observed movements within an individual's own motor repertoire may have differed depending on whether their attention was focused on the body part involved in the movement or the end goal. The priming effect modulated from observation is believed to be most proficient when attention is focused on the body part involved in the movement (Hetu *et al,* 2010). In this study, as in those conducted within the chronic stroke population (Ertelt *et al*, 2007; Franceschini *et al*, 2010), no instructions were given specifically in relation to these parameters, rendering the maximisation of producing a muscle-specific motor pattern unknown which may require consideration in any subsequent research studies utilising action observation. It is of course possible that the ability to produce such a pattern is compromised in some stroke survivors depending on the location of their lesion/corticospinal tract integrity as previously inferred however, in

those that retain this ability, the delivery of the correct instructions could be of paramount importance to maximise the effects of OTI+MP.

Other areas that perhaps also impacted on the results of this study and that may need to be controlled/taken into consideration in future studies include: i) psychological status eg. depression and/or motivation (West *et al*, 2010); ii) psychosocial issues eg. support networks; medication (Wolf *et al*, 2007); iii) motor skills prior to stroke (Richards *et al*, 2008) and iv) age (Cramer, 2008a). Taken together, any one/a combination of the factors discussed may explain why some individuals appeared to benefit from OTI+MP more than others.

One further area that perhaps impacted on the results was the design of the actual study. There are many strengths regarding this that suggest the results obtained are reliable including: i) a robust randomisation and allocation concealment process; ii) blinding of outcome assessors; iii) the application of the intention to treat principle; iv) using a standardised approach to delivering the intervention v) assessing for the ability to imitate prior to inclusion and vi) delivery of the therapy manually by a therapist enabling rapid adjustment as required. The recording of the type and amount of CPT can also be regarded as positive. Had this not been instigated, a discussion surrounding therapy dose would have been impossible as would the duplication of the study should it be required. These factors compare favourably to the previous two studies conducted within this field (Ertelt *et al*, 2007; Franceschini *et al*, 2010), which as discussed within chapter two, section 2.3.4, appeared to be at a high risk of bias due to their study designs and/or unclear annotation.

As well as potential strengths there were however, a number of limitations to the design that additionally require discussion. The use of block randomisation was not optimal as this may have increased the risk of bias occurring when on occasions, up to 50% of the group allocation could be identified by the researcher involved in recruitment. Additionally, bias may have been introduced due to the nature of the study, in which it was not possible to blind the participants, clinical colleagues or the researcher to group allocation. It is therefore likely that participants who received the OTI+MP were more motivated to complete their therapy than those within the control group. A further limitation to the study design is in relation to the outcome measures applied. Although both the motricity index and action research arm test are widely used in clinical research and are believed to be reliable and valid

measures (Bohannon, 1999; Kwakkel *et al*, 1999; Van der Lee *et al*, 2001; Platz *et al*, 2005; Yozbatiran *et al*, 2007), it is possible that they may not have been sensitive enough to have detected small and specific changes in strength and functional gain that may have been crucial in quantifying the level of upper limb recovery made within this specific population. It is known that this issue is likely to affect a number of measures used to ascertain the level of upper limb recovery including the action research arm test (Murphy *et al*, 2011), which is also not designed to differentiate between *true* upper limb recovery and compensation, a potentially important consideration within stroke rehabilitation. The inability to standardize the measures between locations (ie between the inpatient setting and participant's homes if discharged) could additionally have attributed to the results. Finally, and perhaps the most influential limitation to the study design was in relation to the sample size recruited. Here, it is acknowledged that due to employing such a small sample size, it was unlikely that the study was sufficiently powered to have detected a statistically significant difference between the groups (Blowers *et al*, 2006).

Future studies should where possible, put in place the necessary procedures to control for such limitations as described above. For example, having a sufficiently powered sample size would negate the use of such a randomisation procedure as was used within this study. Also, to decrease the risk of performance bias from occurring where individuals may consciously or subconsciously change their behaviour when receiving/providing treatment (Glasziou *et al*, 2003), the use of a placebo or sham therapy/condition should be considered. Such a condition was adopted in the study conducted by Ertelt *et al* (2007), where geometric shapes/symbols rather than overt movement were used when testing the effects of OTI in isolation, effectively blinding the participants to this aspect of the intervention. It may therefore be possible to utilise this method of blinding in future studies investigating the effects of OTI in isolation however, it is acknowledged that providing an adequate placebo/sham condition and therefore blinding participants/researchers specifically to physical therapy delivery (ie. motor practice) is inherently difficult (Moseley *et al,* 2002).

CHAPTER SIX – CONCLUSION

6.1 INTRODUCTION

Chapter five of this research thesis discussed the results that were obtained following the completion of the empirical study. This chapter will now summarize as a whole, the findings discovered during the conduction of this research project in relation to the aims of the empirical research study and the **overall project aim** which were:

6.1.1 Study Aims
To find out:

1. If there was sufficient proof of concept to justify the use of Observation with intent To Imitate (OTI) + Motor Practice (MP) as an adjunct to conventional physical therapy (CPT) in subsequent dose-finding (Phase I) and efficacy (Phase II) trials;

2. If OTI+MP produced more adverse events than CPT in the paretic upper limb in people post stroke.

6.1.2 Overall Aim

To increase/add to the current knowledge base surrounding the use of action observation and imitation as a potential therapy within stroke rehabilitation, through the conduction of a literature review and subsequent empirical research study.

This chapter will also meet **objective three** of this research project which was:

> *To formulate recommendations (if applicable) for the clinical use/future research studies of OTI+MP as a therapy in stroke rehabilitation.*

To ensure that the conclusion is comprehensive, it will commence with a general synopsis revisiting the reasons why new therapies are required within stroke rehabilitation and why one based on action observation and imitation might be suitable. This will then be followed by a summary of the findings obtained from the literature review and empirical research study and finally, future directions and recommendations will be annotated.

6.2 SUMMARY/RECOMMENDATIONS

Stroke is the leading cause of disability within the United Kingdom and the United States of America leading to a loss of independence and a reduction in the quality of life of stroke survivors, as well as placing a considerable economic burden on society. Upper limb paresis is one of the most common forms of disability to be experienced, with a significant number of stroke survivors continuing to suffer even after receiving traditional physical therapy. With life expectancy and advances in medicine continuing to increase, this burden is expected to rise exponentially. The relatively recent increase in knowledge surrounding brain reorganisation after stroke nevertheless, has fostered researchers with an exciting opportunity to develop new therapies that have the ability to have a direct impact on facilitating reorganisation and improving subsequent upper limb recovery. This research is at an early stage with the exact mechanisms of brain reorganisation as yet not clearly elucidated however, it is believed that therapies that are repetitive, intensive and meaningful may lead to efficacious reorganisation. In view of this a number of new therapies based on these principles such as constraint-induced movement therapy and robotics have been developed, both of which have shown promising signs that they may be able to improve upper limb recovery after stroke. These therapies are not however, always appropriate for, or accessible by all stroke survivors such as those with more severe paresis who may not have enough voluntary movement to enable them to participate within such therapies. New therapies are therefore needed to assist this population.

One such therapy that has been suggested is OTI+MP which is based on the concepts of action observation and imitation. OTI+MP has a strong neurophysiological basis with studies from healthy individuals revealing that it may be able to access the motor execution system and prime the muscles for movement, even in the absence of the ability to voluntarily move the upper limb. Studies applying similar therapies in other areas of rehabilitation such as Parkinsons disease, aphasia and following orthopaedic surgery have found improvements in performance and function. In terms of rehabilitation of the paretic upper limb after stroke, a therapy such as OTI+MP has been found to increase function of the moderately paretic upper limb in chronic stroke more than MP alone. The results from the studies conducted within chronic stroke along with the

neurophysiological studies within the healthy population suggested that OTI+MP may be a feasible addition to augment CPT.

The results obtained from the empirical research study conducted as part of this research project however, showed that the addition of OTI+MP to CPT did not significantly improve strength and upper limb function in the more severely paretic upper limb early after stroke anymore than CPT alone. It is possible that this finding may have been confounded by a large number of factors as discussed within chapter five which had they been controlled sufficiently, could have resulted in a different outcome. Nevertheless, despite the potential impact of these factors, a number of promising discoveries were made regarding the potential use of OTI+MP in early stroke including; i) a general trend to greater improvements and more clinically important changes within the intervention group, particularly in terms of gains made in upper limb strength; ii) anecdotal evidence of the acceptability of the intervention to stroke survivors; iii) no occurrence of adverse events; iv) that early after stroke, individuals are able to tolerate on average around 45 minutes of this type of therapy; v) that OTI+MP is likely to benefit some stroke survivors more than others and vi) the feasibility of the trial design. All of these findings support the need for further early phase studies investigating the use of OTI+MP within early stroke prior to progressing to a larger phase II study which does not appear to be warranted at this stage. The basis for these future early phase studies, which will then along with the results obtained from this study inform the design of a phase II efficacy trial in preparation for a subsequent phase III effectiveness trial, should be designed in the first instance to answer the following two research questions:

1. Does the addition of OTI to MP improve recovery in the moderate to severe paretic upper limb early after stroke more than OTI or MP alone?
2. How does lesion location and/or CST integrity impact on an individual's response to OTI+MP in the early stages of stroke?

Although the study conducted as part of this research project has indicated that OTI+MP as a "prime and practice" package may potentially improve upper limb strength and function early after stroke, the most efficacious format of the therapy and whether or not it augments MP has yet to be established within this population, unlike in chronic stroke where it has been proven that the addition of OTI to MP is beneficial. This is of particular importance in relation to treatment response as it

may be that OTI has a different effect on those early after stroke due to the spontaneous recovery that is known to occur at this stage, which has usually ceased late after stroke. As this possible effect is currently unknown and the potential for recovery after stroke could be attributed to more neurophysiological parameters such as lesion location/corticospinal tract integrity as well as behavioural ones (ie initial severity of paresis that was used within this study), it would be pertinent to incorporate the measurement of such parameters in any future studies to enable those who are most likely to benefit from the therapy to be identified. This could be achieved by stratifying participants according to lesion location or baseline white matter tract integrity or by conducting studies in more homogenous populations, for example in those with subcortical stroke only, for which the potential impact of damage to areas of the brain thought to contain mirror neurons may be negligible. Once those who are most likely to benefit have been identified, further studies investigating the most appropriate dose could be instigated. It would also be necessary to control as many other potential confounding factors as possible during all studies, such as ensuring that the sample size recruited was sufficiently powered/outcome measure used were sensitive enough to detect any significant changes, therefore enabling the robustness of the results to be maximised.

In summary, both the literature review and early phase empirical study conducted as part of this research project have established that there is insufficient evidence at this stage to: i) support the use of OTI+MP as an adjunct to CPT early after stroke within clinical practice and ii) to recommend progression to larger phase II clinical trials. There were however a number of promising findings made during this study in respect of OTI+MP and therefore, it is felt that further early phase studies based on the questions posed and principles discussed above should be considered, to provide a clearer view as to whether or not OTI+MP has the potential to be an efficacious adjunct to CPT early after stroke.

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20 November 2008

Professor Valerie Pomeroy
Professor of Neurorehabilitation
University of East Anglia
The Queen's Building
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Norwich
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Dear Professor Pomeroy

Full title of study: **Observation with intent to imitate (OTI) combined with motor practice to enhance upper limb recovery early after stroke: proof-of-concept trial**

REC reference number: **08/H0306/71**

Thank you for your letter of 22 October 2008, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Please accept my apologies for the delay in replying to you, but the Committee requested further clarification on the indemnity arrangements from Sue Steel. This has now been received and considered by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements.

This Research Ethics Committee is an advisory committee to East of England Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

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East Norfolk and Waveney Research Governance Committee **NHS**

Professor Valerie Pomeroy
Faculty of Health
University of East Anglia
Norwich
NR4 7TJ

03 December 2008

Please reply to: Research Governance Committee Office
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Dear Professor Pomeroy

Re: **2008MFE05L (136-09-08) Observation with intent to imitate (OTI) combined with motor practice to enhance upper limb recovery early after stroke: proof of concept trial.**

Following confirmation of a favourable Ethical opinion I am pleased to confirm that your project has been given full approval from the East Norfolk and Waveney Research Governance Committee and Research Management Team and you may start your research.

Please note that this approval applies to the following sites:
- Norfolk & Norwich University Hospitals NHS Foundation Trust
- NHS Norfolk
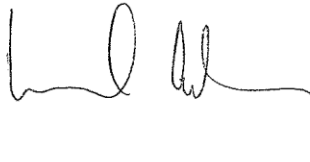
I have enclosed two copies of the Standard Terms and Conditions of Approval. Please sign and return one copy to the Research Governance Committee office. Failure to return the standard terms and conditions may affect the conditions of approval.

Please note, under the agreed standard terms and conditions of approval you must inform this Committee of any proposed changes to this study and to keep the Committee updated on progress.

If you have any queries regarding this or any other study please contact Julie Dawson, Research Governance Administrator, at the above address. Please note, your reference number is **2008MFE05L (136-09-08)** and this should be quoted on all correspondence.

The Committee would like to take this opportunity to wish you every success with this project.

Yours sincerely

Dr Richard Reading
Chair
Consultant Paediatrician – NHS Norfolk

Enc

East Norfolk & Waveney Research Governance Committee – a partnership between:
Norfolk & Norwich University Hospitals NHS Foundation Trust.   NHS Norfolk
Norfolk & Waveney Mental Health NHS Foundation Trust.   James Paget University Hospitals NHS Foundation Trust.

NHS
Norfolk

Participant Information Sheet

Study Title:
Observation with intent To Imitate (OTI) combined with Motor Practice (MP) to enhance upper limb recovery early after stroke: Proof-of-concept trial (Protocol, version 3)

Short title; Observation with intent to imitate to enhance motor recovery after stroke: proof-of-concept.

You are invited to take part in a research study. Before you decide whether you would like to take part you need to understand why the research is being done and what would be involved. Please take time to read the following information carefully. Talk to others about the study if you wish. If you have any questions or would like further information there are some contact numbers at the back of the information pack.

- Part 1 describes the purpose of this study and what will happen if you decide to take part.

- Part 2 gives detailed information about the conduct of this study

Part 1

What is the purpose of this study?

Weakness in the arm and hand is common after stroke. Some treatments may be beneficial but these require you to have sufficient movement in your arm to be able to repeat movements many times. If you have substantial weakness you will find this difficult.

1

What is the purpose of this study?

The aim of this study is to find out whether a new therapy is better than those we already use. The new therapy is called "observation with intent To Imitate and Motor Practice" (OTI + MP).
We will test whether OTI + MP helps you recover the ability to do every day activities including brush your teeth, doing up buttons and making a hot drink with your stroke arm.

OTI consists of watching a therapist doing an activity such as picking up a cup, and then practicing the same activity as best as you can using your stroke arm.

We need to find out whether the new therapy may help people. The people we want to help have substantial weakness in their arm. The weakness is caused by the stroke. Our aim is to help people regain enough movement to participate in more intense therapy and functional activity.

Why have I been invited?

You have been chosen because you have had a stroke within the last 31 days which has resulted in substantial weakness of your arm. You are still having difficulties using it in normal activities. You had no difficulties previously in using your arm or hand before your stroke. You will be one of 24 participants in this study.

Do I have to take part?

No. It is up to you to decide. Your participation in the research study is entirely voluntary. One of the research team (see photographs on page 4) will describe the study to you. You will be given this information sheet.

If you decide to take part you will be asked to sign a consent form to show you have agreed to take part.

You are free to withdraw from the study at any time and you do not have to give a reason. Whether you take part or not, will not affect any of the treatment and care you receive.

If you take part in the study you will continue to receive your routine therapy.

2

What will happen if I decide to take part?

Once you are happy that you want to take part in the study, one of the research team will ask you to sign a consent form. This will usually happen at least 24hours after you have received the information.

Once you have given consent one of the research team will determine whether you are suitable to participate in the study.
In order to do this we will:

- Measure the strength of your grip of your stroke hand;

- Check that you have no other difficulties using your stroke arm other than those caused by the stroke;

- Determine whether you are able to observe a movement and mimic this activity with your unaffected arm.
  To do this we will ask you to watch an arm movement performed by the researcher and then ask you to copy it with your unaffected arm. This will be repeated using 5 activities. This assessment will be videoed and saved on a computer so that another member of the research team can score the accuracy of the imitated movement.

If you are not suitable to participate in the study, you will be told by the research team and you will not be asked to take any further part in the study. Regardless of this decision, you will continue to receive your routine therapy.

3
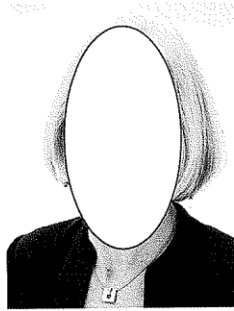
The Research Team

Professor

Research Therapist

Research Therapist

Research Therapist

Research Associate
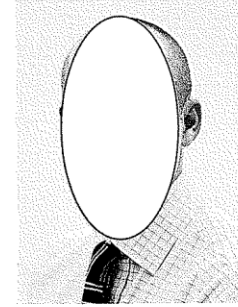
Research Technician

The research will take place in the hospital.
However if you return home before your involvement in the study is finished we may ask if we can visit you at home to complete the study.

4

Initial measurement of your arm

If you are suitable to participate in the study some measurements will need to be taken to find out which activities you are finding difficult and how much strength you have in your arm.

You will be asked to complete a number of small tasks which will then be repeated at the end of the study. This will include measuring the strength in your stroke arm and hand and your ability to pick up a number of different shaped items.

These will take approximately 30-40 minutes.

After the first assessment all participants will be divided into 2 groups at random. One group will receive the additional therapy, one group will not. You therefore have a 50% chance of receiving OTI + MP.

- Group 1 (control group) will not receive additional therapy but continue with their routine therapy.

- Group 2 (treatment group) will receive the OTI + MP in addition to their routine therapy.

Random allocation is important to ensure that recovery in group 2 is not just due to routine therapy.

You will be identified by a number. None of your personal details are given. A researcher will find out which group you have been allocated to by a telephone call.

Can I choose which group I get allocated?

No. In order to find out whether this treatment is effective or not participants have to be randomly allocated to either of the groups. The researcher responsible for taking the measurements at the beginning and end of the study will not know who was in each group and therefore will not be able to influence the findings in any way. This is called a blind trial. You must not tell this researcher which group you are in. This means not telling him or her anything about your treatment.

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Group 1 - Control Group

If you are in the control group you will receive your routine physiotherapy.
You will not receive the new therapy (OTI + MP)
You will still be invited for the initial and final measures

Group 2 - Treatment group

If you are in the treatment group you will receive the new therapy (OTI + MP), on a daily basis for the next 15 working days. A researcher will visit you for the therapy sessions, which will take 60 minutes. If you get tired the researcher will give you the rest you need during the treatment session.

What does OTI + MP involve? What will I have to do?

You will sit alongside the researcher and watch them carry out an activity for 1-2 minutes. Then for 4-6 minutes you will do the same activity as the researcher and they will continue to do it at the same time as you.
You may practice up to 6 different activities in one session.

Example of OTI + MP therapy. Activity: Pouring water from a jug
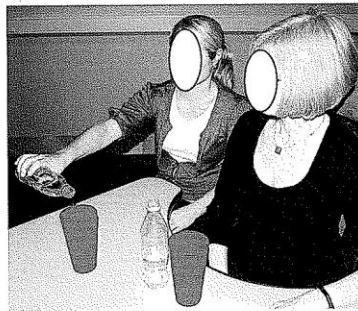
a) You watch the therapist do the activity.
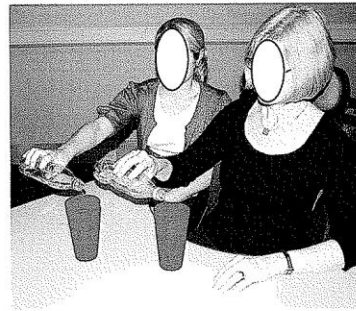
b) You then practice the same activity with the therapist as best as you can using your stroke arm.

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Examples of activities:
- Picking up a cup
- Turning over cards/magazine/newspaper
- Cleaning a table
- Unscrewing lids from jars/bottles
- Pouring water

Activities will be chosen deciding on what you find difficult and what you want to improve. We can make activities easier or more difficult as your ability to move changes.

Final Measures
After the intervention period (15 week days) both groups will see the researcher again where he/she will re-assess your hand and arm doing the same measures as before.

You will be involved in the research for between 3 and 4 weeks.

7

Diagram to show the procedure for the study

A member of the Clinical Team will have approached you to determine whether you agree to be approached by the research team

↓

The study will be explained by a member of the research team. You will be given an information sheet. You will have at least 24 hrs to decide if you want to take part in the study

↓

If you want to be in the study you will sign the consent form with a researcher

↓

You will be assessed to see if you can be included in the study

↓

All participants - Day 1
A researcher will measure:
- Your grip and arm strength
- Find out what activities you find difficult

↓

All participants – Day 2
You will be told which group you have been allocated to:
1. Control group
OR
2. Treatment group

Treatment group - (day 3-17) You will receive 15 days of OTI + MP therapy for up to 60 minutes a day and also continue routine therapy	**Control group - (day 3–17)** You will continue your routine therapy

All participants – day 18
A researcher will re-assess your arm using the same measures as day 1   8

Expenses

The study will take place within the hospital and therefore there will be no travel expenses. If you return home during the study we may ask to visit you at home.

You will not be out of pocket if you take part in the study.

Are there any possible risks with this study?

There is a small risk that you may experience some pain or discomfort if you overwork your arm in therapy. This will be closely monitored. Rest periods can be given more often and the time of therapy can be altered should discomfort occur. Therapy can be stopped at any time. If you want to stop being involved you just tell us.

What are the possible benefits of taking part in the study?

We do not know if the therapy is effective, which is why you receive OTI + MP in addition to your routine therapy. Previous studies have found that OTI + MP might help people in the later stages of stroke recovery (at 6 months after stroke).

9

What happens when the study stops?

This is the first study of OTI + MP in the first month after stroke. The results of this study will not be strong enough to tell us whether or not OTI + MP definitely helps recovery. The results will tell us whether it is worth doing further research. It would therefore not be right to continue with OTI + MP after this study stops.

Involvement in the study will not affect any routine therapy or follow up appointments.

What if there is a problem?

If you have any complaint about the way you have been dealt with or any harm is caused during the study this will be addressed. Detailed information relating to this is outlined in part 2.
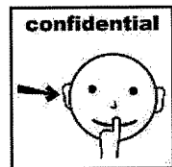
Will my taking part in the study be kept confidential?

Yes, all the information about you and your participation in the study will be kept strictly confidential. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in part 2.

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This completes part 1 of the information sheet.
If this information interests you and you are considering participation, please continue to read additional information in part 2 before making any decision.

If you have any queries you can contact Tracy Cowles or Valerie Pomeroy:

Contact details:

Research Physiotherapist		Chief Investigator
The Queens Building University of East Anglia Norwich NR4 7TJ		The Queens Building University of East Anglia Norwich NR4 7TJ
@uea.ac.uk		@uea.ac.uk
01603 59****		01603 59****

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Part 2
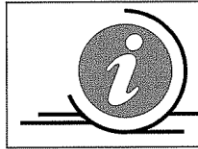
What happens if new information about the research therapy comes along?

Sometimes in research, new things are found out about new therapies. Very few studies have been done about this therapy (OTI) and this study is to find evidence to justify a larger study. If however, new information is published then you will be told.

What happens if I no longer wish to continue with the study?

You may withdraw from the study at any time without giving a reason. If you withdraw from the study, we will need to use the data collected up to your withdrawal.

Withdrawal will not affect your care or treatment.

complain

What if there is a problem or something goes wrong?

If you have any concerns about any aspect of this study, you should first contact Tracy Cowles or Professor Pomeroy. They will do their best to answer your questions or resolve the problem (contact details given at end of part 1 of this information sheet).

If you are still unhappy or wish to make a formal complaint you may do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

Alternatively you could seek advice or report a complaint to the Patient Advice and Liaison Service at Norfolk and Norwich University Hospital NHS Trust, 01603 289035 or email PALS@nnuh.nhs.uk

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What if there is a problem or something goes wrong?

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements.

If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation against the University of East Anglia, but you may have to pay your legal costs.

The normal National Health Service complaints mechanisms will still be available to you.

Will anyone else know I am doing this?

The research team will liaise with the medical team and clinical therapists. They will need to ensure you are well enough to participate and ensure that they know when you are taken off the ward for measures or therapy sessions.

If the research team are concerned at any time about your health during your participation in this study they will report these concerns to the clinical team
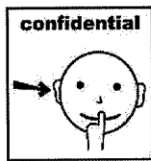
Will my taking part in this study be kept confidential?

If you chose to participate then confidentiality will be taken very seriously. All information which is collected about you during the course of the research will be kept strictly confidential and only details relevant to the study will be extracted from your records.

These will include details and diagnosis of your stroke, including test results such as your scan. We will also need to collect personal information such as date of birth and address.

You will be given a study number for the purpose of collecting and analysing data. This means you will not be recognisable.

The data will only be accessed by authorised persons within the research teams and the research and development office of the NHS Trust, who ensure the quality of the research carried out.

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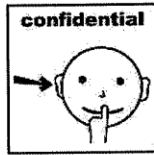
Will my taking part in this study be kept confidential?

Data will be stored securely in the research office during the study and for 5 years after the study. Long term data is then stored in a secure room in the NHS Clinical Trials Research Unit at University of East Anglia for 25 years.

All procedures for handling, processing, storage and destruction of data are compliant with the Data Protection Act 1998.

What will happen to the results of the research study?

The results of the study will be analysed and used to justify whether or not a larger scale study is required to prove effectiveness of this therapy.

The results will be published in an academic journal but individual participants will not be identifiable.

Who is organising/funding the research?

The lead for this study is the University of East Anglia. The research will be carried out as part of the research team's normal workload. The Dunhill Medical Trust have funded this study.

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Who has reviewed the study?

An earlier version of the study was reviewed by The Stroke Association.
Feedback has been incorporated into this research plan (protocol).
The study has been developed in conjunction with the Norwich Clinical Trials
Unit who are also supporting conduction of the study. The Cambridgeshire 3
Research Ethics Committee have approved the study and it will be monitored
by a Trial Management Group.

Thank you for taking the time to read this information. If you choose to
participate, you will be given a copy of the participant information sheet and
the signed consent form for your own information.

15

NHS
Norfolk

Centre Number:

Study Number:

Participant Identification Number for this trial:

Consent Form

Title of Project: Observation with intent To Imitate (OTI) combined with Motor Practice (MP) to enhance upper limb recovery early after stroke: Proof-of-concept trial

Name of Researcher:

1)

information
i

I confirm that I have read and understood the information sheet dated 04.01.2010, Version 4 for the above study.

I have had the opportunity to consider the information, ask questions and have had these questions answered to my satisfaction.

I have read and understood the information sheet

| Yes | No |

Please initial or tick the relevant box as able

1

2)

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

I understand I can stop at any time

Yes   No

3)
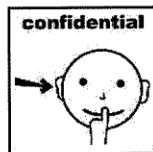
I understand that relevant sections of my medical notes and data collection during the study may be looked at by individuals from the University of East Anglia. I give authorized individuals to have access to my records.

The research team can look at my information

Yes   No

2

4)

I agree for the first assessment, which will determine whether I am suitable for participation in this study to be videoed.

> **I agree for my first assessment to be videoed and observed by the research team**
>
> **Yes**   **No**

5)

I agree that my consultant, nurses and therapists in the clinical team can be informed of my participation in the study. I agree for them to be told of any concerns that the research team may have about my health during the study.

> **The ward staff can be told I am in the study and informed if there are any concerns about my health during the study**
>
> **Yes**   **No**

3

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6)

I agree to take part in the study

I agree

Yes

No

_____   _____   _____
Name of participant   Date   Signature

_____   _____   _____
Researcher   Date   Signature
(Person taking consent)

When completed; 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

4

The Motricity Index
Modified for OTI Study
(Arm Section Only)

Participant ID ……………………………… **Date** ………………………..

Examiner ………………………… **Paretic side** ………………………

Baseline / Outcome measure/Screening

Placement of subject
The patient should be sitting in a chair or on the edge of the bed, but can be tested lying if necessary.

Scoring for arm
Test 1 (pinch grip)

0	No movement
11	Beginnings of prehension (any movement of finger or thumb)
19	Grips cube, but unable to hold against gravity
22	Grips cube, held against gravity, but not against weak pull
26	Grips cube against pull, but weaker than other side
33	Normal pinch grip

Tests 2-3

0	No movement
9	Palpable contraction in muscle, but no movement
14	Movement seen, but not full range/not against gravity
19	Movement; full range against gravity, not against resistance
25	Movement; full range against resistance, but weaker than other side
33	Normal power

	Paretic	Non-Paretic
Arm (in sitting position) 1. Pinch grip; 2.5 cm cube between thumb and forefinger		
2. Elbow flex from 90 degrees forearm on table palm up, voluntary contract/movement; full range = 90 to approx.130 degrees.		
3. Shoulder abduction; from against chest, in 90 degrees elbow flexion; full range = 0 to 90 degrees.		
Arm Score = (1) + (2) + (3) + 1 (to max 100)		

Score Sheet for the Action Research Arm Test

Participant ID................................   Date........................

Examiner ....   **Paretic Side:** Left / Right

Baseline / Outcome Measure

Subscale 1: Grasp (to shelf)		Non-Paretic	Paretic
1.	Block, 10cm³ If score = 3, subtotal score =18 & proceed to Subscale 2		
2.	Block, 2.5cm³ If score = 0, subtotal score = 0 & proceed to Subscale 2		
3.	Block, 5cm³		
4.	Block, 7.5cm³		
5.	Cricket Ball		
6.	Sharpening Stone		
Subtotal (max 18)		/ 18	/ 18
Subscale 2: Grip			
7.	Pour water from one glass to another If score = 3, subtotal score = 12 & proceed to Subscale 3		
8.	Displace 2.25cm alloy tube If score = 0, subtotal score = 0 & proceed to Subscale 3		
9.	Displace 1cm alloy tube		
10.	Put washer over bolt		
Subtotal (max 12)		/ 12	/12
Subscale 3: Pinch (to shelf)			
11.	Ball bearing, held between ring finger and thumb If score = 3, subtotal score = 18 & proceed to Subscale 4		
12.	Marble, held between index finger and thumb If score = 0, subtotal score = 0 & proceed to Subscale 4		
13.	Ball bearing, held between middle finger and thumb		
14.	Ball bearing, held between index finger and thumb		
15.	Marble, held between ring finger and thumb		
16.	Marble, held between middle finger and thumb		
Subtotal (max18)		/ 18	/ 18
Subscale 4: Gross Movement			
17.	Hand to behind head If score = 3, subtotal score = 9 and finish the test		
18.	Hand to top of head		
19.	Hand to mouth		
Subtotal		/ 9	/ 9
ARAT Total Score (max 57)		/ 57	/ 57

Additional Comments:

Study Number:

Group Allocation:

Were any adverse events/effects experienced during the study by the participant?

Yes/No (Delete as appropriate). If **yes**, complete box below giving further details.

Further Details

Researcher_____   Date _____

Appendix C version 1 28/03/2007
Date:.....................

Upper Limb Treatment Recording Form

Patient ID:.........................,......   Therapist ID:...............................

No. of therapists used: ....   No. of assistants used.............   Est duration of upper limb Rx...........

Aims:

1. Postural Control [ ]	2. Musculo-skeletal range of motion [ ]	3. Oedema management [ ]
4. Alignment [ ]	5. Manipulative ability of the hand [ ]	6 Sensory ability [ ]
7. Muscle activity Paretic limb [ ]	8. Transport ability of the arm [ ]	9. Prevent/ reduce pain [ ]
10. Muscle activity Non paretic limb [ ]	11. Incorporate arm into balance and mobility activity [ ]	12. Awareness of 2° complications [ ]

Gross position of patient during activities used:

1. Supine [ ]	2. Prone [ ]	3. Sidelying on unaffected side [ ]	4. Side lying on affected side [ ]
5. 4-point kneeling [ ]	6. 2-point kneeling [ ]	7. Unsupported sitting [ ]	8. Supported sitting [ ]
9. Asymmetrical sitting [ ]	10. Perch Sitting [ ]	11. Standing [ ]	12. Prone standing [ ]

Setting

1. Gym [ ]   2. Ward [ ]   3. Hydrotherapy pool [ ]   4. Other (please state)...... ... ...

Equipment Used:..

Treatment Activities:

1. Soft tissue mobilisation
1.1 Stroking [ ]
1.2 Effleurage [ ]
1.3 Lymph drainage techniques [ ]
1.4 Petrissage (kneading/wringing/picking-up/rolling) [ ]
1.5 Specific compression (trigger points) [ ]
1.6 Myofascial release [ ]
1.7 Frictions [ ]

2. Joint mobilisation
1.1 Accessory Movements [ ]
1.2 Passive Movements [ ]
1.3 Active Movements [ ]

3. Facilitation of muscle activity/movement
3.1 Mental Imagery [ ]
3.2 Patient Generated Cueing [ ]
3.3 Therapist Generated Cueing [ ]
3.4 'Hand on' to induce a desired motor response [ ]
3.5 Active Assisted [ ]
3.6 Facilitated Arm/Hand Activity from another body part [ ]
3.7 Restricted use of non-paretic limb [ ]

4. Positioning
4.1 Side lying hemiplegic side [ ]
4.2 Side lying non-hemiplegic side [ ]
4.3 Supine lying [ ]
4.4 Half lying [ ]
4.5 Sitting in armchair [ ]
4.6 Forwards lean sitting [ ]
4.7 Sitting in wheelchair [ ]

5. Specific sensory input
5.1 Tactile Stimulation [ ]
5.2 Proprioceptive Stimulation [ ]
5.3 Electrical stimulation [ ]

6. Splinting techniques
6.1 Shoulder support [ ]
6.2 Elbow support [ ]
6.3 Wrist/hand support [ ]

Splinting material used ....

7. Exercise to increase strength
7.1 Resistance from the therapist [ ]
7.2 Resistance from body weight [ ]
7.3 Resistance from equipment [ ]
7.4 Gravity neutral repetitive movement [ ]

8. Balance and mobility incorporating upper limb activity
8.1 In, or from, lying [ ]
8.2 In, or from, kneeling [ ]
8.3 In, or from, sitting [ ]
8.4 In, or from, standing [ ]
8.5 In walking [ ]

9. Upper limb functional tasks
9.1 Bilateral functional activities [ ]
9.2 Unilateral reaching activities that are object directed [ ]
9.3 Unilateral reaching activities that are spatially directed [ ]
9.4 Dexterity exercises [ ]

10. Education for patient and/or carer
10.1 To encourage self monitoring of upper limb [ ]
10.2 Transfers training [ ]
10.3 Limb handling and positioning skills [ ]
10.4 Written/ visual/ photo exercise programme [ ]

11. Other interventions / techniques
11.1 Acupuncture [ ]
11.2 Ultrasound [ ]
11.3 Compression [ ]