AN INVESTIGATION OF THE OPTIMUM INTENSITY OF PHYSIOTHERAPY AFTER STROKE

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ABSTRACT

Background

Physiotherapy is a central feature of organized stroke care but there is little direct evidence to support its use. In particular we do not know the optimum amount of physiotherapy for individual patients and recent trials have been inconclusive. We conducted an individual-patient-data meta-analysis of trials testing increased levels of physiotherapy input.

Methods

We carried out a literature search (up to the end of December 2002) and included all randomised controlled trials of intensity of physiotherapy. We also contacted authors of four trials that were not fully published by that date but have subsequently reported. A Collaborative group was formed and trialists provided individual patient data for analysis. Using standard methods (Stewart and Clarke 1995), data were cleaned and categorized by patient details, intervention and outcomes.

We compared intended physiotherapy dose against change in outcome for those studies with available data. We used multivariate logistic regression to examine the following outcomes in relation to patient characteristics (age, severity of disability and arm impairment at baseline) and treatment characteristics (target, total treatment contrast, time to start treatment, daily treatment contrast and duration of treatment), measuring differences between augmented and standard groups and interactions between the subgroups.

Primary outcome: overall disability.
Secondary outcomes:
overall impairment
survival
improvement in arm and leg impairment
improvement in arm and leg function
change in activities of daily living (ADL) measured by the Barthel Index (BI).
length of hospital stay
treatment success - "Good recovery" - greater than median recovery (measured by BI) in the control group.
treatment success - "Excellent recovery" - greater than the upper quartile of recovery (measured by BI) in the control group.

Results

We incorporated 9 trials (951 subjects).

We found no statistically significant differences between patients receiving intensive or standard amounts of physiotherapy, in terms of overall disability or overall impairment scores, length of hospital stay or survival.

Secondary analyses showed improvements in Motricity Index scores for the upper limbs (5.2 units, 95% CI 1.5 to 8.8, P=0.0058) and lower limbs (6.8 units, 95% CI 2.2-11.4, P=0.0042). Improvements were also seen in Action Research Arm Test scores (1.8 units, 95% CI -1.2 to 4.8, P=0.25) in younger patients (under 70 years) and those with higher baseline Barthel scores, and in recovery of walking speed (increase of 0.056 m/s, 95% CI -0.018 to 0.130, P=0.14) (when the target of treatment was lower limb or gait focused).

There was no significant difference in change in ADL (measured by BI (7 trials)) between the groups (0.15 units of change in BI, 95% CI –0.38 to 0.67, P=0.58)..

There were increased odds of a "good recovery" i.e. (improvement of 6 points or up to the maximum of 20 / 20 on BI),(odds ratio 1.33; 0.96 – 1.85; P=0.09) and of "excellent recovery" (> 8 points or up to the maximum on BI),(odds ratio 1.47; 1.03 – 2.05; P=0.04) in the augmented group.

The higher contrast trials in our study (typically 15 – 44 hrs additional physiotherapy, with earlier onset at 7-10 days after admission, higher daily contrast and longer duration) are more likely to show treatment effects than lower contrast trials, with respect to impairment measured by the Motricity index and disability measured by the BI.

Conclusion

Modest increases in the intensity of physiotherapy after stroke did not produce substantial changes in the primary outcomes. Targeted additional therapy in selected patients may improve limb impairment and walking speed.

Our results confirm what might be expected and provide estimates of the modest treatment effect likely in these domains.

Individual patient data meta-analyses provide the opportunity to explore subgroups in order to answer clinically relevant questions and guide further research. Large numbers of subjects are required for randomised controlled trials (RCTs) of intensity of physiotherapy. Considering the challenges involved in running such trials we recommend the use of similar outcome measures in order to facilitate future meta-analysis.

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AUTHOR'S DECLARATION

I performed the research described and composed this thesis whilst I held the post of Research Physiotherapist at the University of Glasgow's Academic Section of Geriatric Medicine. The initial part of the research (forming a collaborative group, writing the protocol, obtaining funding and ethical approval) was initiated and led by Professor Peter Langhorne of the Academic Section of Geriatric Medicine, based at the Royal Infirmary in Glasgow.

My personal contribution was:

To develop the existing protocol and methods and co-ordinate a randomised controlled trial of intensity of physiotherapy establishing co-operation and participation across three hospital sites in Glasgow.

To identify and carry out a screening assessment on all patients admitted to rehabilitation units in Drumchapel, Stobhill and Lightburn hospitals in Glasgow between July 1999 and February 2001.

To perform initial assessments and randomise suitable patients into the trial.

To monitor the patients and staff providing the intervention during the trial.

To lead the analysis of the data collected during the trial.

To carry out a systematic review of published literature on intensity of physiotherapy after stroke.

To act as principle grant holder, setting up and co-ordinating a collaborative group of researchers that had performed similar trials, in order to carry out an individual patient data meta-analysis. I obtained data from their studies and assisted with the interpretation and analysis of this data, allowing the Robertson Centre for Biostatistics at the University of Glasgow to perform the statistical analysis.

To report on the trial, the meta-analysis and compose this thesis.

Ian Wellwood September 2005

LIST OF ABBREVIATIONS

The following abbreviations are used throughout the thesis.

ADL	–	Activities of daily living
ARAT	–	Action Research Arm Test
BI	–	Barthel index
CI	–	Confidence interval
GAPS	–	Glasgow Augmented Physiotherapy After Stroke study
IPD	–	Individual patient data
IQR	–	Inter quartile range
MI	–	Motricity index
OR	–	Odds ratio
PINTAS	–	Physiotherapy Intensity After Stroke
RCT	–	Randomised controlled trial
SD	–	Standard deviation
SIGN	–	Scottish Intercollegiate Guidelines Network
SMD	–	Standardised mean difference
UK	–	United Kingdom

CHAPTER 1
INTRODUCTION

Introduction

This thesis examines the subject of the optimum intensity of physiotherapy input for patients after stroke. In this introductory chapter I describe some of the problems of stroke, how these are currently managed, including physiotherapy, before stating my hypothesis and the questions about intensity of physiotherapy that I aim to address. I also define some of the terms I will use, and finally, describe the structure of the thesis, laying out how I set out to address these questions.

The problem of stroke

Information on the importance of stroke and the potential impact of developing treatments that may reduce its effects is widely available and well described (Bonita 1992, Warlow 1998, Warlow et al. 2001). However, it does bear repeating briefly in this introduction.

Stroke is the third greatest cause of death worldwide (Warlow 1998)(Wolfe 2000) and one of the biggest causes of handicap in the community (Bonita & Beaglehole 1988)(Khaw 1996)(Warlow et al. 2001). The incidence of first ever in a lifetime stroke (where it has been studied, in the predominantly white population of the world) is estimated at about two per 1000 per year and about four per 1000 per year in people aged 45 – 84 years. In the United Kingdom (U.K.) it is estimated to be approximately 145 per 100 000 (Rothwell et al. 2004). There are approximately 15,000 new, first ever strokes and 70,000 existing strokes each year in Scotland. The rate of stroke recurrence is about 5% per year (with a higher rate in the initial weeks and months after first stroke) (Warlow 1998).

Some authors have described a small reduction in the incidence of stroke reported worldwide (Bonita 1992) though the exact explanation for this remains uncertain (Warlow 1998). This reduction may be attributable to the development of effective primary (and secondary) prevention strategies or to trends in risk factors for cerebrovascular disease. Alternatively, it may reflect difficulties in collecting accurate data over time in a number of countries.

Despite this apparent reduction, the number of patients presenting with stroke is still likely to be substantial. With life expectancy increasing, populations will contain larger proportions of elderly people. Increasing age is a risk factor for stroke, therefore the number of people with stroke in absolute terms is likely to increase (Bonita 1992). The problems associated with stroke seem set to continue to present themselves to patients and their carers, clinicians, those responsible for health service provision and the societies in which they live.

In this thesis I use a widely accepted definition of stroke: "a clinical syndrome characterized by rapidly developing clinical symptoms and/or signs of focal, and at times global loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin" (Hatano 1976). I did however, exclude patients diagnosed with sub-arachnoid haemorrhage.

In broad terms, patients with stroke can be divided into three groups; those that have a minor stroke with symptoms which are mild and are likely to make a speedy and complete or near complete recovery (approximately 30% of patients); a middle band of patients who have considerable deficits that require rehabilitation; and those with severe stroke that are unlikely to survive beyond the first month after stroke onset (approximately 20 - 28% of cases)(Warlow 1998) (Wolfe et al. 1999).

Up to 50% of surviving patients are left with some sort of residual neurological deficit (Effective Health Care 1992) such as motor loss (hemiplegia), possibly with loss of upper limb function and the ability to walk, visual loss, altered muscle tone, loss of communication, loss of cognitive function and sensory or perceptual problems. These may result in difficulties in self-care and activities of daily living (ADL) (with about a third of all patients requiring some assistance with ADL up to 6 months after their stroke) (Bonita & Beaglehole 1988).

In addition to the personal costs involved, these patients require considerable health service and community resources. Costs based on studies over the past 25 years, estimate that 4 – 7.6% of hospital expenditure can be attributed to stroke (Hakim & Bakheit 1998) or approximately two billion pounds in 1999 in the UK (Ebrahim 2000).

Health service costs vary between countries and estimates put costs at about £8,000 per patient in Sweden in 1983 and £6,000 per patient in a later study in Scotland in 1988 (Isard & Forbes 1992). A more recent comparison of stroke care provision estimated costs for conventional hospital care in Newcastle, England to be £7480 per patient (McNamee et al. 1998). A more comprehensive estimate including community and social services, family costs and loss of productivity may be more like £70 000 per patient in an estimate in the United States of America in 1990 (Taylor et al. 1996).

The greatest proportion of acute hospital inpatient expenditure (more than 90%) can be attributed to nursing and "hotel" costs (Warlow et al. 2001). The length of hospital stay varies greatly from patient to patient, and can depend on a number of factors including clinical subtype of stroke, the patients' age, sex and functional dependency and the views of the consultant caring for them (Hakim & Bakheit 1998).

Tackling the problem of stroke

If some form of effective treatment was available for those patients requiring stroke rehabilitation then considerable improvements in patients' abilities, independence and quality of life might be made.

The group of patients with a poor prognosis and high death rate are often the target of studies of interventions aimed at saving life. However, some researchers have reservations about developing interventions that may prevent deaths but result in very dependent survivors. If there were proven effective rehabilitation treatments, then this might encourage further development of promising acute treatments, safe in the knowledge that survival might not necessarily mean dependence and disability.

Improved knowledge of effective treatments would also allow finite resources to be targeted to maximum effect and to reduce waste. Any method that reduces treatment times, in particular hospital inpatient stay, may be particularly useful in reducing costs. So far, the most effective way of improving stroke patient outcomes is with stroke units. This was recognised in an overview of methods of managing patients with stroke (Stroke Unit Trialists Collaboration. 1997). This overview provided good evidence of benefits to patients with stroke that are managed in a stroke unit as opposed to a general medical ward. These benefits included improved survival, decreased dependence in

activities of daily living, decreased institutionalisation and decreased length of hospital stay (by up to 8%). Compared to general medical management, for every 100 patients treated in a stroke unit, 3 deaths and 2 admissions to institutional care are avoided and an additional 5 patients are discharged home (Stroke Unit Trialists Collaboration 1997) (Stroke Unit Trialists Collaboration 2003). There is some further evidence that these benefits may be sustained over a longer period (up to 10 years after stroke) (Indredavik et al. 1999).

Stroke Units are difficult to define precisely and vary widely between different health care systems. They do however, appear to have a number of common features, including a co-ordinated, multi-disciplinary team that is specialised in stroke care (Stroke Unit Trialists Collaboration 1997) (Langhorne & Dennis 1998) (Langhorne & Pollock et al. 2002). Overall, this multi-faceted, complex intervention is, at present, poorly understood. In 1989 the World Health Organisation (WHO) Task Force on Stroke recognised this problem and stated that: "Controlled clinical trials are essential if the role of rehabilitation, its indications, and its contraindications are to be adequately understood" (WHO Task Force on Stroke 1989). There have been many more clarion calls echoing this statement over the past decade, giving rise to the term "unpacking the black box of rehabilitation". Though there are increasing numbers of trials and studies of rehabilitation, there remains a great deal to discover about the individual components of stroke unit rehabilitation and how they interact (Wade 2001) to produce their beneficial effect.

One of the recognised core components of rehabilitation within a multi-disciplinary stroke unit team is physiotherapy (Stroke Unit Trialists Collaboration 1997) (Langhorne & Dennis 1998). Whilst it seems reasonable to assume that physiotherapists play a part in the restoration of patients' mobility after stroke, there are many aspects of physiotherapy intervention that require to be evaluated (Legg et al. 2000)(Pomeroy & Tallis 2000)(Pomeroy & Tallis 2002)(Scottish Intercollegiate Guidelines Network (SIGN) Guidelines 2002). Amongst these is the need to determine which patients benefit, at which stage after stroke, from which treatments and in which setting. I was particularly interested in determining the optimum amount of physiotherapy that should be provided for patients with stroke.

Defining physiotherapy

Before proceeding, it is worth defining physiotherapy as it will be used in this thesis, looking at its historical background and then describing current physiotherapy practice in the treatment of stroke.

Physiotherapy is the process of treatment of disease and injury by physical means (as opposed for example to pharmaceutical and surgical means). Commonly, physiotherapy utilises treatment methods such as exercises, movement, thermal treatments e.g. heat packs or ice, electrotherapy, massage and education. Treatment is often given in order to resolve or minimise a patient's impairment, disability and handicap. Neurological physiotherapy is a sub-specialty focused on the treatment of patients diagnosed with neurological disease or disorders of the nervous system. It is usually administered by specialists but often draws on other branches of physiotherapy and the application of general principles. It often takes place in the context of a multi-disciplinary team and has a role focused on the restoration of movement or mobility and function. Neurological physiotherapists work worldwide in a number of settings including hospital in-patient and outpatient departments, in the community or patients' own homes (SIGN Guideline 2002).

Historical context

Historically, patients with stroke were not always treated with physiotherapy, even in its broadest sense. The diagnosis and pathology of stroke were not clearly understood and physical treatments were applied to patients for a wide variety of reasons (Warlow et al. 2001). These included massage, heat and even electricity from natural or man-made sources. Some patients with mobility disability secondary to paralysis did receive some form of physical assistance in an attempt to compensate for their disability.

In the UK, physiotherapy as we might recognise it, is first mentioned with the upsurge in the use of spa treatments and hydrotherapy that became popular in the late eighteenth century in England in spa towns such as Bath and Leamington Spa. Later, Scotland was to have the "Hydros" at Peebles and along Speyside. Hydrotherapy was a fashionable treatment for a whole host of ailments but there is little information on stroke specific treatment from this time. Treatments may have depended upon the patients' belief in its benefit or their budget, rather than any prescribed regime that was recorded. Massage and movement of the limbs were often incorporated into spa treatments.

Even with the development of the physiotherapy profession in the UK, there is remarkably little recorded about the treatment of patients with stroke. The Society of Trained Masseuses was established in 1894 to promote "medical rubbing" (mostly carried out by nurses) and to distinguish therapeutic massage from the unsavoury image that massage had at the time, and to some extent retains today. At the turn of the twentieth century the Swedish Institute a school for remedial exercise introduced Swedish exercise therapy to the UK and within 10 years the Incorporated Society of Trained Masseuses was also responsible for training and examining medical gymnastics and electrotherapy. Many of the techniques taught in those times persist to this day in an amended form and are still the basis of today's physiotherapy treatments.

The numbers of trained masseuses increased greatly during the First World War. In 1943 the Chartered Society of Physiotherapy was formed and with the development of the National Health Service in 1947, it controlled standards and provided training for women and men entering the profession (Thornton 1994). Records of the training and treatment of stroke in the early days of the profession give little reference to the amount of therapy that should be given to patients. Early treatments still consisted of "therapeutic massage" and passive movements to the limbs. Often patients were given treatments allowing them to maximise the use of their unaffected limbs, e.g. strengthening exercises in order to compensate for a limb weakness on the opposite side. Splinting materials were employed to control abnormal muscle function and generally the use of callipers, splinting and wheelchairs appears to have been more commonplace than today. The aim of treatment was often "the attainment of a safe, not a normal, mode of travel" (Perry 1969).

In contrast to this compensatory or functional approach, the 1950s and 1960s saw an increase in the popularity of methods broadly based on contemporary understanding of the physiology of the nervous system. Some of these methods are still practiced today with some modification and have some ardent followers despite there being little sound evidence to support their use.

The Bobath approach (Bobath 1990)(Davies 1985) broadly follows a neuro-developmental sequence similar to that seen in a normal developing infant. A therapist promotes normal movement patterns and facilitates movement, with "abnormal" reflex

reactions being discouraged. Johnstone (Johnstone 1978) had a similar approach but focussed on stability of the proximal joints often employing inflatable plastic splints to support the limbs. In contrast such "abnormal" patterns and reflex movements are allowed and encouraged in another two approaches advocated by Temple Fay (Kidd et al. 1992) and Brunnstrom (Brunnstrom 1970), who considered the mass movement patterns to be a necessary stage in developing motor control.

The latter two approaches involved treating patients (both adult and children with a variety of neurological conditions including stroke) for "an hour or so per day or even every other day" (Kidd et al. 1992). A review by Bower describes the Bobath approach as lasting for 30 – 60 minutes per session, with 1 – 5 sessions per week (Bower 1993).

An alternative was a neuropsychological approach termed "conductive education" developed by Peto, in Hungary during the Second World War. In the Peto Institute in Budapest a continuous, 24 hour approach is taken to re-educate movement (though used largely in the treatment of cerebral palsy in children, adults with neurological disease are treated) (Cotton & Kinsman 1983). This approach places the emphasis on the patients' own efforts, with conceptualisation of tasks, verbalisation and feedback from a "conductor" and repetition, often in a group setting, along with the use of specialised equipment and furniture.

In the late 1980s two Australian physiotherapists, Carr and Shepherd described a "motor relearning programme" for stroke based on an understanding of kinematics and kinetics of normal movement, motor control processes and motor learning. Although popular in Australia and increasingly employed and taught in the UK it is still less popular in the UK than the Bobath approach. It recommends that patients repeatedly practise movement tasks focussed on function in order to achieve recovery (Carr & Shepherd 1987).

Although there have been, and still are, several other recognised physiotherapy approaches to treating stroke e.g. Rood, Knott and Voss they are not widely practised (Bower 1993)(Partridge 1995)(Davidson & Waters 2000).

There have been many trends in physiotherapy treatment for stroke over the post-war period, with most, surprisingly, not specifying their intensity. Many are based on developmental work aimed at the treatment of children with cerebral palsy. Whilst some specific regimes were popular for children, ranging from some contact every few weeks with a physiotherapist, to 5 minutes treatment, 5 times a day, to several hours per day, the same cannot be said for adult treatment. Many of the paediatric methods have been advocated and used in treatment of adult stroke, with claims that the physiological principles of treatment are similar. However without the emphasis of educational and physical development (and the necessary resources, often based in educational institutions) and practical difficulties involved in dealing with physically demanding disabled adults e.g. it is difficult to carry out passive movements to the limbs of a 100 kg man for 6 hours a day, these rigid regimes have never been as popular in adult as paediatric environments.

None of the popular proponents of contemporary physiotherapy, with the exception of Carr and Shepherd (motor relearning programme), clearly specify a dose of therapy or the manner in which it should be applied. Many merely put forward a philosophy or principles of treatment to be followed. Most suggest "as much as tolerated" or that exercises or therapy should be carried out "daily" or "as often as possible". The majority adhere to the idea of individual assessment and avoid giving a formula or a regime for stroke treatment. Such regimes were commonplace in the physiotherapy treatment of other conditions, for example the "DeLorme and Watkins" and "Macqueen" regimes to allow muscle strengthening after musculo-skeletal injury (Hollis 1981).

What does today's physiotherapy involve?

Physiotherapy treatments with patients with stroke remain diverse (Pomeroy & Tallis 2002) (SIGN Guidelines 2002). Typically they consist of exercises which may be active; with the patient participating and carrying out the movement under their own volition; or passive when the patient receives full assistance to carry out the movement from the therapist; or active/assisted which is somewhere between the other two types, usually the patient being asked to join in with the movement as much as possible.

The movements may be assisted or facilitated by the therapist or resisted by a number of means (e.g. manual resistance, body weight resistance, weight resistance). Generally, the aims of the treatment are discussed with the patient and often goals are negotiated. These may be based around reducing impairment e.g. reducing abnormal muscle tone, reducing disability e.g. practising the functional task of standing up from a chair or reducing handicap e.g. practising walking outdoors in order to allow access to community facilities.

There are differences of opinion as to the best exercise treatment approach physiotherapists should use with patients with stroke. In the UK the two most popular approaches are Bobath (also known as "Normal Movement") and the Motor Relearning Programme (MRP) (also known as "Movement Science"). There are some regional differences in the claimed use of these techniques (Davidson & Waters 2000). There is also considerable debate as to their efficacy and difficulties in discriminating between the approaches in order to define the interventions (Langhammer & Stanghelle 2000)(van Vliet et al. 2001). Many therapists (up to 87% in a recent national survey in the UK (Davidson & Waters 2000)) admit to using an eclectic approach, varying their approach with and specifically around each patient's assessed needs.

Other techniques may be employed such as the application of thermal treatments e.g. ice packs, the provision of mobility aids or equipment, splinting, electrotherapy treatments, or techniques aimed at relieving pain such as trans-cutaneous nerve stimulation (TENS) or acupuncture. Physiotherapists are also involved in multidisciplinary teams, helping patients to adjust to changes in their abilities and providing information to patients and their relatives.

Example of physiotherapy treatment

To illustrate how physiotherapy services are delivered an example of a typical physiotherapy treatment in a stroke unit is given below:

Patients who are unable to stand due to hemiplegia, reduced muscle tone and a loss of standing balance reactions would be encouraged and physically assisted to stand up at an early stage after their stroke (as early as the first day after their stroke in some units (Langhorne & Pollock et al. 2002)). This process aims to assist regaining functional

muscle control in the anti-gravity muscles in the trunk and lower limb and to stimulate the muscles that provide joint stability through weight bearing. The physiotherapist encourages symmetry of movement and weight bearing and discourages the use of the unaffected side merely to compensate for any weakness. The patient might repeatedly practise rising from a plinth (which may be raised to make the task easier) into a standing posture with assistance of the physiotherapist. If this is particularly difficult, more than one physiotherapist may be required or electrical hoisting equipment may be employed. Massage techniques (brushing or rubbing with the fingers) may be used directly on the weak muscle groups that would normally be involved in the movement, in order to stimulate contraction. The procedure would be explained to the patient and verbal feedback and encouragement would be given throughout the session. Several attempts to stand might be made and the patient allowed to take short rests between each attempt. The physiotherapist assesses the patient's posture and ability to control the movement and to maintain their balance. The upper limb would be supported throughout the treatment and time spent assisting the limb through passive or active / assisted movements in order to maintain range of motion at the joints. Further functional, goal-based movements (e.g. stretching out to reach for a cup then grasping this and lifting it towards the mouth) to stimulate the normal movement patterns would also be practised. The movement is supervised, assisted if necessary and corrected to minimise any abnormal movement patterns or associated abnormal reactions or reflexes. A typical treatment session might last 30 – 45 minutes and would probably occur once on a weekday. Time may also be spent recording assessments and treatment notes, encouraging the patient to perform exercises or activities on their own and discussing treatment with relatives and other multidisciplinary team members.

Similar treatments are carried out throughout the country most days of the week. However, despite some encouraging results in the recent research (Langhorne et al. 1996) (Kwakkel et al. 1999) it is still not known how many times the treatment should be repeated or for how long it should last.

From these observations of current and historical practices, we are given little indication of how today's physiotherapists working in the UK have arrived at their level of intervention. Rather than being based on scientific evidence, current levels of intensity are likely to reflect customary work practices, exercise tolerance (for both the patient

and therapist), the patients' ability to take in new information, demand for services and available resources, clinical opinion and the time of onset of symptoms. Generally, most physiotherapy in the UK is available in the early stages after stroke.

If we could determine the optimum physiotherapy input for patients with stroke we may have an impact on levels of impairment, disability, handicap experienced by patients, as well as health costs. It might also contribute to our understanding of the process of rehabilitation and physiotherapy.

Difficulties in investigating physiotherapy

Our uncertainty about the optimum intensity of physiotherapy may exist for several reasons: it may be in part due to a lack of research skills, experience and understanding within the physiotherapy profession; a lack of interest (some twenty or thirty years ago, stroke was seen as a "Cindarella service" - often overlooked and under-funded); a lack of time dedicated to the question, or the practical difficulties in implementing clinical trials. These possible reasons reflect those perceived by stroke rehabilitation professionals as barriers to implementing evidence-based practice (Pollock et al. 2000) and may indicate something of the UK's health care culture.

One way of investigating the efficacy of physiotherapy would be to carry out a randomised controlled trial of physiotherapy with two groups of patients with stroke; one receiving treatment and the other receiving none, then comparing their outcomes. However, physiotherapy is now so well established (at least in the UK) as a key element to rehabilitation that this proposal is unlikely to gain approval from local ethical authorities (Rice-Oxley & Turner-Stokes 1999). Such studies, if they gained approval, may have difficulty in recruiting patients who might fear they were to miss out on treatment that patients and their relatives perceive to be beneficial. Indeed, the amount of physiotherapy received by patients is an area in which patients and their relatives have expressed satisfaction and dissatisfaction with their hospital care (Pound et al. 1994(a))(Pound et al. 1994(b))(Wellwood et al. 1995(a)).

In order to evaluate physiotherapy after stroke we therefore have to take a pragmatic approach (Roland & Torgerson 1998). In this thesis I am not concerned with any particular physiotherapeutic intervention, but with examining the effect of different

intensities of physiotherapy as it is currently, commonly provided in hospitals in the UK to patients after stroke. This approach reflects current practice and in turn allows results to be readily interpreted, widely generalised and implemented.

Unlike a trial of a drug where a clear prescription can be made, involving dose strength (concentration) and frequency of administration, there are difficulties when we try to compare intensities, doses or input units of physiotherapy.

We need to define whether we are discussing the duration of treatment or the degree of effort or exertion (concentration) used during that treatment session. We also need to decide whether we are examining the direct intervention of the physiotherapist (face-to-face contact), or any indirect effects such as what the patient themselves carry out e.g. unsupervised exercise, practise of techniques or strategies taught by a physiotherapist but perhaps then used with other rehabilitation team members or carers. Most studies in the past have settled to measure the amount of face-to-face contact time the physiotherapist spends with a patient. Throughout this thesis I will use the term intensity to refer to the duration of physiotherapy treatment. This is the amount of time spent by the physiotherapist that can be directly attributed to each patient i.e. face-to-face contact and indirect contact time (such as record keeping or telephone conversations) in connection with delivering care for that individual patient.

Both drug and physiotherapy trials may suffer from problems with compliance if the patients are not directly supervised, taking their medication or their prescribed exercise regime.

In considering trial design, a placebo is often easy to design and administer as part of a drug trial. This is less easy to specify in physiotherapy trials especially to find "dummy" treatments that might be substituted in place of rehabilitation exercises. Standardisation of treatment is also reasonably easy in drug trials. The human interaction involved in the physiotherapeutic process, by its nature, makes the standardisation of the intervention and its delivery complex, though this is not altogether impossible for example by the use of strict treatment or trial protocols, following "care pathways" or standardised interventions such as home exercise regimes delivered in a standard way such as by booklet or video recording.

Attempts to examine intensity

Several observational studies (Table 1.1) have attempted to quantify the actual amount of physiotherapy (or "therapy") that patients receive. These arose partly to investigate rehabilitation interventions and partly from concerns that patients apparently spent long periods of the day unoccupied. The duration of inpatient therapy ranged from an average 43 minutes (Newall et al. 1997), to 21 minutes on a medical ward and 36 minutes on a stroke unit (Lincoln et al. 1996), to 45 minutes (Wade et al. 1984). Physiotherapy ranged from 30 minutes (day hospital) to 90 minutes (outpatient department) (Gladman et al. 1991) with an average of 60 minutes on a domiciliary visit (Ballinger et al. 1999). Locally, an unpublished survey indicated that acute stroke patients in rehabilitation units in Glasgow received an average of 45 minutes of physiotherapy five days a week (Langhorne et al. – unpublished feasibility study).

Table 1.1 Duration of physiotherapy treatment

Study	Setting	Average treatment time (minutes) per weekday
Wade et al. 1984	Inpatient	45
Gladman et al. 1991	Day hospital	30
Gladman et al. 1991	Outpatient	90
Lincoln et al. 1996	Stroke unit	36
Lincoln et al. 1996	Medical inpatient	21
Newall et al. 1997	Inpatient	43
Ballinger et al. 1999	Domiciliary	60
Langhorne et al. (unpublished data)	Stroke unit	45

There are also considerable variations in physiotherapy service provision between countries (Beech et al. 1996)(de Weerdt et al. 2000). A direct comparison of clinical outcomes achieved in areas or countries where there is a difference in intensity is likely to be complex due to different service provision and constraints, case mix and heterogeneous interventions.

There may also be practical problems with data collection on the intensity of physiotherapy. Whilst some physiotherapy services routinely record the amount of time spent with patients, many do not, with data being limited to clinical records of treatment and a record of face-to-face contacts.

Probably the most accurate and helpful way of assessing intensity is to carry out a randomised controlled trial (RCT). Those intensity RCTs that have been published are reviewed in the next chapter. They had an average intervention of 45 minutes per day for the "control" groups, reflecting general practice in the UK as described in the observational studies above.

Research questions to be addressed in this thesis

In this thesis I examine the uncertainty of the effect of intensity (i.e. the duration) of physiotherapy treatment on patients with stroke during their rehabilitation in hospital. To do this I will compare outcomes achieved with the provision of a standard amount of physiotherapy with those achieved when additional physiotherapy is provided.

I put forward the hypothesis that intensive physiotherapy after stroke will produce benefits which:

a) speed recovery in terms of impairment and disability.

b) are greater when targeted (e.g. on upper limb recovery).

c) are greater for patients with moderate impairment and little co-morbidity.

d) are greater in the shorter (3 months) than longer term (6 – 12 months).

e) result in a reduced duration of inpatient rehabilitation.

I will attempt to describe any benefits in mobility, function and cost in useful and easily understood terms e.g. by relating to standard scales and giving cost savings per patient.

Structure of the thesis

In chapter 2, I examine the published evidence about intensity of physiotherapy after stroke. I describe how I selected and reviewed the available evidence.

In chapter 3, I describe the randomised controlled trial that aimed to address the hypothesis.

In chapter 4, I introduce the statistical technique of meta-analysis that may be a useful tool to further test the hypothesis. I describe a combined analysis of several trials of intensity (including data from the study in chapter 3).

In chapter 5, I describe forming a collaborative group in order to carry out a detailed individual-patient-data meta-analysis.

In chapter 6, I draw conclusions from the randomised controlled trial and the meta-analysis. I review to what extent I managed to establish satisfactory answers to the questions set out in this chapter. I also discuss some limitations of the work and indicate areas that could be developed for further research.

Summary

- Stroke is a major worldwide health problem that will continue to effect individuals, their carers and society and poses a huge challenge to those charged with providing effective clinical services in order to reduce impairment, disability and handicap.

- Currently, the most effective intervention in the treatment of patients with stroke is care carried out in an organised stroke unit.

- Most stroke units include physiotherapy as part of their treatment. We remain uncertain as to which patients might benefit most and in which ways in response to which type and amount of physiotherapy. We need to determine how best to deliver such services for optimum effect and value.

- Physiotherapy is a well-established part of many health services for people with stroke. It seems to offer some benefits to patients, however there is little evidence to support its routine use. There are practical and ethical difficulties in evaluating this rehabilitation intervention in a scientific manner.

- We know very little about the optimum intensity of physiotherapy either from historical records or reviewing current practice. We have some information from research into the area: observational studies about the intensity of physiotherapy currently delivered and interventional studies. The randomised controlled trials of intensity are reviewed in the next chapter.

- In order to explore the issue of optimum intensity of physiotherapy, I propose a hypothesis and set out a number of research questions that I aim to address in this thesis.

CHAPTER 2
REVIEW OF THE LITERATURE

Introduction

The questions posed in the previous chapter have been of interest to stroke researchers for many years and there have been several attempts to address them. In this chapter I describe some of the studies from over the past 30 years that have added to our understanding of intensity of physiotherapy after stroke.

Aims

In this chapter I aim to:

1). Describe the important literature relevant to physiotherapy intensity.

2). Describe desirable features of rehabilitation trials.

3). Discuss difficulties in researching complex healthcare interventions.

4). Discuss selected studies in relation to the research questions outlined in Chapter 1.

The Literature

Although research into stroke has been carried out for many years there have been relatively few specific studies of physiotherapy and rehabilitation and even fewer of intensity of physiotherapy. However, there has been an increasing amount of interest and number of scientific trials carried out over the past 15 years. This increase in research activity may be attributed to the increasing challenge presented to service providers due to the increasing burden of stroke. Enthusiastic, interested individuals have taken up this challenge at local, professional and political levels. They have largely been responsible for driving the research agenda, prompting initiatives from scientific, government and charitable bodies such as the Kings Fund and the Stroke Association. Many of these bodies made recommendations for action to attempt to reduce the burden of stroke, e.g. guidelines from international bodies such as the European Stroke Initiative (EUSI) (EUSI 2003), from government departments; such as the National Service Framework (NSF) for Elderly People from the Department of Health in England and Wales (Department of Health 2001); and professional bodies such as the Royal College of Physicians (RCP) (Intercollegiate Working Party for Stroke 2002) and the Scottish Intercollegiate Guidelines Network (SIGN)(SIGN 2002).

Although there are moves towards basing such recommendations on scientific evidence many guidelines do not have a clear scientific foundation. Recognising this, many bodies have made recommendations for further investigation into areas including therapy and rehabilitation. In turn, research bodies have, to some extent, responded to these recommendations and funded relevant projects. However the process from proposal to publication can be lengthy.

Searching the literature uncovers a variety of papers, many of which appear relevant to the questions I set out in Chapter 1. However to fully address all my questions on physiotherapy intensity and in order to influence clinical practice and health policy decisions, any trial would have to produce results that are reliable and can be generalised. Unfortunately, such a trial does not appear to exist.

It is difficult to estimate just how large such a trial would have to be in order to change clinical practice in physiotherapy. In an often-quoted example from the field of medicine, the use of aspirin after myocardial infarction was considered beneficial in early small studies (even these are relatively large in comparison to many rehabilitation studies) yet it was not until the large ISIS-2 trial (ISIS-2 Collaborative Group 1988) in the late 1980s, involving over 17,000 patients was conducted and reported that clinical practice started to change. There is little to suggest that therapists are any more liable to accept change than the medical profession and, given that treatment effects of physical therapy may well be more modest than in the last example, it seems likely that large numbers of subjects would need to be recruited in order to change clinical practice.

Reviews of physiotherapy intensity

I undertook a literature search using several electronic databases (Medline 1966 to present, CINAHL 1982 to present and the PEDRO and Cochrane Stroke Group Specialised Trials registers), by referring to recently published reviews and by discussing literature with other researchers and experts within this area.

I found several reviews of the available literature on effectiveness and intensity of physiotherapy (up to 12 reviews over the past 15 years were identified recently by van der Lee et al.) (van der Lee et al. 2001), some narrative in style e.g. (Ernst

1990)(Ashburn 1997), some following the more recent trend towards more formal systematic reviews e.g. (Langhorne et al. 1996)(Kwakkel et al. 1997)(van der Lee et al. 2001). Each considered slightly different aspects of intensity, identified and selected different trials and used different methods to appraise and in some cases analyse the available evidence. The reviewers found the trials to be mostly small, focused on various aspects of stroke e.g. functional ability or arm impairment, and at times arrived at different conclusions. With some exceptions, the earlier studies before 1990 were generally less methodologically rigorous, reflecting an earlier stage of clinical trials, clinical science and review methodology.

The narrative reviews

Ernst noted that many trials were not blinded, non-randomised and had potential for bias (Ernst 1990). He suggested that the physiotherapy approach was immaterial. He also noted that settings were different, interventions varied, outcomes were non-standard and that all subjects showed some early recovery. He came to the conclusion that "if an optimal treatment exists, we have, so far, failed to identify it. Until further evidence emerges, we should therefore select therapies that are most cost-effective and that can be given to the largest number of patients. Well planned clinical trials aimed at finding the best approach and discriminating potential responders from non-responders are urgently needed.".

Pollock et al. (Pollock et al. 1993) and Ashburn in 1997 (Ashburn 1997), highlighted some of the shortcomings of rehabilitation studies: in general they were of poor quality; used insensitive outcome measures e.g. activities of daily living (ADL) scales may not be sensitive to change in motor and sensory impairment – often the level at which the intervention is aimed; lacked detail; used inconsistent definitions; poorly described outlying subjects, and selected different end points at which to measure outcomes. All of these were present on a background of spontaneous recovery after stroke.

Ashburn (Ashburn 1997) recommended researchers include a broader spectrum of patients and use standard measures whilst recognising the limitations of some of the widely used, popular measures such as the Barthel Index. Doing so would allow comparison between studies and facilitate combination in meta-analysis.

Formal reviews

Langhorne et al. used different methods in a well-conducted formal review (Langhorne et al. 1996), and found, like Ernst (Ernst 1990), the evidence for improved outcome with increased intensity of physiotherapy to be lacking and of variable quality. They included a number of studies that would be relevant in answering my questions but included some out-patient based studies. They also concluded that further study was required in order to obtain a definitive answer.

A year later, Kwakkel et al. in their study using clearly stated methods and broader inclusion criteria, concluded that a greater intensity of physiotherapy would lead to benefits (Kwakkel et al. 1997). However, their overview included some confounded trials. They highlighted that trials were small, had problems with blinding and were heterogeneous. Recognising that most recovery is probably spontaneous they recommended that treatment should start as early as possible and also suggested that the treatment approach may be immaterial.

Van der Lee et al.'s review of upper limb physiotherapy had a broad scope and included a wide variety of interventions many of which could be defined as physiotherapy but might not be recognised as normal physiotherapy practice (at least currently in the UK) e.g. constraint induced therapy and robot assisted movement practise (van der Lee et al. 2001).

Individual studies and trials

Even within the relatively small number of studies of intensity of physiotherapy there is remarkable diversity, reflecting a variety of perspectives on the subject; from service evaluation (Smith et al. 1981), to consumer satisfaction surveys (Pound et al. 1994(a)) to investigation of novel treatment techniques (Feys et al. 1998). There are a corresponding variety of study designs to accommodate these perspectives with an increasing number of randomised control trials being conducted, in order to gain scientific credibility and better address clear scientific questions. There are also a wide variety of subjects and participants, interventions, settings, time points and outcomes:

Subjects and participants

The subjects vary considerably in the studies from early acute in-patients (e.g. Kwakkel et al. 1999), seen a few days after onset of symptoms, to patients receiving treatment over a year after stroke (e.g. Wade et al.1992)(Green et al. 2002). Many studies recruited selected patients. In many cases this is because patients are required to give informed consent which may be difficult or impossible to obtain when the stroke has resulted in cognitive or communication impairment. If the studies have been limited by ethical considerations or have not had the option of gaining informed consent from a relative or carer, the sample group can be skewed towards a less disabled group. Some reviewers have commented (Ashburn 1997) that patients at the extremes of severity are not well represented in trials as they are either too sick or too well to detect change or to be maintained in a study.

On the other hand where all patients are included e.g. Partridge et al. 2000 included severely disabled subjects, this better reflects a typical clinical situation allowing results to be generalised. The disadvantage in this is that we would expect different prognoses for different patients after stroke, dependent on for example on their age or the severity of symptoms. Any potential treatment effect being investigated is likely to be diluted and possibly go undetected unless very large numbers of subjects are recruited. Only where there are large enough numbers can sub-group analyses be carried out and may identify groups that did respond or responded better to the intervention.

Slade et al. (Slade et al. 2002) examined intensity of therapy in a mixed group where patients with stroke and patients with head injury were studied. Again this may reflect clinical practice in some mixed neurological rehabilitation units but needs careful interpretation in order to isolate the results that are relevant to patients with stroke.

Some studies examined the intervention when delivered by different therapists. In one study (Lincoln et al. 1999), an experienced "expert" therapist was contrasted with trained therapy assistants working under supervision. Other studies examined "conventional" service provision (Partridge et al. 2000), aiming to reflect normal clinical practice.

In several cases, intensity of "therapy" was considered as "physical therapies"(as opposed to drug or psycho–social interventions) and included occupational therapy in addition to physiotherapy (Smith et al. 1981)(Slade et al. 2002). In these cases "physical therapy" would include the practise of physical tasks, in some cases undertaken by a variety of healthcare workers.

Intervention

Novel interventions have been trialed with a view to evaluating their effectiveness. e.g. the use of sensori-motor stimulation using a rocking chair and arm splint (Feys et al.1998) or patients practising exercises using a mirror (Altschuler et al. 1999) or robot-assisted movement (Volpe et al. 2000). In other studies current clinical practices were evaluated (Sunderland et al. 1992)(Lincoln et al. 1999)(Partridge et al. 2000). One study (Pollock et al. 2002) took an alternative approach, investigating the effect of independent practice of an exercise without direct supervision of a physiotherapist.

Because of the complex nature of physiotherapy, involving interpersonal and physical components, many studies have experienced difficulties in describing what the intervention involves. Most have related intensity of therapy to a component of time. None have considered "intensity" to include how much effort the patient applies or has applied to them during the therapy session. Pragmatically, this reflects how therapy is delivered in a clinical setting and avoids the complex difficulties in attempting to measure therapeutic effort either on the part of the patient or therapist. Most studies have opted to increase the amount of time spent with the therapist by increasing the duration or the number of the sessions delivered. Even this latter approach has difficulties, as for example, delivering two half hour sessions of treatment may be different to delivering a single one hour session due to potential problems with fatigue or training effects that may develop during a single longer session.

Some reviewers (Ernst 1990) argued that the content of the intervention itself was unlikely to be of importance but the duration of contact with the therapist may be. Even if this is the case, in order to be able to generalise results it is important to have a clear description of both the subjects and the methods used in the studies.

Setting

Within the hospital setting there may be confounding from other services. The Stroke Unit Trialists Collaborative group in 1997 (Stroke Unit Trialists Collaboration 1997) shed new light on the effectiveness of stroke units. Their meta-analysis showed outcomes, in terms of survival, dependence and institutionalisation at 12 months after stroke, to be significantly better in patients managed in a stroke unit compared to "conventional care", often delivered in general medical wards. These results mean that some of the previous studies of physiotherapy intensity were in fact confounded, as they compared specialised stroke unit and general medical care (Peacock et al. 1972 - though no details of intensity of therapy are available - quoted in (Langhorne et al. 1996))(Sivenuis et al. 1985) where we might expect a difference in outcome. Generally, better results were found in the stroke unit groups and this had partly been attributed to patients receiving more therapy, however there may be a much more complex interaction of interventions that provides the real explanation of the "stroke unit effect".

With a change in focus from provision of healthcare in institutions towards provision in the community, several intensity studies have been carried out on an out-patient (Duncan et al. 1998) (Smith et al. 1981)(Werner & Kessler 1996) or domiciliary basis (Wade et al. 1992) (Green et al. 2002).

As mentioned in Chapter 1 (page 13) the amount of therapy that is standard in one setting may well be different in another e.g. there are considerable differences in the average amount of therapy delivered in the UK, other parts of Europe (de Weerdt et al. 2000)(McKevitt et al. 2000) and North America (Jette et al. 2005). Comparisons of intensity across national boundaries are difficult to carry out due to other constraints and likely confounding factors between the healthcare systems and cultures. Consequently, these studies rarely go beyond describing the differences.

Timing

In trying to determine the optimum time to deliver services some researchers have provided the intervention at a time when recovery is considered to have reached a plateau and conventional therapy has usually stopped. This may make controlling for treatment effects easier, allow a different study design (e.g. interrupted time series

designs such as ABA crossover) (Wade et al. 1992) to investigate optimal timing or allow ethical considerations to be accommodated (e.g. concerns about denying patients potentially beneficial interventions). As most patients are discharged from treatment soon after leaving hospital this often involves contrasting some treatment with the "normal" amount, which is often none (Green et al. 2002).

Outcomes have also been measured at a variety of end points, e.g. two weeks after stroke, on hospital discharge, at six months or a year after stroke. The baseline for several studies varies and can be the date of admission into acute or rehabilitation hospital, date of recruitment or date of first intervention. These variables can make the comparison of results between studies complex.

Outcomes

To reflect the different interventions used in the studies a corresponding array of outcome measures were employed. Unfortunately, some of these are non-standard, have poorly established measurement qualities and are insensitive to changes likely to be attributed to the intervention. The Barthel index (BI) for example is widely used as a measure of activities of daily living (ADL) or as a disability scale, but is widely acknowledged to have limitations. One study estimates that the Barthel index may underestimate the patients' and carers' problems in up to a third of subjects (Wellwood et al. 1995(b)). With a marked ceiling and floor effect, it is clearly insensitive to certain disabilities e.g. subjects that are deaf, blind, unable to speak and have only one functional arm are able to score full marks on the scale. Some therapists argue that changes in ADL scores are not the primary focus of physiotherapy treatments that may be targeted more at the level of impairment (Ashburn 1997) (Pomeroy & Tallis 2000).

A number of studies reported length of hospital stay as an outcome. With the majority of hospital inpatient costs attributed to nursing care (Warlow et al. 2001), length of stay is sometimes taken as a proxy measure of in-patient costs. Service providers do not want patients to be discharged earlier only to increase the burden on the community services or to be re-admitted. Although hospital costs could be reduced by reduced hospital stay, overall contact or treatment intensity with therapy staff may not be significantly affected if treatment continues after discharge from hospital. Where this outcome measure has

been used we require information about the blinding of "decision makers" (often consultant physicians or the multi-disciplinary team) that decide when the patient will be discharged (e.g. Slade et al. 2002).

Rationale

Comparing the justification for the physiotherapy intervention or "schools of thought" has, to date, not resulted in a contrast of "intensity" in terms of time or duration of contact with a physiotherapist. For example, Langhammer and Stanghelle contrasted the Bobath approach with a motor relearning programme (Langhammer & Stanghelle 2000). The main reasons for this are likely to be a conscious effort to standardise the interventions in as many respects as possible. Alternatively, it may be because the different approaches are generally poor at prescribing a strict treatment regime indicating the intensity of treatment.

Taken as a whole, the literature is limited. It highlights many difficulties in this area of healthcare research and many authors recommend that more high quality studies be carried out.

Difficulties in healthcare research

The methodological difficulties that have been discussed mean that the quality of evidence on which clinical practice is based, may be limited or questionable. Physiotherapy is not unique in experiencing these methodological difficulties. Many branches of healthcare, certain aspects of medicine, surgery, nursing and therapies have, so far, been poorly researched. For example surgical procedures are half as likely to be based on randomised controlled trial (RCT) evidence as internal medicine interventions (McCulloch et al. 2002).

Along with the methodological difficulties mentioned in Chapter 1 (page 3) and the professional barriers described by Pollock et al. (Pollock et al. 2000), there are a number of problems common to those wanting to study complex healthcare interventions (see table 2.1)(McCulloch et al. 2002).

Table 2.1 - Problems in researching complex healthcare interventions

(McCulloch et al. 2002).

Small trial size
Complex (sometimes non-standard) interventions
Difficulty in defining intervention
Difficulties in monitoring the quality of intervention
"Learning curve" for techniques.
Blinding is difficult and impossible in some cases
Testing established practice
Patient uncertainty in consenting to clinical trials
Interventions may develop gradually rather than being research lead.
Difficulties accepting the requirement for RCTs and acknowledging clinical uncertainty.
Limited funding, education, infrastructure and experience of clinical research

Small trial size

Many branches of healthcare research are typified by small, single centre trials that make their results difficult to generalise, or compare to other populations, settings or services. In the case of stroke the interpretation of results is made more complicated by the natural course of spontaneous recovery. Although this is usually dealt with by selecting a randomised controlled trial design, with random allocation of subjects to groups, if the numbers of subjects is small there may not be an even distribution of subjects that are making spontaneous improvement.

Difficulties standardising interventions

It is difficult to monitor the quality of interventions during trials of therapy (and other interventions such as nursing). The processes are often complex, lengthy and subject to variability. Clear definitions of interventions and procedures and pre-trial training to attempt to standardise interventions or gather information about non-standard interventions may be helpful in tackling this problem. Alternatively, sampling using direct observation or video recording may help to detect variations from the prescribed intervention.

Frequently there is poor contrast between treatment groups being investigated and any treatment effect that is dose-dependent may go undetected. Generally speaking, close monitoring of the intervention is required and variation from the treatment protocol should be recorded. Repeated problems in delivering the protocol should raise concerns with the researchers that action needs to be taken e.g. training or retraining, or in extreme cases that the trial should be discontinued.

Some healthcare professionals learn specific techniques and trials may need to acknowledge that there is a "learning curve" where new techniques are being compared or that there are differences in levels of training or experience between those undertaking the intervention. Such a "skill mix" usually needs to be accepted and at a minimum recorded and described.

Blinding

Often there are not suitable placebo or "sham" treatment techniques that can be offered to maintain patient blinding or blinding of the therapist. In some cases this is possible e.g. where equipment is being used, but generally with exercise or physical handling of the patient it is impossible to provide a double-blind intervention, so the single-blind design is common. Maintaining blinding of observation at follow up can be difficult and patients and therapists providing the intervention must take precautions to prevent disclosing the treatment allocation.

Testing established practice

Healthcare researchers have the problem of testing established practice e.g. testing accepted techniques against a placebo or no treatment may become ethically difficult. In the case of stroke, physiotherapy is an accepted component of stroke unit care (Stroke Unit Trialists Collaboration 2003)(Langhorne & Pollock et al. 2002) and as such, it would be difficult to deny patients what may be an important part of their rehabilitation. Some patients may be reluctant to participate in trials of therapy, especially if they perceive these to be straying from established practice. Investigations into why patients make decisions to accept treatment, or to participate in clinical trials, may help in the design of RCTs, making sure that eligible patients understand their options and that recruitment is maximised.

Creeping changes in practice

Healthcare may develop gradually rather than through a research base. In this way small incremental changes to process may be individually insignificant and often go un-researched. However over a period of time a significant change may have occurred. Regular clinical audit as part of routine service delivery may alert researchers to creeping changes in practice or outcomes and may be the basis for recognising the need to carry out RCTs. The trials I reviewed span nearly thirty years, though most were published in the last ten years. We need to assume that "physiotherapy" as an entity has not altered considerably within this period. It seems fair to make this assumption, despite different treatment methods being in vogue or different explanations of the mechanism of treatment being hypothesised at different times. The fundamental underlying physical nature of the use of exercise and movement for treatment appears to have changed very little. However without specific, clear descriptions or records of the interventions (especially in some earlier trials) for comparison, this has to remain an assumption.

Resistance to change

Just as there have been champions of research and scientific evaluation in individual professions there are also a small number of individuals with difficulties accepting the requirement for RCTs, and acknowledging clinical uncertainty. This small minority may refuse to participate in clinical trials or be hesitant to change their clinical practice in the light of sound research findings.

Given that physiotherapy as a profession is still relatively young, small and developing, its current position in developing its research foundations is perhaps understandable. Along with some other professional groups its members might claim there is a lack of funding, education in clinical epidemiology, research infrastructure and experience with which to rapidly tackle these challenges.

Tackling some of the problems

The problems of carrying out research into complex healthcare interventions that have been discussed are not insurmountable. Campbell et al. (Campbell et al. 2000) have described sequential phases of developing RCTs of complex interventions for those

embarking on research into complex interventions such as stroke rehabilitation. They comment that the "use of iterative, phased approach using qualitative and quantitative methods should lead to improved study design, execution and generalisability of results" (see Table 2.2). They further recommend qualitative study of the processes of implementation of interventions in study arms as this may further show the validity of the study findings.

Researchers should aim for adequately powered feasible studies. Preparatory work should establish availability of subjects and resources to deliver the intervention. Where this is likely to be difficult, co-operation between centres can assist in recruitment, however this requires a co-ordinated approach and communication between the centres and a network of researchers willing to concentrate on the same project.

Piloting trials may help identify methodological difficulties before precious resources are committed to a large-scale trial. Where recruitment is likely to be difficult then every effort should be made to include eligible participants. Examining characteristics of subjects who chose not to participate in pilot studies may help identify reasons for difficulties in recruitment e.g. age, gender or method of recruitment approach. Careful, clear wording of recruitment literature and open discussions ensuring true informed consent will often be rewarded with good rates of recruitment. Ashburn recommends including a broader spectrum of patients in terms of their abilities (Ashburn 1997) but this could lead to recruitment problems (because of the requirement for consent in even severely disabled patients) and a dilution of any treatment effect because we would expect different clinical outcomes from the different groups e.g. differences in age and severity of stroke.

Table 2.2 Phased development of RCTs of complex interventions (Campbell et al. 2000)

Stage	Phase	Possible actions
Theory	Pre-clinical	examining previous studies.
Modelling	Phase I	carrying out descriptive studies considering qualitative work around the topic carrying out a survey to look at possible implementation producing a description of services to be investigated.
Exploratory trial	Phase II	carrying out feasibility studies acknowledging the possible presence of a learning curve considering methods to ensure the intervention is applied in a standard way. arranging training if required in order to attain consistency. make recommendations for pilot work / exploratory trials. defining the control intervention. calculation of the sample sizes
Definitive RCT	Phase III	carry out the definitive study
Long-term implementation	Phase IV	dissemination of results, considering generalisation of results planning leading to implementation of results

Campbell et al. go on to recommend that the intervention should be monitored and standardised by pre-trial training. The production of written guidelines or manuals and handbooks can assist researchers to standardise the conduct of the trial. This can be particularly important when several centres are involved and many staff or a turn-over of staff (for long running trials) are likely to be involved in the trial on-going re-training may be required.

Efforts should be made to establish and maintain blinding of the participants or observers. This could be simple measures such as reminding subjects or those who are aware of treatment allocation not to disclose this to the blinded assessor or to avoid documentation being available or out of sight from the observer. Carrying out follow up assessments at a different location to that where the intervention is provided may help to ensure that blinding is maintained.

The use of standard measures with established measurement qualities (Hobart et al. 1996) allows comparison between studies, making interpretation and generalisation of results easier and facilitates combination in meta-analysis.

Desirable features of a randomised controlled trial are summarized in Table 2.3. (Mulrow & Oxman 1997, Langhorne & Dennis 1998).

Table 2.3

Desirable features of randomised controlled trials

Clearly stated aims and objectives (focussed question)
Adequate number of subjects based on power calculation
Explicit inclusion and exclusion criteria
Description of groups at baseline
Efforts to reduce selection bias e.g. concealed randomisation of subjects
Monitoring of clearly defined intervention
Subjects in groups receive similar treatment apart from the intervention
Double blind intervention
Reporting of adverse events
Use of standardised outcome measures with known measurement qualities (reliability and validity)
Blind assessments
Complete follow up of subjects
Intention to treat analysis

In terms of reporting, the results from trials should be disseminated as widely as possible. However not all results are likely to reach the public domain due to publication bias (discussed in Chapter 4). This can perpetuate difficulties in carrying out trials as researchers are denied the opportunity to discover the difficulties experienced by other researchers and to discuss possible solutions. Additionally, where small trials could be combined in a meta-analysis, unpublished trials are likely to be missed or difficult to obtain by those carrying out secondary research.

Where formal research is difficult or impractical a culture of audit or descriptive studies may still provide important information and help to establish the foundations or basis of clinical trials. This may be as simple as getting staff accustomed to data gathering and handling and the rigour required to successfully run a trial in a clinical setting.

Finally, Wade warns of the potential for Type III error – an error of interpretation of results (Wade 2001) when considering trials of complex interventions. Recommending that as "there are likely to be interdependent components of the rehabilitation "black box" and if individual studies find negative results then these should be further investigated in the context of the other components".

Addressing my research questions

My questions in Chapter 1 are best addressed using a randomised controlled trial design. When I tried to relate the available results of the RCTs in the literature to my questions, some trials were clearly more relevant than others.

A number of trials focused only on outpatient interventions (Smith et al. 1981)(Werner & Kessler 1996) (Duncan et al. 1998) or were examining late intervention out-with the hospital setting (Wade et al. 1992)(Green et al. 2002). Some studies featured unusual interventions that did not reflect physiotherapy practice in the UK: using a rocking-chair and a splint to give sensory-motor stimulation (Feys et al. 1998); patients practising arm movement on their own with the use of a mirror (Altschuller et al. 1999) and self-practise of rising from the chair (Pollock et al. 2002). Some other studies, although contrasting intensity of therapy, appeared to be more focused on investigating the intervention rather than the intensity of the intervention (Carey 1990) (Walker et al. 2000).

The studies that seemed more relevant to establishing if intensive physiotherapy after stroke would produce benefits are described below.

Lincoln et al. 1999

In what is clearly the largest physiotherapy intensity study to date, with 282 patients, Lincoln et al. carried out a high quality single-blind RCT comparing the effect of increased physiotherapy on arm function (Lincoln et al. 1999)(Parry et al. 1999(a)). Additionally they investigated the effects of this treatment when administered by a qualified physiotherapist or by a trained supervised assistant. Their study followed a typical approach found in UK practice, mostly based on the Bobath approach, though was limited to upper limb intervention and involved a highly experienced and motivated therapist. They aimed to give ten hours of additional therapy over a 5 week period.

They recruited acute patients up to 5 weeks after stroke. Subjects were randomly allocated to control, additional therapy with a qualified physiotherapist or additional therapy with a therapy assistant working under supervision. Outcomes were assessed at the end of intervention (5 weeks), 3 and 6 months after stroke using arm function and ADL measures (Rivermead Mobility Index (RMI), Rivermead Mobility Assessment (RMA) (Arm section), Action Research Arm Test (ARAT) and the Barthel Index (BI).

They found no differences between the groups with no significant effect on arm function. This negative result may be due to the content of the therapy, patient selection, chance or possibly a lack of intensity, as only half of the patients allocated to the additional therapy groups completed the programme.

A post-hoc analysis, examining sub-groups suggested that less severely impaired patients benefited from intervention from a supervised therapy assistant rather than a qualified physiotherapist. It is possible that there was more contrast in the content of the sessions delivered by the supervised assistant. The qualified therapist may have spent more time discussing treatment and negotiating with the patient whilst the assistants may have spent a greater proportion of the time actually carrying out exercises.

Kwakkel et al. 1999

In a well conducted single blind RCT Kwakkel et al. investigated the effects of different intensities of arm and leg rehabilitation on the functional recovery of activities of daily living, walking ability and dexterity of the paretic arm (Kwakkel et al. 1999).

Within 14 days of onset of primary middle cerebral artery stroke, patients, recruited from seven hospitals, were randomly assigned to one of three groups: to receive a rehabilitation programme with the emphasis on the arm; a programme with the emphasis on the leg and a control group that immobilised the arm and leg using an inflatable splint. The intervention was applied for 30 minutes per day for 5 days per week for a period of 20 weeks. This was over and above their normal rehabilitation programme. The intervention was described in treatment diaries (in blocks of 15 minutes). It was not reported who provided the treatment.

Their primary outcome measures were ability in activities of daily living as measured by the Barthel Index (BI), walking ability described by functional ambulatory categories and upper limb dexterity assessed by the Action Research Arm Test (ARAT) at 6,12, 20 and 26 weeks after stroke.

They found higher scores in the leg training group for all of the outcomes and a small improvement in dexterity in the arm group. These effects had disappeared by week 20. They concluded that increased intensity of physiotherapy produced short-term benefit and that exercise therapy produces benefit in the area at which it is aimed. They went on to follow up their subjects at 9 and 12 months (with un-blinded assessments) but found no significant differences between the groups.

It is difficult to generalise from their results to the general stroke population. They recruited approximately 3% of patients admitted to their hospital, all of whom had marked disability (a BI score of 9/20 or lower) and were non ambulant. They achieved positive results though, taken overall, the study is probably not large enough to actually change clinical practice. Some other studies have had a limited contrast between treatment groups and Kwakkel et al.'s results may reflect their ability to maintain

treatment contrast by immobilising the control group in inflatable splints and that their intervention started early.

Partridge et al. 2000

Partridge et al. carried out a single-blind, randomised controlled trial of physiotherapy intensity reported in 2000 (Partridge et al. 2000). They recruited 114 patients and followed them up at 6 weeks and 6 months using a variety of less frequently used outcome measures: timed walk (over 5m); profiles of recovery (POR); 2 arm function tests; the step:time ratio; a 6 item ADL scale; a 5 item quality of life scale; the functional reach test; timed sit to stand; the Hospital Anxiety and Depression index (HAD) and a measure of perceived locus of control over recovery (RLOC).

In this pragmatic study the researchers included all patients referred to their stroke unit and aimed to contrast 30 minutes treatment with 60 minutes treatment. They could detect no significant difference between the groups using their outcomes. The intervention probably reflected UK practice, however their sample included many patients with poor prognosis (elderly, incontinent of urine, communication impaired and with low mood). The outcomes they selected make interpretation of the results difficult for those unfamiliar with the measures and comparison across studies is complex. Some elements were not reported with little detail of those patients that failed to complete the trial (21 / 114, approximately 17%). It is unclear whether those patients died, withdrew or were intolerant of the intervention. Although they had set out to tackle relevant and interesting aspects of stroke physiotherapy the researchers concluded that their study lacked precision.

Richards et al. 1993

In 1993 Richards et al. reported a pilot RCT to investigate the effect of early, intensive, gait-focused physical therapy on ambulatory ability in acute stroke (Richards et al. 1993).

Patients were randomly allocated to one of 3 groups: conventional physiotherapy; and groups that received intensive physiotherapy that either started early or at the usual (conventional) time. The subjects were assessed at entry, 6 weeks, 3 and 6 months later.

by a blinded independent evaluator using standard measures: gait analysis; gait speed;. Fugl-Meyer (leg and balance) and the ambulatory component of the Barthel Index.

They reported modest short-term benefit that disappeared at 3 and 6 months. This was a small study that was focussed on the lower limb and attempted to address several questions at once. Because of the small numbers involved (27 subjects in 3 groups) and the subjects being described only as "middle band" of severity it is difficult to generalise from the results.

Slade et al. 2002

In a study with a focus on reduction of length of hospital stay and costs, Slade et al. carried out a randomised controlled single-blind trial examining the cost effectiveness of increased intensity of "therapy" (physiotherapy and occupational therapy) on a mixed group of patients in a neurological rehabilitation unit (Slade et al. 2002).

Their experimental group were younger than in many of the other studies, reflecting inclusion of head injured patients and those with multiple sclerosis (87 /141 (60%) were stroke patients). They aimed to deliver 67% enhancement of therapy, though actually provided 59% enhancement, the equivalent of one and a quarter hours of physiotherapy and occupational therapy. They looked to length of stay as a measure of cost effectiveness.

They found an average reduction in length of hospital stay of 17 days with cost saving calculated as £1737 per patient. The ability to generalise results to other stroke units is limited due to the limited reporting of sub-groups according to their condition.

Sunderland et al. 1992

Sunderland et al. conducted one of the earlier trials, reported in 1992, with many good features. It was a single blind RCT to investigate the effect of an enhanced physical therapy regime on upper limb recovery (Sunderland et al. 1992).

It was a relatively large trial with 135 patients and featuring the use of high quality standard measures and blinded assessments. They contrasted two groups that received

therapy for the arm (32minutes v 20 minutes). They assessed outcome by using the Extended Motricity index, Motor Club Assessment, passive movement and pain, Frenchay Arm Test (FAT), Nine Hole Peg Test (9HPT) and Barthel index at 1, 3 and 6 months.

They found a small but statistically significant difference in recovery of strength, range and speed of movement in favour of the experimental group after 6 months. The treatment effect was more marked in the mildly impaired group and was still present at 6 months but was lost at longer-term follow up at one year. Again, the two groups had a limited contrast (mean of 12 minutes).

Do these studies answer my questions?

Returning to my original questions in Chapter 1, it is worth discussing to what extent they are addressed by these studies.

"Does the provision of intensive physiotherapy after stroke produce benefits which:"

a) *lead to reductions in impairment and disability.*

The results from several trials suggested small but significant benefit from increased physiotherapy intervention, at least in the short term (Sunderland et al. 1992) (Richards et al.1993) (Kwakkel et al. 1999), whilst others have reported little or no measurable benefits (Lincoln et al. 1999) (Partridge et al. 2000).

Most studies do not address the effect of physiotherapy on "mobility", with many reporting outcomes in terms of activities of daily living or impairment using a variety of measures.

b) *are greater when targeted (e.g. on upper limb recovery).*

Three studies consider the arm in isolation (Sunderland et al. 1992)(Lincoln et al. 1999)(Miller et al. 2000 (abstract)) whilst one (Richards et al. 1993) concentrated intervention only on the lower limb. Kwakkel et al. randomised subjects to upper or lower limb groups.

c) *are greater for patients with moderate impairment and little co-morbidity.*
Sunderland et al. found most benefit for "mild" cases.

d) *are greater in the shorter (3 months) than longer term (6 – 12 months).*
Short term benefit was noted in the trials by Sunderland et al., Richards et al. and Kwakkel et al. The other trials either did not demonstrate a difference or did not have comparable follow up points.

e) *result in a reduced duration of inpatient rehabilitation.*
Slade et al. was the only trial to use length of stay as their primary outcome measure. Patients with greater intensity of therapy were discharged from hospital sooner than the control group, however we do not know if this resulted in a reduction of overall rehabilitation time. Rehabilitation treatment may have continued on an outpatient basis.

The trials available in the late 1990s still did not appear to have adequately tackled the methodological problems or reached a clear answer to these questions. Therefore the issue of increased intensity of physiotherapy remains on the research agenda (Legg et al. 2000).

Conclusion

There are several studies in the literature that examine physiotherapy intensity after stroke, however these are mostly relatively small, inconclusive and at times arrive at contradictory conclusions. The trials are varied and none seem to adequately address the questions set out in the first chapter. Many demonstrate the problems associated with physiotherapy trials and investigating complex healthcare interventions. This lack of evidence could be due to differences in trial methodology, patient selection, therapy technique, outcome measures or simply due to chance. It seems that Ernst's conclusion that "Well planned clinical trials aimed at finding the best approach and discriminating potential responders from non-responders are urgently needed." despite some high quality trials in the intervening years still held true ten years later.

With this in mind and acknowledging the methodological challenges, a group in Glasgow set out to complete a randomised controlled trial of intensity of physiotherapy after stroke. This trial is described in the next chapter.

Summary

- I discuss and review some of the important papers that have examined intensity of physiotherapy after stroke in relation to the research questions.

- Many trials have limitations and demonstrate problems common to research into complex healthcare interventions.

- Some solutions and desirable features in trial design are proposed.

- I conclude that there is still a lack of evidence about the optimum intensity of physiotherapy and that further well-conducted, randomised controlled trials may be useful. I go on to describe such a trial in the next chapter.

CHAPTER 3

THE GLASGOW AUGMENTED PHYSIOTHERAPY AFTER STROKE (GAPS) STUDY

Introduction

In this chapter I describe a randomised controlled trial of augmented physiotherapy that I helped develop and co-ordinate, aiming to address my questions.

Background

The systematic reviews discussed in the last chapter (Langhorne et al. 1996(a)) (Kwakell et al.1997) (van der Lee et al. 2001) suggest that augmented physiotherapy may speed up recovery after stroke. The apparent effects were modest but could contribute to patients achieving their potential and returning home at an earlier stage. However, because the available studies were small and heterogeneous there was a lack of reliable, practical information on the relationship between physiotherapy intensity and patient outcomes.

Few of the previous trials have specifically focussed on the recovery of mobility, an obvious choice since it is a core activity of physiotherapy and a key factor in determining functional outcomes after stroke. If the "natural" rate of recovery after stroke cannot be altered then increasing therapy input above conventional levels would be a waste of effort and resources. However if the period in which the patient remains dependent (and in hospital) can be reduced then a reduction in nursing and "hotel" costs (currently over 95% of hospital stroke costs) could be achieved through an increase in therapy input (currently accounting for only 1% of costs) (Warlow et al. 2001).

Having identified this issue (Langhorne & Dennis 1996), in 1998 a group led by Professor Peter Langhorne, successfully applied for funding from the Stroke Association to carry out a randomised controlled trial. I was employed by this group to develop the existing protocol and methods and co-ordinate the trial, setting out to answer the basic question

"Does the provision of additional in-patient physiotherapy after stroke speed up the recovery of mobility?".

With mobility as our primary outcome, we wanted to use sound methods and attempt to address some of the limitations of the previous studies.

We wanted specifically to develop and address five key questions:

a). Does augmented physiotherapy speed recovery in terms of the achievement of mobility milestones, patient activity and quality of gait.

b). Does augmented physiotherapy allow patients to be fit for and able to return home earlier.

c). Does augmented physiotherapy improve patient satisfaction with care.

d). Does augmented physiotherapy result in sustained benefits (in terms of mobility, activities of daily living, and quality of life)

e). Does augmented physiotherapy result in cost recovery through improved patient outcomes or reduced length of hospital stay.

Subjects

We included patients admitted to stroke rehabilitation wards at Stobhill, Drumchapel and Lightburn Hospitals, in Glasgow. I visited each of the hospital sites once or twice a week to screen all new admissions. I did this by asking staff on the wards and physiotherapy department and checking the admissions register and the casefiles of all patients on the rehabilitation wards. In addition, the physiotherapy staff, including the project's research physiotherapists, were asked to contact me by telephone if any potential subjects were admitted. I was also aware of

some potential subjects that would be transferred from an acute hospital where I continued to have clinical duties.

All subjects had a clinical diagnosis of stroke within the previous 1-4 weeks and were able to tolerate and benefit from mobility rehabilitation i.e. they had independent functional sitting balance, no major co-morbidities, no major communication deficit or cognitive impairment, and were previously independent (pre-stroke Rankin score of less than 3)(Wade 1992).

These criteria were determined by casenote review and discussion with relevant ward staff e.g. the treating speech and language therapist was consulted to estimate the patient's ability to understand recruitment information. Cognitive impairment was routinely recorded with the Abbreviated Mental Test (AMT) score, with a score of less than or equal to 8 / 10 being considered as impaired (Hodkinson 1972). Functional sitting balance, i.e. the ability to sit unsupported with the feet on the ground for a period of at least approximately one minute, was taken from the casenote or after discussion with the treating physiotherapist. Major co-morbidities were noted as recorded in the casenote by medical staff. These were: dementia; arthritis that limited activities of daily living; unstable angina that limited exercise; chronic obstructive pulmonary disease (COPD) that limited exercise; major surgery in the past 3 months; poorly controlled diabetes; myocardial infarction in the past 3 months and peripheral vascular disease that limited exercise.

We recorded the type of stroke (Bamford et al. 1991) and in the case of hemiplegia, the side affected.

Methods

Feasibility

Several pilot investigations to support this project had been carried out before funding was awarded. The systematic reviews of the randomised controlled trials (RCTs) mentioned previously (Langhorne et al. 1996) indicated that a doubling of therapy time might produce measurable improvements in recovery. Physiotherapy input at the three sites was established as involving approximately
30 – 45 minutes per day (Monday to Friday) direct therapy time. Pilot observations

indicated that over 900 patients would be admitted to the study sites during an 18 month recruitment period of whom 25% (225 patients) would meet the trial inclusion criteria. Of these the majority (>80%) would regain independent walking taking a mean (SD) of 18 (11) days to recover walking over 10 paces, 26 (15) days to recover walking over 10 metres and 45 (25) days to return home. The peak walking speeds averaged 0.32 (0.08) metres/sec.

Power calculation

Based on these figures and taking into account possible attrition, we estimated that recruiting 100 patients would give the study an 80% power (at 5% level) to detect a 7-day reduction in the time taken to recover independent walking and 0.05 metres/sec increase in walking speed. The trial was unlikely to have adequate power to show a significant improvement in activities of daily living (ADL). It was designed to be compatible with previous RCTs of intensive physiotherapy to facilitate a combined prospective meta-analysis.

Ethical approval

We applied for and obtained ethical approval on all three hospital sites.

Randomisation

After giving informed consent, patients were randomly assigned (through a telephone randomisation procedure based at the Roberson Centre for Biostatistics at the University of Glasgow) to one of two groups: a) conventional in-patient stroke services including conventional physiotherapy input (30 – 40 minutes per day, 5 days per week), or b) conventional stroke services plus additional physiotherapy input (to approximately double the total daily physiotherapy time to 60 – 80 minutes per day, 5 days per week).

Randomisation was stratified by site, age (75 years or over), and disability level (Barthel Index greater than or equal to 10) at recruitment.

Due to limited resources to supply the intervention, patients were only put forward for randomisation when we could ensure that the intervention could be delivered. Thus when several patients were receiving additional intervention we delayed randomisation for suitable subjects. Once resources were available patients were put forward for randomisation as soon as possible.

Intervention

Because of the great diversity of symptoms that stroke patients experience, we considered it impossible to designate in advance a standard treatment for all patients. The three centres were chosen as they have similar physiotherapy approaches representative of normal UK practice (Sackley & Lincoln. 1996) (Davidson & Waters 2000). Outline treatment schedules were developed based on the approach of Edwards et al. (Edwards et al. 1991) by the trial management group to ensure consistency of treatment categories. Treatment was broadly based on the "Normal Movement" (Bobath) approach i.e. using a knowledge of normal movement to inform a problem solving approach to the assessment and treatment of the individual patient. The range of techniques included normalising tone and sensory input, re-education of balance reactions and facilitating selective movement to achieve functional independence. The overall goals were to improve, maintain or prevent deterioration of physical skills. Specific functional objectives included the establishment of independent sitting balance (already achieved in our patients), standing balance, upper limb function and walking.

Recording the treatment

A standard format for recording the type and amount of therapy was also developed and tested (see Appendix I). These recorded patient identification details, the treating therapist, position and activity of the intervention, the focus of the treatment e.g. upper limb functional re-education, and the number of minutes spent with the therapist in the various components of the treatment session. Time was split into "direct" contact time e.g. "hands-on" treatment, direct supervision of exercises and discussion, or "indirect" contact time e.g. written recording, reporting at case conferences, telephone conversations. The number of minutes was taken to the nearest 5 minute "unit". These timesheets were completed for each contact with the patient. I collected these sheets on my visits to the hospitals, checking they were completed correctly. Therapists were encouraged to complete the forms as soon as possible after contact with the patient.

Monitoring the treatment

I informally monitored the amount of time the therapists were spending with the patients, depending on their treatment allocation. Where patient treatment times

were less or more than expected I would discuss the therapists' reasons for this being the case. Without influencing the content of the therapy, the treating physiotherapists were reminded to try to maintain a treatment contrast of twice as much therapy for those subjects in the treatment arm of the trial.

By this monitoring and having research physiotherapists on two of the sites we attempted to maintain consistency of intervention and accuracy of records by reducing any delay in completion of data collection. Monitoring the intervention was complex, as staffing levels normally fluctuate according to staff leave for holidays, sickness and training. Therefore at certain times during the study some of the intervention group would receive less therapy input than at other times. We had to accept that this would be the case and concentrated on maintaining a contrast between the groups within the available physiotherapy service at any one time. To try to minimise this problem the two half-time research physiotherapists that we employed provided "back fill" time support for physiotherapists delivering the extra therapy. This resource could be drawn on to ensure the trial was seen as a priority by those providing the clinical service. This "pooling" of these staff also allowed us to examine treatments being provided by a broad variety of physiotherapists e.g. junior staff, senior staff, and therapy assistants and undergraduate students working under supervision. This reflects how services are normally provided to patients rather than an intervention that is provided by a single highly trained and skilled, enthusiastic specialist.

Other interventions

Patients in both groups had the normal access to occupational therapy, speech and language therapy, nursing and medical interventions whilst inpatients and after discharge in the community.

Outcome measures

We used the following outcome measures (see table 3.1). Copies of the data collection forms are given in Appendix II along with references, a description and rationale for the use of these measures.

Table 3.1 Outcome measures for each domain and the timetable for follow up.

Measure	Baseline	Weekly while inpatient up to 10 weeks	4 weeks	3 months	6 months
Impairment					
Motricity Index	√	√	√	√	√
Trunk control test	√	√	√	√	√
10 metre walking test (preferred gait speed)		√	√	√	√
Functional reach test	√	√	√	√	√
9 hole peg test			√	√	√
Rivermead Visual Gait Assessment (RVGA)			√	√	√
Gait analysis			√	√	√
Disability (activities)					
Barthel Index (BI)	√	√	√	√	√
Nottingham Extended Activities of Daily Living Index (NEADLI)				√	√
Mobility milestones	√	√	√	√	√
Action Research Arm Test (ARAT)			√	√	√
Rivermead Mobility Index (RMI)		√	√	√	√
Portable electronic activity monitor			Once at 3 weeks		
Handicap (participation)					
Rankin (Oxford Handicap scale)	√			√	√
Quality of Life					
Euroquol	√				√
Patient satisfaction scale				4 weeks after dis-charge	

We selected these measures because they are established, reflect the domains that interested us, have (in general) known measurement properties (reliability, validity, sensitivity) and are practical to administer to patients in a hospital environment (with the exception of the patient satisfaction scale which was sent as a postal questionnaire). In addition to these we assessed patients' medical complications, use of equipment and use of community resources.

We used the following methods related to the key questions.

Question a). Does augmented physiotherapy speed recovery in terms of the achievement of mobility milestones, patient activity and quality of gait?

We carried out the follow up schedule, gathering data on the two groups as outlined in Table 3.1.

We examined the Mobility Milestones (Partridge et al. 1987, Smith and Baer 1999) for differences in terms of levels of achievement, time taken to achieve each milestone and the change in status ("how many milestones were passed on the journey to recovery" e.g. from having no milestones (just able to sit) to walking 10 metres involves "gaining" 3 milestones, whereas being able to take 10 steps to being able to walk 10 metres involves gaining just the one milestone.). We also tested to see if those changes were sustained.

Patient activity was measured using an "activity monitor" developed by the Bioengineering Unit, University of Strathclyde (Suckalingham 1993). The "activity monitor" was able to classify, on a continuous basis, the activity of the patient into the two primary classifiers – sitting and standing - using the output of a single sensor attached to the patient. This sensor consisted of a commercial miniature pressure transducer connected to a flexible, fluid-filled tube. The fluid-filled tube and sensor were taped to the lateral side of the patient's unaffected leg (Fig. 3.1). The pressure measured depends on the end-to-end length of the tube, which changes during activity. The transducer produces a simple output that is characteristic of the posture or activity of the subject (Fig. 3.2). Data were recorded on a data logger [Biomedical Monitoring Ltd, UK] on a single occasion, 3 weeks after

randomisation. The patients wore the monitor from early morning to just before going to bed at night (their "waking day"). The outcome measures of "proportion of time spent upright" and "number of transitions between sitting and upright per hour" were recorded for the patients' waking day.

In addition to this, we divided the day into the period before 4:30pm (the time during which activity was considered to be directly influenced by the physiotherapists) and after 4:30pm (the time during which activity was dependent on the patient's own ability and motivation, and nursing staff assistance) to look for differences in activity. This allowed us to compare patient activity during the period therapy staff were on duty with the period they were not, in order to establish if there is a difference. It also allowed us to compare the activity before 4-30pm between the two groups of patients to see if the augmented group were indeed more active. Comparing the two groups after 4-30pm would also indicate if the augmented group were less active later in the day, perhaps due to fatigue.

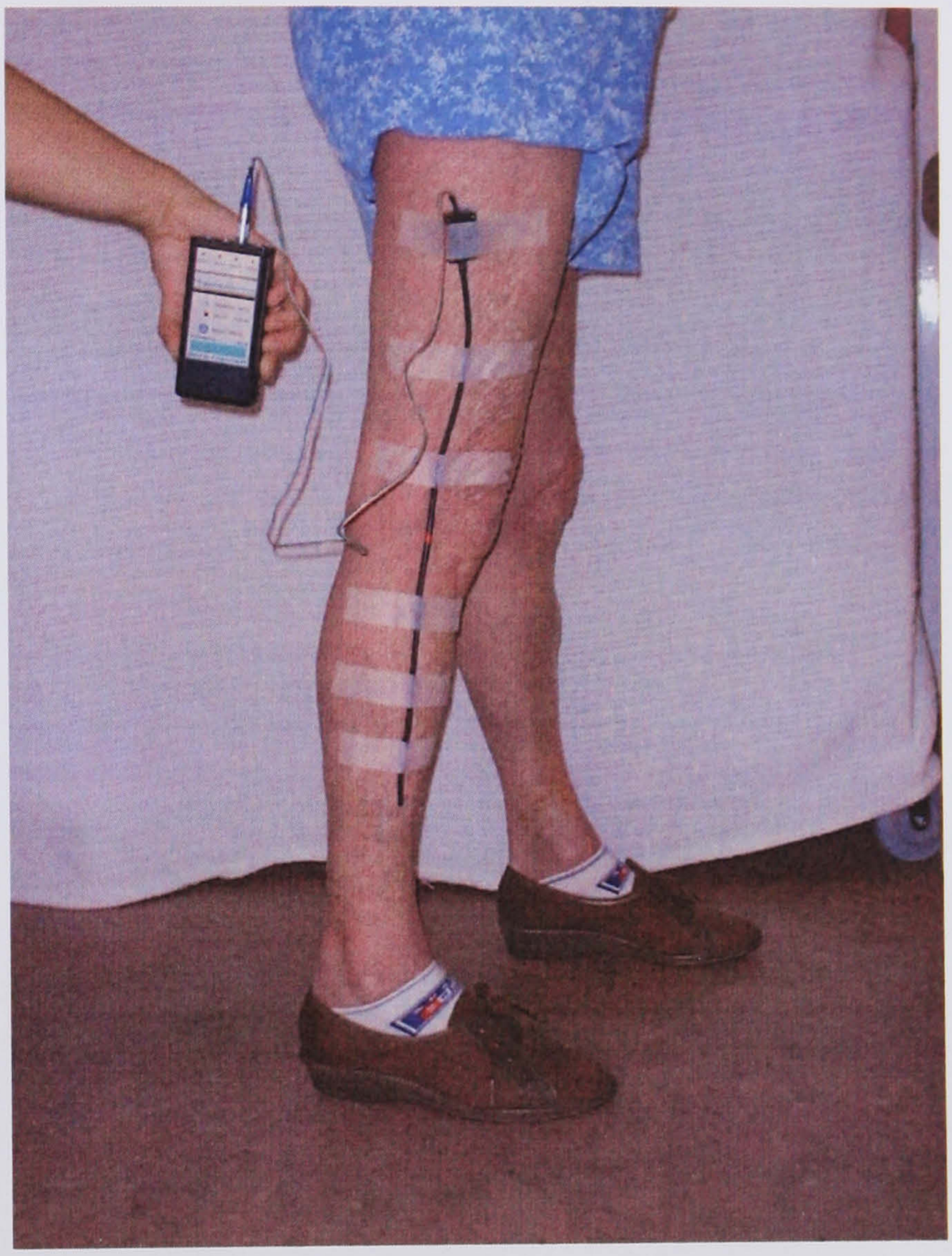


Figure 3.1 Activity monitor attached to patient's unaffected leg
(image – T. Egerton)

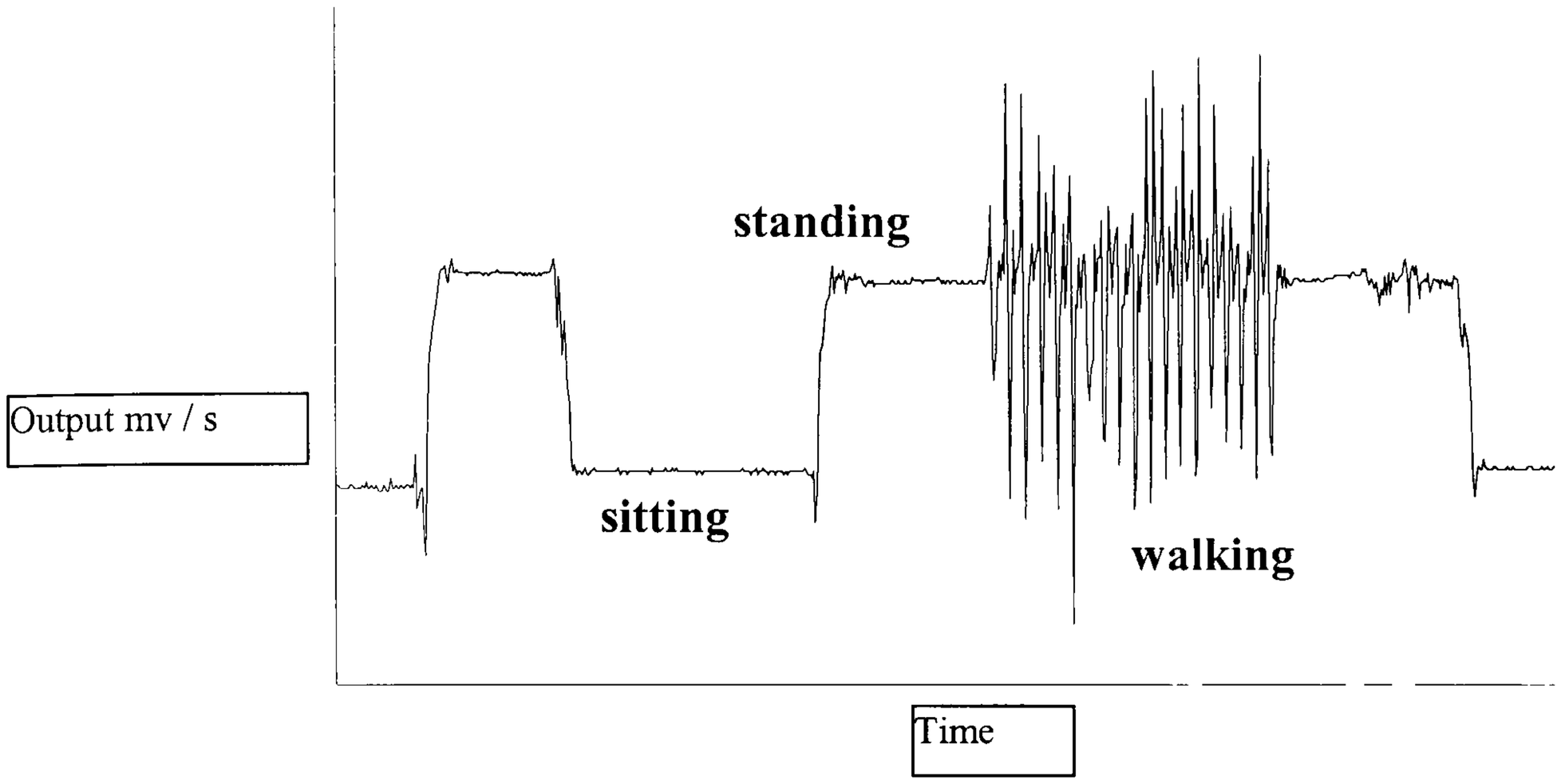


Figure 3.2 Output from the activity sensor. Different output levels are seen for sitting, standing and walking.

We compared the patients' quality of gait using walking speed and a "body worn gait analysis system". This system (Granat et al. 1995) consisted of shoe insoles that incorporated four force-sensitive resistors [Interlink Electronics, Luxembourg], acting as switches, placed at the position of the heel, head of the first metatarsal, head of the fifth metatarsal and the big toe. They were mounted on thin plastic film cut to the shape of the subject's feet. The subjects walked along a walkway of 12m and all data were collected on a data-logger [Biomedical Monitoring Ltd, UK] worn around their waist. This allowed us to measure speed and symmetry. Symmetry was calculated as the ratio of the swing time of the unaffected leg to the swing time of the affected leg. Again, we examined for differences between the two groups in terms of levels of achievement, speed to achieve these levels and to see if those changes were sustained.

Question b). Does augmented physiotherapy allow patients to be fit for and able to return home earlier?

We recorded the patients' length of stay in hospital, reasons that might have delayed discharge and the frequency of complications and adverse events.

Although we did not expect to see statistically significant changes in these domains we included two commonly used measures; the Barthel Index and the Rankin Handicap Score.

Question c). Does augmented physiotherapy improve patient satisfaction with care?

We compared responses from the two groups to a patients' satisfaction questionnaire sent to them four weeks after discharge from inpatient rehabilitation.

Question d). Does augmented physiotherapy result in sustained benefits (in terms of mobility, activities of daily living, and quality of life)?

We examined all of these variables for differences between the two groups over time. We expected the amounts of data to vary considerably from patient to patient depending on their length of stay in hospital. We therefore identified "key" time lines as being: randomisation, 4 weeks, 3 months and 6 months after randomisation to examine if change was sustained.

Question e). Does augmented physiotherapy result in cost recovery through improved patient outcomes or reduced length of hospital stay?

We measured levels of impairment, disability, handicap, dependency and quality of life as described above.

With the vast majority of acute stroke costs being related to inpatient nursing care and hospital overheads we compared length of hospital stay as our main estimate of cost. Outwith this, any cost differences between the groups were likely to be attributable to the following events:

i).complications whilst the patients were in hospital,
ii).community support being requested at discharge,
iii). the provision of equipment and adaptations,
iv).the rate of adverse events in the months after stroke,
v). use of community services.

The first two were monitored during the patients' stay by notes review and discussion with the treating therapists and then from reviewing their notes on discharge. Complications were considered to have been present if noted in the patients' medical records. We did not attempt to define, quantify or verify any of the complications. Adverse events were recorded at patient follow up interviews at 3 and 6 months, where we asked directly "Since leaving hospital have you had any falls?" and "Have you had

any other problems or illnesses since leaving hospital?". We relied on the patients' self-report for data on these and the provision of equipment and services as we did not have resources to confirm these data e.g. by consultation with the patients' general practitioner or social services.

We were also interested in possible differences in the patient groups that may be attributable to their treatment allocation:

a). Survival

b). Discharge destination

c). Complication rates, e.g., falls, fractures, depression, pressure sores, painful shoulder, extension (recurrence) of stroke

d). Use of services, e.g. follow up in the community (particularly physiotherapy), day hospital referral.

e). Use of equipment e.g. adaptation to home, wheelchairs.

We specifically monitored for adverse events and the possible complications of pain, falls and fatigue at patient interview by the blinded assessor at weekly, 3 and 6 month follow up. During the weekly follow-up interviews whilst in hospital, patients were asked: "During the past week have you had any pain?, During the past week have you had any falls? During the past week have you been feeling tired?".We did not attempt to specifically define or quantify these areas but asked the patients to report what they had experienced.

The primary outcome measures used to answer our questions were: the Mobility Milestones, Rivermead Mobility Index, gait speed and length of hospital stay (thereby costs). We used other outcome measures to monitor the effects of treatment e.g. did increased intensity of physiotherapy lead to a decrease in the rate of complications or onward referral to community services such as day hospital.

Blinding

All assessments were carried out in an area separate from where treatment was delivered. Ms Egerton was not allowed access to patients' notes, treatment timetables or the ward areas where she might have become aware of the treatment allocation. Physiotherapy assistants brought the patients to and from the assessment area. Patients

were reminded not to disclose their treatment group allocation before each assessment and staff members were instructed not to discuss patient care when Ms Egerton was present.

Analysis

Data were gathered on each of the sites for information on input and outcomes. The blinded assessor, Ms Thorlene Egerton, left her assessments in a file and these were collected at least weekly. Once the assessments were made she had no access to previous assessments for comparison. All other data such as time sheets and registration documents were collected by me and kept in a secure central location for safekeeping, to be checked for completeness and to avoid unblinding. I had regular meetings with Ms Egerton to ensure that all documentation had been submitted and received. Data were then "masked" to remove any patient names, photocopied, batched and delivered to the Robertson Centre for Biostatistics at the University of Glasgow for management and analysis. The data were "double entered" to reduce the chance of errors and a code used to indicate treatment allocation. We remained blinded to the code of the data until all analyses were completed.

All analyses were according to the intention-to-treat principle, using all available data for each measurement at the appropriate visit. No formal adjustment was made for multiple comparisons.

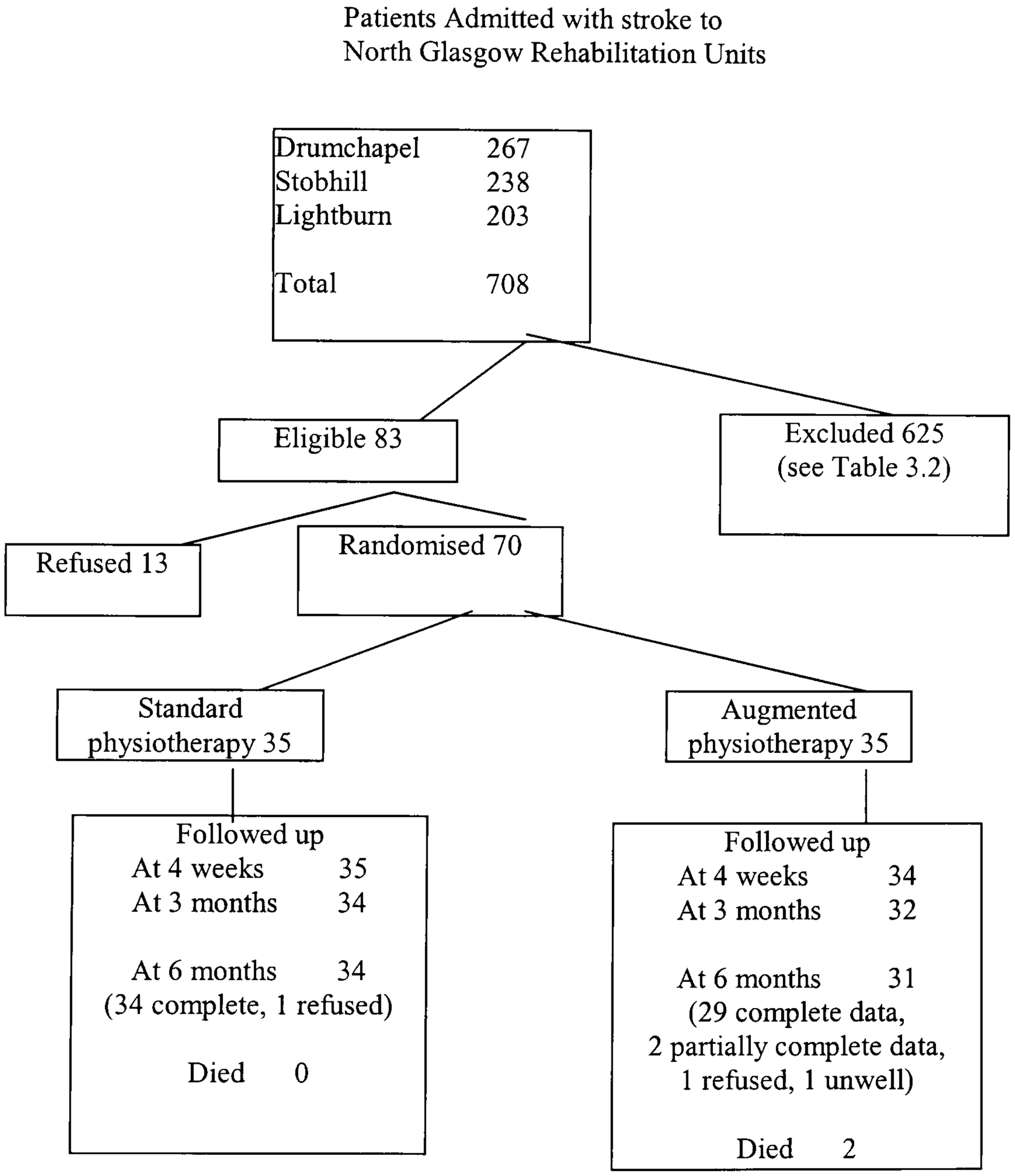
The Bioengineering Unit at the University of Strathclyde interpreted, analysed and reported on data gathered from the activity monitor and gait analysis system using custom written software. Ms Egerton gathered all these data, then delivered the downloaded data directly to the University of Strathclyde, remaining blinded to treatment allocation.

We analysed the data at the 1month, 3 month and 6 month outcomes. Patients were assessed weekly (up to a maximum of ten weeks) during their hospital stay or until discharge. For those subjects discharged within ten weeks, their best scores for the following outcomes were used in the analyses: fastest 10m walking speed; maximum RMI score, maximum Motricity index score; maximum trunk control test and best functional reach. Other outcomes were only measured at 1 month, 3 month and 6 month assessments.

Results

Between 22 July 1999 and 12 February 2001, I screened 708 patients (Drumchapel 267, Lightburn 203 and Stobhill 238) from which we recruited 70 (9.9%) to our study. Thirty-five patients were randomised to each arm of the study (figure 3.3). Thirteen eligible patients refused to enter the study.

Figure 3.3 GAPS study recruitment and randomisation



The reasons patients were excluded from the study are given in Table 3.2 (categories are not mutually exclusive). Some patients could not be randomised because we had limited resources e.g. when the sites had several subjects on augmented treatment they sometimes felt that if another patient was randomised to

augmented therapy by the randomisation centre they would not have sufficient resources to maintain the target treatment times. However, when resources became available or subjects were discharged we immediately reconsidered these subjects. Although we did not formally record the number of subjects excluded in this manner they were considered to be small in number.

Seven patients were lost to follow up. Two (3%) patients died during the study, one of these during the intervention stage (soon after randomisation, but considered not to be related to physiotherapy treatment). Two patients (3%) were too unwell to be followed up, due to stroke-related illness. Three (4.5%) patients refused to complete the follow up schedule. No patients were withdrawn from the intervention. Blinding of the assessor was maintained in 556 / 579 (96%) of the follow up assessments.

Table 3.2 Reasons for exclusion from study

Exclusion (categories not mutually exclusive)	Number of patients
Communication impairment	237
Previous history of stroke	171
Cognitive impairment (AMT<=8)	169
No sitting balance	101
Pre-stroke Rankin >2	39
Dementia	26
Unconfirmed stroke	24
Carcinoma	24
Arthritis limiting ADL	23
Unstable angina (limits exercise)	21
COPD limiting exercise	16
Major surgery (3 months)	14
Poorly controlled diabetes	13
Recent MI (3 months)	10
PVD limiting exercise	6

AMT = Abbreviated Mental Test score, ADL = Activities of daily living
COPD = Chronic Obstructive Pulmonary Disease, MI = Myocardial infarction
PVD = Peripheral vascular disease

The randomisation was stratified by centre (Drumchapel, Lightburn, Stobhill) and disability level (dichotomised as Barthel < 10, or ≥ 10) and age (<75 years, ≥75 years), and the number of subjects within each of these stratum are reported in Table 3.3.

Table 3.3 Number of subjects per group stratified by study centre, disability level and age

	Standard (n= 35)(%)	Augmented (n = 35)(%)
Study centre		
Drumchapel	14 (40.0)	15 (42.9)
Lightburn	5 (14.3)	6 (17.1)
Stobhill	16 (45.7)	14 (40.0)
Disability level		
Baseline Barthel < 10	12 (34.3)	11 (31.4)
Baseline Barthel >=10	23 (65.7)	24 (68.6)
Age		
Age <75	27 (77.1)	28 (80.0)
Age >=75	8 (22.9)	7 (20.0)

The baseline characteristics of the subjects are summarised, split by randomised treatment group in Table 3.4. Continuous covariates, such as age, were reported as means (with standard deviation) whilst categorical covariates, such as gender, were reported as numbers (with percentage) of subjects. No formal comparison of baseline equality between the randomised groups was performed.

Note: All baseline values are expressed as percentages unless otherwise stated.

Table 3.4 Baseline characteristics of subjects in GAPS study*

	Standard (n= 35)	Augmented (n = 35)
Age (mean, SD)	66.9 (10.4)	67.8 (10.6)
Sex - Female	51.4	31.4
Days after acute admission (mean, SD)	25.4 (17.9)	21.9 (14.1)
Days after admission to rehabilitation unit (mean, SD)	15.26 (14.0)	13.1 (10.9)
Stroke classification		
R side of brain	42.9	45.7
TACI	20.6	17.1
PACI	50.0	42.9
LACI	23.5	28.6
POCI	2.9	5.7
Other	2.9	5.8
Barthel Index score (mean, SD)	10.3 (3.1)	11.8 (3.3)
Trunk Control Test (mean, SD)	68.4 (24.1)	71.9 (23.0)
Motricity Index (mean, SD)	100.4 (43.4)	110.4 (43.2)
Pre-stroke Rankin =0	48.6	51.4
Pre-stroke Rankin =1	40.0	28.6
Pre-stroke Rankin =2	11.4	20.0

*Values include all patients with available data; n is the maximum number in each group.

SD = Standard deviation

Intensity of treatment

The intensity of physiotherapy input between the randomised groups is summarised in terms of the total number of hours and the average number of hours per study day (defined as the ratio of total hours of physiotherapy by total days in study) in Table 3.5(a). The columns show the overall (total) number of treatment hours per patient and within this figure the number of hours the treating physiotherapists considered they were specifically treating the upper or lower limbs or other areas.

Table 3.5 (a): Intensity of physiotherapy input in GAPS study: hours

	Total		Upper Limb		Lower Limb		Other	
	Stand (n=35)	Aug (n=35)	Stand (n=35)	Aug (n=35)	Stand (n=35)	Aug (n=35)	Stand (n=35)	Aug (n=35)
Number of hours mean (SD)	21 (16)	33 (21)	5 (5)	10 (7)	5 (4)	9 (7)	11 (10)	15 (11)
Number of hours / study days	0.41	0.73	0.12	0.18	0.11	0.21	0.19	0.34

Stand = Standard, Aug = Augmented, SD = Standard deviation

The mean (95% confidence interval) number of physiotherapy sessions per patient was greater in the augmented therapy (43; 35-51) than the standard therapy group (32; 24-40) (Table 3.5(b)). This equated to an average number of physiotherapy treatment hours in the augmented therapy group (34 hours total; 10 hours on upper limb work; 9 hours on lower limb; 15 hours other work) which was greater than that of the standard therapy group (21 hours total; 5 hours on upper limb; 5 hours on lower limb; 11 hours other work). The average number of treatment hours per weekday differed by 0.45 hours (i.e. 62 vs 35 minutes – 27 minutes). No formal comparison was made of these rates since the augmented group was intended to receive about double the physiotherapy of the standard group.

Table 3.5(b). Intensity of physiotherapy input in GAPS study: sessions

	Standard (n=35)	Augmented (n=35)
Number of sessions mean (SD)	32 (24)	43 (26)
Number of sessions /study days	0.61	1.00

SD = Standard deviation

Activity levels

Activity monitoring data were available for 41 (58%) patients (19 standard, 22 augmented). These were analysed in terms of the patient's average number of transitions to the upright position per hour. Upright events are changes from a non-upright position (sitting or lying) to upright (standing or walking). The mean for the standard group was 1.7 (SD 1.26) upright events per hour ranging form 0.25 to 5.62 per hour. The mean for the augmented group was 2.6 (SD 1.21) per hour ranging from 0.73 to 5.76. There was a significant difference between the two groups (Mann-Whitney U, $p = 0.007$) where the augmented group appeared to be more active in terms of how frequently they stood up.

We also examined the mean proportion of time spent standing or walking. The average proportions for the standard and augmented group respectively were 4.8% (SD 7.8, minimum 0.4%, maximum 34.6%) and 8.0% (SD 5.7%, minimum 0.7%, maximum 18.9%). There was a significant difference between the two groups

(Mann-Whitney U, p = 0.002) where the augmented group appeared to be more active in terms of how much of the time they were standing or walking.

When we analysed the activity over different periods of the day we found the augmented group were more active (more transitions and a greater average proportion of their time spent standing or walking) during the day (from 8-30am until 4-30pm). There was no significant difference in activity between the groups in the period after 4-30pm. indicating that the increased patient activity occurred during the period therapy staff members were at work.

Primary Outcomes – Mobility

Mobility disability – "Mobility Milestones"

Disability as assessed by Mobility milestones (visit at which subject achieved standing, walking 10 paces, and walking 10 metres) was visualised (Figures 3.4 – 3.6) by plotting the proportion of patients having achieved the milestone at each visit (baseline, 4 weeks, 3 months, 6 months).

The time to achieving each milestone was formally compared using a log-rank statistic (Table 3.6) by ascertaining the visit (baseline, weeks 1-10, 3 month or 6 month) at which the milestone was achieved, and assuming the milestone was achieved on the day of that visit. Subjects who did not achieve the milestone were censored at either their death, end of study, or withdrawal.

Table 3.6 GAPS study. Comparison of achievement of "Mobility Milestones"

Milestone	Standard (n=35)(%)	Augmented (n=35)(%)	P-value (log-rank)	Hazard ratio (95% CI)
Standing	35 (100.0)	34 (97.1)	0.25	1.34 (0.81, 2.23)
10 paces	31 (88.9)	32 (91.4)	0.20	1.39 (0.84, 2.30)
10 metres	32 (91.4)	33 (94.3)	0.12	1.48 (0.90, 2.43)

CI = Confidence interval

The hazard ratios give the overall relative chance of an event on treatment as compared to control and account for both censoring and time-to-event. The results show an increased chance of patients receiving augmented physiotherapy achieving each "milestone". However the confidence interval is wide and the estimated differences do not reach statistical significance.

Figure 3.4
Proportion of patients achieving standing at each visit in standard treatment and augmented physiotherapy groups

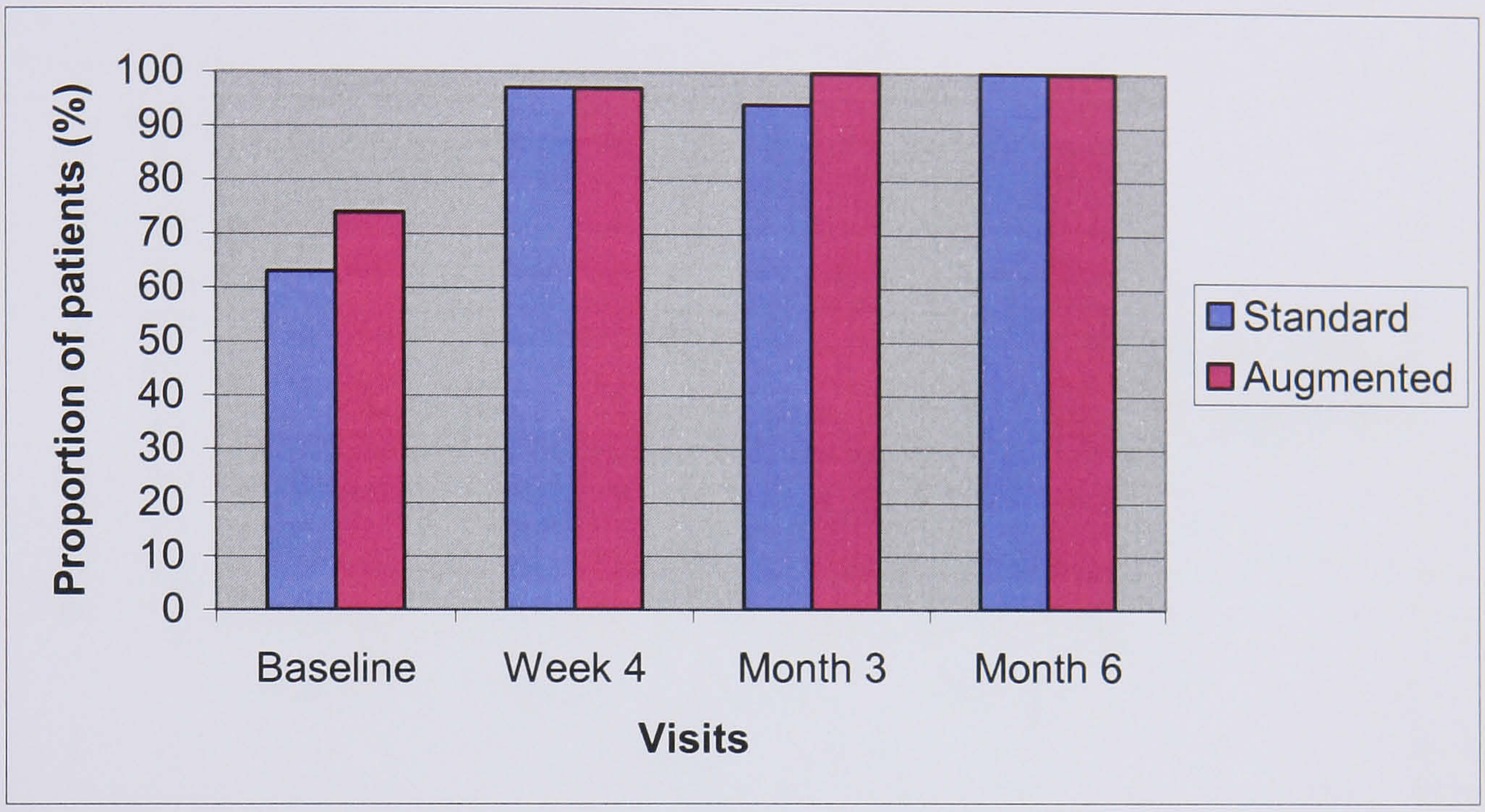


Figure 3.5
Proportion of patients achieving 10 steps at each visit in standard treatment and augmented physiotherapy groups

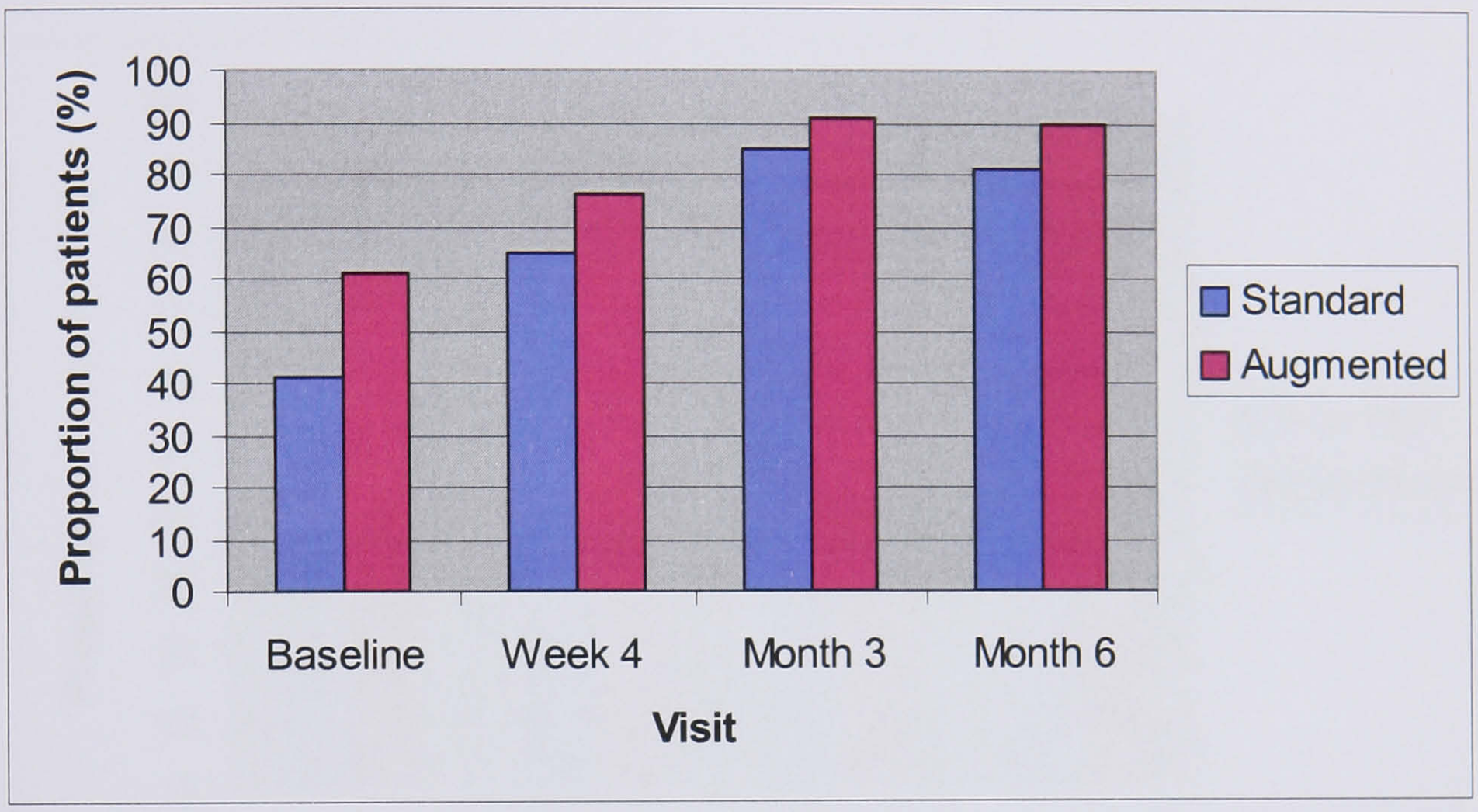


Figure 3.6
Proportion of patients achieving 10-metre walk at each visit in standard treatment and augmented physiotherapy groups

Mobility disability – Rivermead Mobility Index (RMI)

The Rivermead Mobility Index scores were compared between the two randomised treatment groups using two-sample t - tests (Table 3.7). We were unable to compare change over baseline as this was not recorded at randomisation. However, a comparison was made with the scores from the Week 1 follow up assessment.

Table 3.7 GAPS study. Rivermead Mobility Index (RMI) scores

	Standard Mean (SD)	Augmented Mean (SD)	Mean Difference (95% CI)	P-value
Week 1	4.56 (2.64) n=34	5.18 (2.43) n=34	0.62 (-0.61, 1.85)	0.32
Maximum achieved at weeks 1-10	8.26 (2.81) n=35	8.79 (3.03) n=34	0.54 (-2.50, 1.94)	0.45
4 weeks	6.97 (3.49) n=34	7.39 (3.30) n=33	0.42 (-1.23, 2.08)	0.61
3 months	8.06 (3.65) n=34	9.66 (3.33) n=32	1.60 (-0.12, 3.32)	0.07
6 months	9.06 (4.03) n=34	10.20 (3.08) n=30	1.14 (-0.67, 2.95)	0.21
Change from week 1 to 3 months	3.54 (2.80) n=33	4.69 (2.75) n=32	1.14 (-0.23, 2.52)	0.10
Change from week 1 to 6 months	4.45 (3.15) n=33	5.07 (2.74) n=30	0.61 (-0.88, 2.10)	0.41

SD = Standard deviation, CI = Confidence interval

The mean differences between the groups shows a small improvement in RMI score for those patients receiving augmented physiotherapy. These differences do not reach statistical significance at any timepoint, though the 3-month follow up approaches statistical significance.

Mobility impairment – Walking speed

Impairment as measured by the median 10 metre walking speed was compared between the two randomised groups at 4 weeks, 3 month and 6 month visits by Wilcoxon rank sum tests and approximate 95% confidence interval for the difference in medians calculated. A further variable was derived by taking the fastest speed (m/s) to complete the 10m walking test in any of the first 10 weeks, and then comparing between the groups as above (Table 3.8).

Table 3.8 GAPS study. 10 metre walking speed (m/s)

	Standard Median	Augmented Median	Median Difference (95% CI)	Wilcoxon P-value
Fastest speed achieved weeks 1-10	0.53 (n=28)	0.63 (n=31)	0.04 (-0.16, 0.23)	0.70
4 weeks	0.56 (n=21)	0.60 (n=24)	0.00 (-0.19, 0.23)	0.97
3 months	0.53 (n=27)	0.54 (n=30)	-0.03 (-0.19, 0.15)	0.77
6 months	0.45 (n=29)	0.65 (n=26)	0.09 (-0.11, 0.28)	0.42

CI = Confidence interval

The differences between the groups were small at all timepoints and did not reach statistical significance.

Length of stay

To assess the impact of augmented treatment on resource utilisation, length of hospital stay was compared between the two randomised groups using both two sample t-tests and Wilcoxon rank sum tests. Approximate parametric 95% confidence intervals for the difference in mean stay were calculated.

As randomisation took place on average two weeks after transfer to rehabilitation, and rehabilitation was on average about ten days after admission for stroke, the total length of stay contains a considerable period prior to randomisation. We therefore compared the time from admission for stroke to discharge for rehabilitation, and then admission to rehabilitation to randomisation, and then randomisation to hospital discharge, using the same method as for total length of stay (Table 3.9).

The results show a reduction in the mean length of stay (total length of stay, from rehabilitation admission and from randomisation) for patients in the augmented group, however there was a wide distribution of length of stay and the differences did not reach statistical significance.

Twelve (17.1%) patients were considered to have had their discharge delayed for some external reason (e.g. awaiting social work intervention).

Table 3.9 Mean length of hospital stay (days)

	Standard (n=35)				Augmented (n=35)				Mean Differ-ence (95%CI)	T-test P-value
	Min	Max	Med	Mean (SD)	Min	Max	Med	Mean (SD)		
Total length of stay (LOS)	14	222	63	80 (52)	18	171	59	67 (34)	-12 (-33, 8)	0.24
LOS to rehabilitation	2	39	8	10 (9)	2	31	7	9 (6)	-1 (-5, 2)	0.47
LOS since rehabilitation admission	10	208	50	70 (50)	14	164	49	59 (33)	-11 (-31, 9)	0.28
LOS from rehabilitation to randomisation	2	60	10	15 (14)	2	41	9	13 (11)	-2 (-8, 4)	0.48
LOS since randomisation	8	180	36	54 (43)	4	123	34	45 (27)	-9 (-26, 8)	0.29

LOS = Length of stay, CI = Confidence interval, SD = Standard deviation
Min = Minimum, Max = Maximum, Med = Median

Secondary outcomes
Impairment

Results from the Motricity Index, Trunk Control Test, Functional Reach Test, or the 9 Hole Peg Test are given in Tables 3.10 to 3.13 respectively.

Table 3.10 GAPS study. Motricity Index scores

	Standard Mean (SD)	Augmented Mean (SD)	Mean Difference (95% CI)	P-value
Baseline	100.4 (43.4) n=35	110.4 (43.2) n=35		
4 weeks	111.2 (45.4) n=34	119.1 (46.5) n=33	7.9 (-14.6, 30.3)	0.49
Maximum weeks 1-10	124.8 (44.8) n=35	130.1 (45.7) n=34	5.3 (-16.4, 27.1)	0.63
3 months	120.4 (42.2) n=33	130.1 (44.1) n=32	9.7 (-11.7, 31.1)	0.37
6 months	121.5 (51.3) n=34	124.2 (41.6) n=30	2.7 (-20.9, 26.2)	0.82
Change at 6 months from baseline	22.6 (27.3) n=34	20.0 (20.4) n=30	-2.6 (-14.8, 9.6)	0.67

CI = Confidence interval, SD = Standard deviation

Table 3.10 shows no statistically significant differences in mean Motricity Index scores between the groups at any time-point or in change from baseline measurement at 6 month follow up.

Table 3.11 GAPS study. Trunk Control Test scores

	Standard Mean (SD)	Augmented Mean (SD)	Mean Difference (95% CI)	P-value
Baseline	68.4 (24.1) n=35	71.9 (23.0) n=35		
4 weeks	84.2 (21.9) n=34	85.2 (17.5) n=33	0.9 (-8.8, 10.6)	0.85
Maximum weeks 1-10	90.5 (17.1) n=35	93.6 (9.6) n=34	3.0 (-11.9, 9.7)	0.37
Change at week 4 from baseline	16.0 (23.9)	14.5 (23.1)	-1.5 (-20.1, 10.0)	0.80

CI = Confidence interval, SD = Standard deviation

Table 3.11 shows no statistically significant differences in mean Trunk Control Test scores between the groups at any time-point or in change from baseline measurement at 4 week follow up.

Table 3.12 GAPS study. Length of functional reach (cms)

	Standard Mean (SD)	Augmented Mean (SD)	Mean Difference (95% CI)	P-value
Baseline	17.0 (7.7) n=19	19.7 (5.9) n=22		
Maximum reach weeks 1-10	24.0 (7.0) n=34	25.1 (6.5) n=33	1.2 (-2.1, 4.4)	0.49
4 weeks	20.6 (7.3) n=32	20.9 (7.5) n=30	0.3 (-3.4, 4.1)	0.87
3 months	21.5 (6.1) n=31	21.2 (7.4) n=31	-0.3 (-3.7, 3.2)	0.87
6 months	22.8 (7.6) n=31	21.5 (5.4) n=29	-1.3 (-4.7, 2.2)	0.46
Change at 6 months from baseline	8.3 (9.4) n=18	3.1 (6.6) n=21	-5.1 (-10.3, 0.1)	0.05

CI = Confidence interval, SD = Standard deviation

Table 3.12 shows no statistically significant differences in mean length of functional reach between the groups at any time-point. There was however, a statistically significant difference in change from baseline measurement at the 6 month follow up.

Table 3.13
GAPS study. Nine Hole Peg Test affected side – time to achieve one peg (seconds)

	Standard Median	Augmented Median	Median Difference (95% CI)	Wilcoxon P-value
4 weeks	3.4 (n=12)	2.8 (n=10)	-0.3 (-1.7, 1.0)	0.38
3 months	3.1 (n=14)	2.8 (n=13)	0.0 (-0.9, 3.1)	0.96
6 months	3.2 (n=15)	3.2 (n=13)	0.1 (-1.2, 1,8)	0.89

CI = Confidence interval

Table 3.13 shows no statistically significant differences between the groups for median times for Nine Hole Peg test at any time-point.

Disability

Further measures of disability were compared between the two randomised treatment groups using two-sample t - tests for the Barthel Index, (Table 3.14) (including change over baseline at 6 months) and the Nottingham Extended Activities of Daily Living Index (Table 3.15).

Table 3.14 GAPS study. Barthel Index scores

	Standard Mean (SD)	Augmented Mean (SD)	Mean Difference (95% CI)	P-value
Baseline	10.3 (3.1) n=35	11.8 (3.3) n=35		
4 weeks	14.1 (3.7) n=34	14.6 (3.4) n=33	0.5 (-1.2, 2.2)	0.55
3 months	16.1 (3.3) n=33	16.6 (2.8) n=32	0.7 (-0.9, 2.2)	0.39
6 months	16.2 (4.2) n=34	16.9 (2.7) n=31	0.7 (-1.1, 2.3)	0.45
Change at 6 months from baseline	5.9 (4.1) n=34	5.1 (3.7) n=31	-0.9 (-2.8, 1.1)	0.37

CI = Confidence interval, SD = Standard deviation

Table 3.14 shows no statistically significant differences in mean Barthel index scores between the groups at any time-point or in change from baseline measurement at 6 month follow up.

Table 3.15
GAPS study. Nottingham Extended Activities of Daily Living (NEADL) Index

	Standard Mean (SD)	Augmented Mean (SD)	Mean Difference (95% CI)	P-value
3 months	22.2 (11.0) n=34	27.6 (12.8) n=32	4.0 (-2.0, 9.9)	0.19
6 months	26.2 (13.1) n=34	29.1 (11.5) n=30	1.5 (-4.6, 7.7)	0.54

CI = Confidence interval, SD = Standard deviation

Table 3.15 shows no statistically significant differences in mean Nottingham Extended Activities of Daily Living Index scores between the groups at either time-point.

Action Research Arm Test scores for the affected arms for the two groups of patients are compared and presented in Table 3.16.

Table 3.16 GAPS study. Action Research Arm Test scores - Affected Arm

	Standard Median	Augmented Median	Median Difference (95% CI)	Wilcoxon P-value
4 weeks	23 (n=35)	22 (n=34)	1 (-4, 14)	0.52
3 months	30 (n=33)	29 (n=32)	0 (-6, 14)	0.78
6 months	30 (n=33)	29 (n=28)	1 (-6, 12)	0.67

CI = Confidence interval

The median differences in Action Research Arm Test scores did not reach statistical significance at any time-point.

Handicap

Handicap (as measured by the Rankin score) was dichotomised as 0–2 or 3–5 and compared between the two randomised groups using a Chi-square test (Tables 3.17 a & b).

Table 3.17(a). GAPS study. Rankin Handicap Score 3 months

Rankin Handicap Score	Standard (n=34)(%)	Augmented (n=29)(%)	Chi-squared test P-value
0-2	8 (23.5)	7 (24.1)	0.95
3-5	26 (76.5)	22 (75.9)	

Table 3.17(b). GAPS study. Rankin Handicap Score 6 months

Rankin Handicap Score	Standard (n=34)(%)	Augmented (n=31)(%)	Chi-squared test P-value
0-2	13 (38.2)	11 (35.3)	0.82
3-5	21(61.8)	20 (64.5)	

The number of subjects that required some form of assistance (scores 3 – 5) reduced over time as patients regained independence, however the differences between the groups did not reach statistical significance at either time-point.

Quality of life

Quality of Life was analysed by two sample t-tests on the visual analogue score on EuroQoL at 6 months (Table 3.18). Change over baseline at 6 months was also compared.

Table 3.18 GAPS study. Quality of life (visual analogue scale from Euroqol)

	Standard Mean (SD)	Augmented Mean (SD)	Mean Difference (95% CI)	P-value
Baseline	52.4 (18.9) n=29	53.7 (18.2) n=32		
6 months	51.8 (23.5) n=32	62.3 (24.6) n=29	10.5 (-1.8, 22.8)	0.09
Change	-2.0 (20.8) n=26	9.78 (30.8) n=27	11.7 (-2.8, 26.3)	0.11

CI = Confidence interval, SD = Standard deviation

Table 3.18 shows no statistically significant differences in mean EuroQual scores between the groups at any time-point or in change from baseline measurement at 6 month follow up.

We sent out 64 patient satisfaction questionnaires at 4 weeks after the patients' discharge from inpatient rehabilitation. Six patients were not followed up with a questionnaire (one patient died in hospital, five patients remained in care facilities beyond their hospital stay). Forty-seven (67%) patients responded, seventeen failed to respond. We grouped the responses (strongly agree/agree and strongly disagree/disagree) for the analysis and used Fisher Exact Tests to compare the groups (Table 3.19).

Table 3.19
GAPS study. Patient satisfaction questionnaire at 4 weeks post discharge

Question	Standard		Augmented		Fisher's Exact Test P-value
	SA/A n (%)	SD/D n (%)	SA/A n (%)	SD/D n (%)	
Happy with amount of recovery	20 (95.2)	1 (4.8)	19 (76.0)	6 (24.0)	0.11
Satisfied with type of therapy	20 (95.2)	1 (4.8)	24 (96.0)	1(4.0)	1.00
I have had enough therapy	7 (35.0)	13 (65.0)	12 (50.0)	12 (50.0)	0.37

SA/A = "Strongly agree" / "Agree" SD/D = "Strongly disagree" / "Disagree"

Table 3.19 shows no statistically significant differences in responses to the questions between the two groups.

Complications

Data on complications were listed (Table 3.20). We further analysed those we considered to be particularly relevant to rehabilitation physiotherapy (falls, shoulder pain, other pain and fatigue). These were compared between the randomised groups using tabulated Fisher Exact Tests at 4 weeks, 3 months, 6 months and at any time during the study (Table 3.21).

There were no serious adverse events (i.e. serious injury or deaths directly attributable to the intervention) during the trial.

Table 3.20 GAPS study. Complications whilst patients were in hospital

Reported Illness	Standard (n=34*)	Augmented (n=35)
Patients reporting any illness	25 (78.1)	29 (82.9)
Events		
Deep venous thrombosis	0 (0)	1 (2.9)
Pulmonary embolus	0 (0)	0 (0)
Urinary tract infection	1 (2.9)	2 (5.7)
Chest infection	2 (5.9)	0 (0)
Other infection	0 (0)	1 (2.9)
Fracture	0 (0)	0 (0)
Depression	5 (14.7)	2 (5.7)
Anxiety	4 (11.7)	2 (5.7)
Confusion	0 (0)	0 (0)
Pressure sore	1 (2.9)	2 (5.7)
Painful shoulder	3 (8.8)	5 (14.3)
Other pain	13 (38.2)	18 (51.4)
Recurrence/extension of stroke	0 (0)	2 (5.7)
Cardiac condition	5 (14.7)	1 (2.9)
Seizure	0 (0)	0 (0)
Fall	10 (29.4)	10 (28.6)
Other	17 (50.0)	19 (54.3)

* One patient still in hospital after 6 months – no discharge forms completed.

Table 3.21 Number of patients (%) experiencing "Complications" / adverse reactions possibly related to physiotherapy input at any time during the GAPS study

	Standard (n=35)	Augmented (n=34)	Fisher Exact Test P-value
Falls	20 (57.1)	20 (58.8)	1.00
Shoulder pain	27 (77.1)	26 (76.5)	1.00
Other pain	30 (85.7)	31 (91.2)	0.71
Fatigue	32 (91.4)	32 (91.2)	1.00

Across all the follow up time-points there were no statistically significant differences in the number of complications reported by the two groups.

Resource use

Further data on resource utilisation (community support requested at discharge (Table 3.22), provision of equipment and adaptations at discharge (Table 3.23), and use of community services at 6 months post stroke (Table 3.24)) were compared between the two randomised groups using Fisher Exact Tests. We found no statistically significant differences between the groups in these areas.

Table 3.22 GAPS study. Community support being requested at discharge

Service	Standard (n=32)	Augmented (n=34*)	Fisher's Exact Test P-value
Home help	11(34.4)	11(32.4)	1.00
District nursing	6 (18.8)	2 (6.1)	0.15
Day hospital	28 (87.5)	28 (82.4)	0.73
Outpatient physiotherapy	1 (3.1)	2 (5.9)	1.00
Physiotherapy home visit	6 (18.8)	5 (14.7)	0.75
Day centre	0 (0)	0 (0)	N/A
Meals on wheels	2 (6.3)	0 (0)	0.23

*data available on 33 subjects for district nursing. N/A = Not applicable

Table 3.23 GAPS study. The provision of equipment and adaptations at discharge

	Standard (n=32)	Augmented (n=34)	Fisher's Exact Test P-value
Aids or appliances	22 (68.8)	17 (50.0)	0.14
Adaptive equipment or alterations to property	25 (78.1)	22 (64.7)	0.28
Wheelchair	19 (59.4)	21 (38.2)	1.00

Table 3.24 GAPS study. Use of community services at 6 months after stroke

Service	Standard (n=34)	Augmented (n=31)	Fisher's Exact Test P-value
Home help	7 (20.6)	8 (25.8)	0.77
District nursing	5 (14.7)	1 (3.2)	0.20
Day hospital	16 (47.1)	13 (41.9)	0.80
Outpatient physiotherapy	4 (11.8)	2 (6.4)	0.67
Physiotherapy home visit	5 (14.7)	1(3.2)	0.20
Day centre	1 (2.9)	0 (0)	1.00
Meals on wheels	1(2.9)	0 (0)	1.00

Discussion

We were unable to demonstrate any significant differences between the two groups of patients in any of the main outcome domains we studied. Notably there was a lack of difference in mobility outcomes, where we might reasonably have expected differences and where our efforts were concentrated.

It could be that increasing the intensity of physiotherapy with the type of patients we recruited has no effect on the outcomes we measured. Alternatively, there may be a difference which we have failed to demonstrate, i.e. type II error. There are several possible reasons that our study might have this type of error:

1). Number of subjects (Lack of statistical power)

In our feasibility study we overestimated the numbers of patients that would be admitted with stroke; we admitted just over 700 patients in 19 months (we estimated 900 in 18 months). We relaxed our entry criteria several months into the study to try to improve our randomisation rate. We accepted patients who were admitted more than 4 weeks prior to screening (one of our initial criteria), allowing "slow starters" to be included. However, most of our patients were randomised within the original time "window". We also accepted patients with "mild" communication and cognitive impairment. Unfortunately, these changes had little effect on our randomisation rate. Finally, we extended the randomisation period as much as possible within the available funding, in order to recruit more patients.

We were also constrained by limited resources to provide augmented treatment. Eligible patients arrived in batches and some were excluded or started late because we were unable to guarantee that if they were randomised to the augmented arm of the trial, we could provide the intervention. In our feasibility study we overestimated the number of eligible patients. Our patients were more disabled, took longer to walk and return home than we planned for and therefore our power calculation was imprecise.

Although our number of subjects was small our drop-out rate was low in comparison to some other studies e.g. Lincoln et al.1999, Partridge et al. 2000. We were selective in our inclusion criteria. This gives the problem of being able to

generalise any findings but we felt that if even the "fittest" 10% of stroke patients can be identified as potentially benefiting from a more intense treatment then this should be pursued.

If the fittest group could be shown to benefit from increased physiotherapy then this may be of clinical significance and provide persuasive evidence for an ethics committee to allow more disabled patients, particularly those with more significant communication and cognitive deficits to participate in similar trials, based on informed consent from relatives. These patients are often excluded from clinical trials. There is little evidence so far that increased physiotherapy with this subgroup of stroke patients is effective. Several techniques used by physiotherapists require the patient to be aware of instructions or to understand a treatment technique. Physiotherapy intervention with this group requires investigation in the future.

Relatively few patients eligible for the study refused to take part. This indicates that patients can be persuaded to participate in trials with random allocation of rehabilitation treatments and that they are willing to accept uncertainty of efficacy of treatment. Although some patients expressed a preference to be in one group over another, no patients withdrew during the treatment phase of the study.

2). Inadequate differences in physiotherapy intensity

Despite our attempts to standardise our interventions it proved difficult to maintain a treatment ratio of 2:1 (augmented to standard) treatments. We managed to provide a ratio of about 1.6:1 overall. This may well have diluted any expected treatment effect.

The potential for variation in a complex human interaction makes monitoring and regulating behaviour in a rehabilitation environment difficult. For example at times treatment was interrupted because the patient felt unwell or treatment was extended because they were performing well or have made progress within the session. On one of the hospital sites (Lightburn) there were no specific resources available to provide additional treatment.

We speculate that many therapists, used to a high degree of professional autonomy, do not find it easy to follow a tightly structured treatment regime. It was therefore difficult to guarantee the delivery of different intensities of treatment, especially over several hospital sites with many changes of members of staff over a prolonged period.

Our intervention seems likely to reflect normal UK practice, involving a broad spectrum of individual interventions, delivered by different clinicians. In our study we avoided the subjects being treated exclusively by an "elite", specialised, highly-trained and motivated research clinician. Our patients were treated mostly by senior and junior qualified physiotherapists, occasionally by physiotherapy undergraduate students and assistants - both under supervision, in addition to the senior physiotherapists specifically employed by the study. There is no suggestion that one staff group provided a different intensity whilst working with the patient.

3). Outcome measures lacked sensitivity

In our follow up assessments we were looking for differences in the levels of achievement of mobility milestones (overall and in relation to the baseline measures), speed of these achievements and whether they were sustained. Most of the weekly follow up visits were conducted seven days apart. They therefore may have been sensitive to changes in performance on a weekly rather than a daily level. We administered a large battery of follow up tests. Patients may have experienced either fatigue or a learning effect when carrying out the tests, but these phenomena should be evenly distributed between the groups at randomisation. Despite the length of the follow up tests (the longest administered at 6 months took about an hour to complete), very few patients dropped out of our study during the follow up phase.

The definitions used by Smith and Baer in their Milestones paper (Smith and Baer 1999) were amended during the study. We kept our working definition the same throughout the study for consistency. The Mobility Milestones appears to be a useful measure but may have a ceiling effect with our patients (over 90% achieved 10 m walking) and is not sensitive to change in higher-level mobility.

We did not expect to see significant differences between the groups based on their survival or ADL scores in any sample this small, and this turned out to be the case.

Another of our secondary outcome measures, complication rates, showed slightly fewer falls and more shoulder pain than reported in some other studies (Davenport et al. 1996)(Langhorne et al. 2000) but with little difference between the groups. The complications of pain, falls and fatigue were all assessed by simple interview question e.g. "In the last week have you had any falls? Yes / No". We depended on the patients' responses and only attempted to quantify falls by their seriousness in the "key" time lines of 4 weeks, 3 and 6 months. Our measures of complications may be insensitive to the actual levels of adverse events due to our use of non-standardised measures, our dependence on patients' recall and that we did not include alternative methods of confirming clearly defined complications due to limited resources.

4). Error or bias

We aimed to minimise bias by using remote telephone randomisation.

By chance, despite the randomisation process, there were differences between the groups in baseline levels of disability (about 1.5 points on the Barthel index) and impairment (about 10 points on the Motricity index) (Table 3.4, page 57). These differences may have produced a baseline bias that influenced our results. We did not adjust our analysis in order to correct for these baseline differences. The factors we considered to be predictive of outcomes were identified a priori in the statistical plan and were stratified at randomisation (centre, age, Barthel index score). In a larger sample these should be more evenly distributed. We did not pursue what would be a more complex secondary analysis of the variables that appeared to differ at baseline. Our analyses did include change over baseline scores and this may have helped interpret our results. However, the best method of reducing the potential for baseline bias is to randomise a large sample.

We tried to maintain blinding of our assessor by following a strict protocol avoiding contact with treating therapists and carrying out assessments away from treatment areas. Despite this we were still unblinded in a small number of cases. Where possible if one assessor had been unblinded another assessor who remained blinded

was brought in to regain blinded status for the remainder of the patient's follow up assessments.

We attempted to reduce measurement error by selecting standard measures and applying them in a standard manner, using a training programme and manual designed by the principal assessor, Thorlene Egerton. The majority of assessments were undertaken by the one assessor in an attempt to reduce inter-rater error.

Although our independent assessor was blinded the treating physiotherapists were not. They were encouraged not to disclose or discuss the patients' allocation with other members of the multi-disciplinary rehabilitation team but at times the patients' allocation would have been obvious. This could have influenced decisions to discharge the patient at an earlier or later stage thus biasing our length of stay results.

Patients' reports of uptake of services, recall of complications and healthcare events can be inaccurate. We did not have resources to confirm these reports with their general practitioner or with a carer or through hospital admissions register but any inaccuracy should be evenly distributed between the groups by the randomisation process.

5). Technical problems

We experienced considerable technical problems with two of our secondary outcome measures the activity monitor and gait analysis system. These problems may lead to incomplete or "missing" data sets in the majority of patients.

The two groups in the study were compared, looking for differences in activity levels, with more time spent upright being assumed to be more active. We were able to establish whether our patients were sitting or upright. The monitor is able to differentiate activities (e.g. walking, sitting standing) more accurately in other patient groups e.g. orthopaedic patients after total hip replacement. However, the complex data received by the monitor when a stroke patient is walking is difficult to typify and differentiate a gait pattern from a standing pattern.

One useful function of the monitor is its ability to examine selected patients' activity during different parts of the day. Generally, the activity monitor was well tolerated by the patients and they were able to wear it for several hours at a time. However, as we only have a single "snapshot" of our patients' activity, we are unable to examine change over time or speed of any change. Patients were assessed around 3 weeks after randomisation, but varied in the length of time since their stroke event. A number of patients were discharged before their assessment at 3 weeks. This may bias our available results towards a more disabled (and possibly less active) group.

We also had technical problems with our gait analysis equipment. The readings were not available for some of our patients due to breakdown of equipment and the severity of gait abnormalities in some others made them difficult to analyse. The analysis was unable to pick up on some key points of gait quality such as scuffing of the foot on swing-through phase, and foot symmetry during stance phase of the gait cycle. The equipment would seem better suited to small scale studies where there is easy access to technical support and study designs that allow re-testing of patients should there be any difficulties. Our study required robust equipment that would be used on several clinical sites with patients that were attending on a single occasion as an outpatient.

This was the first use of this equipment in a clinical trial with stroke patients and has contributed to the further development of the system.

The results obtained by Ms Egerton and the group at Strathclyde University, although limited to a "snap shot" sample in a limited number of patients, help to confirm that the augmented group were more active. We can assume that this was, at least in part, due to the increased time spent with the physiotherapist.

Other measures and methodological issues

Length of stay

We did not see any statistically significant reduction in the length of hospital stay, therefore the vast majority of costs will be similar for the two groups. Actual

hospital costs could be calculated on a simple cost per bed per day in a rehabilitation unit basis, but these were assumed to be similar across the three hospitals.

There were no significant differences in additional marginal costs between the two groups. The frequency of provision of equipment, referral for health and social services in the community and the occurrence of major complications (e.g. hip fracture) was similar between the groups or so infrequent as to be attributable to chance.

The Euroquol is a widely used quality of life scale, but it was generally not well completed by our patients. In particular many patients struggled to complete the visual analogue scale, confirming Price's findings (Price et al. 1999) that this type of scale can be difficult for patients after stroke. Unfortunately there are few alternatives that we could have used that are as straight-forward and quick to administer.

The postal satisfaction questionnaire was reasonably well received by patients with 47 of the 64 (73.4%) we sent being returned. We waited four weeks after discharge from inpatient rehabilitation before contacting the patients. We believed this would be a reasonable length of time for them to be settled, yet not too long for them to have forgotten their hospital experience. As with all questionnaires it is possible that the responses reflect the views of the person that completes them (in some cases this may not have been the patient due to their disability).

Our comparison was based on the total amount of time spent by the physiotherapist on the patients' care. In addition to this we monitored and described our intervention in some detail. To do this we developed a simple tool to record physiotherapy intervention beyond simple timing of contact with our patients. Although there were no apparent differences in intervention between the two groups this has not been formally compared. Our recording tool would need to be investigated with regard to its measurement properties before further data could be analysed with any degree of confidence.

One of the reasons for monitoring the intervention was to see if the therapists were focussing their treatments in such a way that might influence our outcomes. For example were all efforts being made to discharge patients in the augmented group earlier perhaps by issuing them with wheelchairs and encouraging early home discharge or focussing purely on gait re-education (largely speaking ambulant patients with an upper limb weakness can be discharged and followed up as an outpatient for their continuing therapy needs). There is no indication that this was the case.

There may be a difference in the delivery of the intervention. There is little known about the effect of delivering the augmented dose over different sessions e.g. are two half hour sessions the same as one full hour session? The augmented dose was delivered over more than one session in a number of subjects. There may be a threshold of benefit in any one dose of physiotherapy and this would be worth exploring as fatigue or training effects may influence the efficacy of treatment.

In comparison to some earlier studies we recruited relatively late after onset of stroke. This represents the normal time spent by patients in the acute setting prior to transfer to a rehabilitation facility and is probably fairly typical of UK service provision. This may have reduced our ability to detect early change (though this is likely to be largely spontaneous recovery) or to target a time "window" when therapy may be more beneficial. As mentioned this was partly due to our requirement to recruit more patients.

Although we targeted the fittest subjects we reasoned that they were most likely to tolerate treatment and demonstrate any treatment effect. We would then have been in a position to consider the effect on less able patients in further trials.

Some patients had discharge delayed because of difficulties in service provision or environmental adaptation e.g. delays in social services. These should have been evenly distributed across the groups but we do not know this.

Conclusion

Increasing the intensity of physiotherapy in hospital with the selected patients in our study did not produce statistically significant benefits in terms of their mobility, length of hospital stay or patient satisfaction. No significant effect on patients' mobility was noted during their hospital stay or up to follow up at 6 months after randomisation. Length of hospital stay with these patients is not significantly reduced when physiotherapy intensity was increased by about 60% over standard levels. We were unable to recommend any change in current clinical practice based on our results.

We had difficulties with patient recruitment and in maintaining a sufficient difference in intensity between the two intervention groups. Our assessors succeeded in following up our patients, gathering large amounts of data and remaining "blinded" in most cases. The trial was sustained over an extended period with limited resources. In this time we gained considerable co-operation from patients and clinical staff on all the sites. The technology we used to assist in the measurement of patients' performance had some technical limitations. However, it has a role to play and should be developed further and tested for use in clinical trials in the future.

Some of our difficulties, and perhaps our results, highlight that physiotherapy after stroke is a complex and challenging intervention to investigate. Our study did not set out to achieve the definitive answer to the intensity question. Any one small trial is unlikely to change clinical practice. However, we specifically tried in our study design (by selecting common outcome measures, administered at common end-points) to allow the results to be pooled in any future meta-analysis of intensity of physiotherapy. This is what I go on to describe in the following chapter.

Summary

- In 1999 the GAPS Collaborative group set out to answer the basic question *"Does the provision of additional in-patient physiotherapy after stroke speed up the recovery of mobility?"*.

- We carried out a randomised controlled trial across three centres in Glasgow, using sound methods and attempting to address some of the limitations of the previous studies. We aimed to provide twice the standard amount of physiotherapy input to those patients in the intervention group. Our primary outcomes were mobility disability (achievement of mobility "milestones", Rivermead Mobility Index), mobility impairment (as measured by 10 metre walking speed) and length of hospital stay. Our secondary outcomes included measures of impairment, disability and handicap.

- Over an 18 month period I screened over 700 patients of whom 70 were recruited and randomised (35 to each group) to the trial. A blinded assessor regularly followed these subjects up to 6 months after randomisation, administering a battery of standard outcome measures.

- Our analyses showed that increasing the intensity of physiotherapy in hospital with the selected patients in our study did not produce significant benefits in terms of their mobility, length of hospital stay or patient satisfaction. No significant effect on patients' mobility was noted during their hospital stay or up to follow up at 6 months after randomisation. Length of hospital stay with these patients is not significantly reduced when physiotherapy intensity was increased by about 60% over standard levels.

- Although we were unable to recommend any change in current clinical practice based on our results, they contribute to the pool of data and knowledge in this area.

CHAPTER 4
SYSTEMATIC REVIEW OF PUBLISHED LITERATURE ON INTENSITY OF PHYSIOTHERAPY AFTER ACUTE STROKE

Introduction

From the previous chapters it can be seen that there are many difficulties and challenges in carrying out research into physiotherapy and rehabilitation after stroke. None of the previous studies have been definitive and our own study, whilst successfully addressing some of the previous problems, highlighted the fact that all of the trials are relatively small and lack statistical power. Research has, so far, failed to give clear guidance to service providers and clinicians.

In this chapter I describe the process of systematic reviews of trials and the statistical approach of meta-analysis. This is a more rigorous method of evaluating the trials that were described in Chapter 2. I now describe a systematic review and meta-analysis of the available trials of intensity of physiotherapy.

Aims

In this chapter I aim to:

1). Describe the process of systematic review and meta-analysis.

2). Carry out a systematic review of the published literature on intensity of physiotherapy after stroke in which I:

a). Define my criteria for inclusion in the review.

b). Find all relevant trials of intensity of physiotherapy.

c).Carry out the review of the published data in a systematic fashion.

d).Describe the trials.

e).Analyse the results of the published trials and draw conclusions.

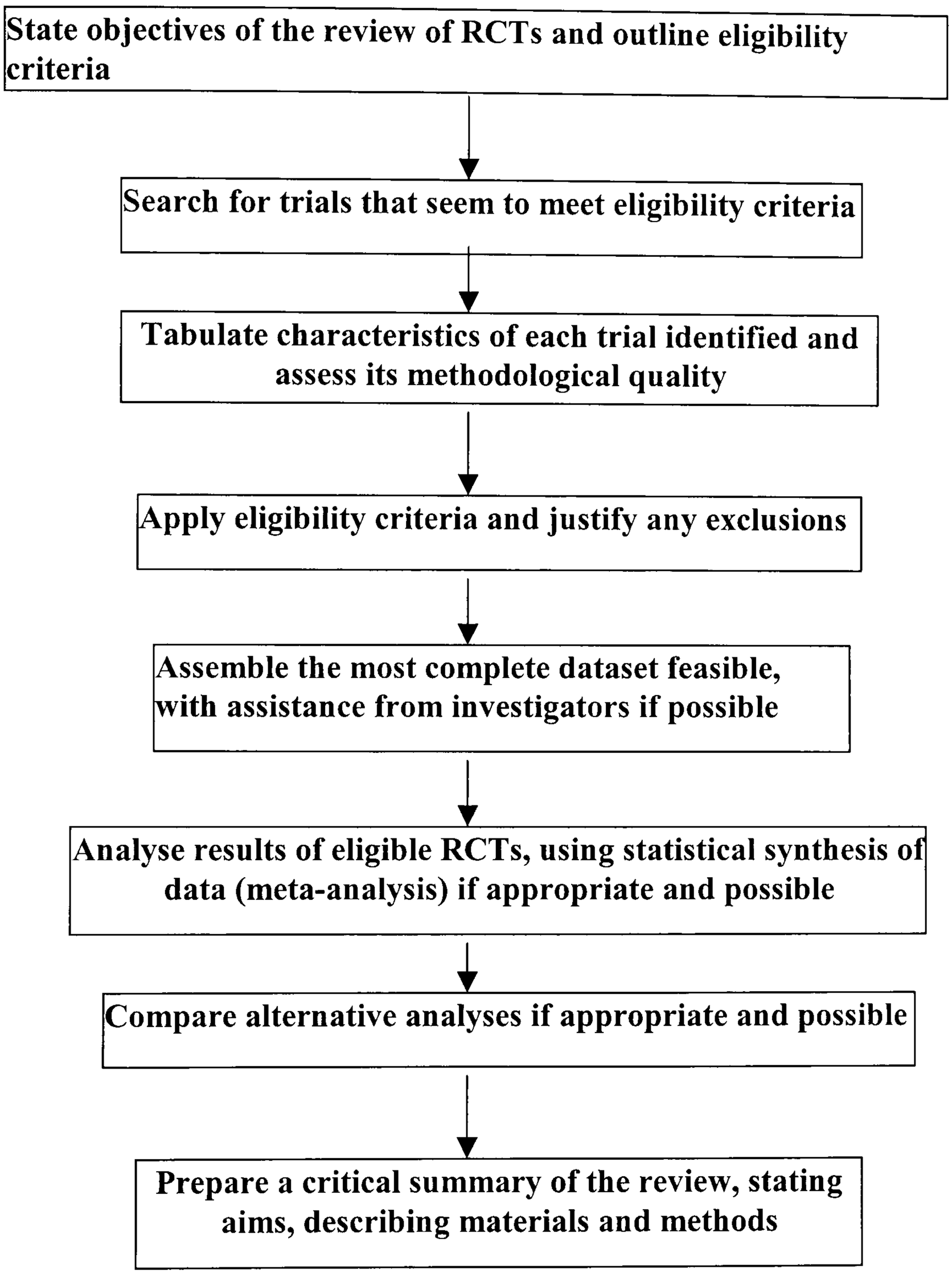
3). Discuss the findings.

Description of systematic reviews

A systematic review can be defined as "an overview of primary studies that contains an explicit statement of objectives, materials, and methods and has been conducted according to explicit and reproducible methodology." (Greenhalgh 1997).

Systematic reviews have several advantages over conventional narrative reviews like the one carried out in Chapter 2 (Mulrow 1994). By explicitly stating their methods, bias in identifying and rejecting studies is limited. Additionally, conclusions can be more reliable and accurate because of the methods used. They may lead to quantitative systematic reviews (meta-analyses) that increase the precision of the overall result. Results of different studies can be formally compared to establish generalisability of findings and consistency (lack of heterogeneity) of results. Reasons for heterogeneity (inconsistency in results across studies) can be identified and hypotheses generated about subgroups. Systematic reviews can also improve access to information for healthcare providers, researchers and policymakers, thereby possibly reducing delays between research discoveries and implementation of effective diagnostic and therapeutic strategies. Figure 4.1 outlines the process of systematic review of randomised controlled trials.

Figure 4.1 Methodology for a systematic review of randomised controlled trials (Greenhalgh 1997)



Assessing validity

Systematic reviews should include an assessment of both the internal and external validity of the included trials (Juni et al. 2001).

1). Internal validity in studies.

Internal validity reflects the degree to which a trial has avoided error and bias. Thus the way that the trial has considered bias, and incorporated methods to reduce or minimise it within the trial, can be evaluated. This is usually done by careful and explicit trial design, conduct and analysis. The Cochrane Collaboration handbook sets out simple criteria against which trials can be judged as having low, moderate or high risk of bias (Mulrow & Oxman 1997). An alternative is to use a quality scale related to a checklist of criteria that the reviewers consider important. Such checklists can be used, sometimes producing a summary score, with or without weights e.g. the Jadad and Chalmers quality assessment scales (in Juni et al. 2001). In practice there are over thirty such scales but no accepted "gold standard" quality assessment score and most of the rating schemes that are employed are arbitrary. Until a "gold standard" is developed the Cochrane Collaboration handbook recommends that reviewers should use simple methods.

Reviewers require to understand the validity of the trials, and what steps, if any, the researchers took in order to reduce bias. Four different types of bias in trials are described (Mulrow & Oxman 1997):

Selection bias: This describes systematic differences in the groups being compared, e.g. there is a problem at randomisation leading to the non-random allocation of subjects to one group rather than another.

High quality randomisation procedures reduce the possibility of selection bias at the stage of assignment of treatment. Ideally, someone that is remote from the trial should carry out the randomisation, reducing the possibility of influencing the randomisation. This might be the case for example when open random number lists or other methods are used, that potentially allow the randomising researcher to anticipate treatment

allocation and make a conscious or subconscious decision that could influence the group allocation.

Performance bias: This describes systematic differences in the care provided, other than from the intervention being evaluated. Performance bias may include: contamination, where the intervention being investigated is provided to both groups, and / or co-intervention, i.e. the provision of an unintended intervention to either group.

Attrition bias: This describes systematic differences in how withdrawals from the trial are handled, e.g. there is an inconsistent or incomplete approach to pursuing subjects being followed up.

Detection bias: This describes systematic differences in outcome assessment. The process of blinding of subjects and researchers may reduce performance and detection biases where both the subject and the investigator are unaware of the allocation of treatment or intervention being provided. Any placebo effect from the intervention should be evenly distributed between groups if the trial design is double blind. These effects are often complex and subtle. Double blind trials may be more complex to organise and in some situations may not be feasible, e.g. due to the nature of the intervention or for ethical reasons. None of the intensity of physiotherapy trials discussed in Chapter 2 were double blinded. Whilst double blinding is possible in some physiotherapy trials, most only achieve single blinding (blinding of outcome assessments).

Although there is an emphasis on the methodological quality of trials, only concealment of randomisation and blinding of assessments have been empirically demonstrated to affect outcomes (Schulz et al. 1995). There remains a considerable amount of research to be carried out into the various methods that can be utilised in the systematic review process.

2). External validity (generalisability) in studies.

The external validity of a trial i.e. the extent to which results of a trial provide a correct basis for applicability to other circumstances, can be more difficult to establish and is a

matter of judgement. This should include a consideration of the subjects, the intervention, the setting and the outcomes that were selected by the researchers (Juni et al. 2001). This in turn will be dependent on the availability of this information to the researchers carrying out the meta-analysis. Guidelines on the content of reports of trials and recommendations on minimum reporting standards (e.g. Begg et al. 1996) may be helpful in standardising the availability of such information, allowing judgements to be made (Altman & Bland 1998).

Sources of data to be used in meta-analyses

When performing a meta-analysis, there are several different sources from which the data can be based:

I). Published data

II). Published data and supplementary additional information or data provided by the authors that were not included in the publication.

III). Individual patient data (IPD) supplied by the trialists.

I). *Meta-analyses based on published data*

These have the advantage of being relatively quick to carry out but may be limited by the quality of the data available for the synthesis (Egger et al. 2001).

However, important trials may be as yet unreported or awaiting publication and small or pilot studies may not be fully reported e.g. published only in abstract form. Authors are often limited by journals as to what they can report. Most trials have considerably more information that cannot be presented within a limited space or format. Just because an aspect of a study was not reported, does not necessarily mean it was not carried out. Added to this, many trials without a "positive" result may not get into print. So-called publication bias is common, with positive results increasing the likelihood of presentation and publication, especially in high profile journals (Egger & Davey Smith 1998).

This latter point is debated and a larger study of publication bias in trials in the USA (Dickersin et al. 1992) did not find sample size or type of study design to be important factors. Instead they found that trials with external funding (especially those funded by government agencies rather than commercial interests such as pharmaceutical companies), multiple data collection sites and significant results were positively associated with publication. They also proposed that many studies, rather than being rejected by journal editors, were in fact, never submitted by their authors for publication.

One solution to avoid publication bias is to require all research to be registered before starting allowing reviewers to search for topics and studies that have been carried out but not widely reported. This may be tied in with ethical or funding approval but may also be down to the diligence of the researchers recognising the importance or potential importance of combination of trial results in meta-analyses. There is general acceptance that there is now improved access to information on trials with data held on electronic registers such as the Cochrane Trials Register and "Register of Registers" being readily searched.

If publication bias (or other biases such as English language bias, multiple publication bias and inclusion bias) is a concern there are methods by which it can be estimated, e.g. plotting of results in a funnel plot, and in some cases a statistical adjustment made to allow for non-included studies (Egger & Davey Smith 1998) (Sterne et al. 2001).

II). *Meta-analyses based on published data and supplementary additional information*

Alternatively, researchers may contact the authors and ask for further information or clarification on points that are unclear. Further unreported information may be available by using this approach and results can be updated and potentially more data can be included in the dataset.

In a study of attitudes towards meta-analysis (Cook et al. 1993) there was acceptance amongst the meta-analysts surveyed that where available, unpublished results should not be systematically excluded from meta-analyses. In this case the trial's results should be

handled in the same manner but the results of the meta-analysis should be presented as including and excluding the unpublished results.

Some authors may be reluctant to release results for inclusion in meta-analyses because they fear it may jeopardise publication of their results in their own right. This fear may be justified; in Cook et al.'s survey, nearly half of the journal editors surveyed, stated if they were considering a study for potential publication, prior publication in a meta-analysis would have a bearing on their decision (Cook et al. 1993).

III). *Meta-analyses based on individual patient data (IPD)*

Probably the most information can be gathered by asking the authors to submit their original "raw" data for meta-analysis. Often considered the "gold standard" method, its real strength is that it provides the opportunity to review all the available data, for each study to be re-analysed, then compared to the other trials in the dataset. It allows subgroup analyses and time-to- event analyses that may not be available when dealing with summarised or compound data based solely on published results. However IPD meta-analysis is considerably more time consuming and requires more resources.

IPD meta-analyses are better if there is a consensus between the trialists and they all agree to submit their data. If there is a lack of co-operation, or for some reason the trialists are unable, or do not wish to collaborate, then the analysis can continue but the situation should be made explicit.

Every effort should be made to include all the relevant trials as the advantages of this method are lost if trials are excluded from the meta-analysis. Detailed searching should uncover published results, but is dependent on the search skills of the researcher (Dickersin et al. 1994), their access to librarian assistance and methods of indexing and searching the various databases. Hand searching and checking registers of trials, personal correspondence and discussion amongst researchers, many of whom are involved in reviewing grant applications or journal articles as well as undertaking primary research, can also assist in uncovering trials that have been carried out, or are ongoing, but have not been published.

The advantages and disadvantages of aggregate data and IPD meta-analyses are outlined in Table 4.1 (Stewart & Clarke 1995).

Table 4.1
Possible benefits and disadvantages of reviews of aggregate data and individual patient data (IPD)
(Stewart & Clarke 1995)

Possible benefits of collecting aggregate data from trialists

- Include unpublished trials
- Include all randomised and non-randomised patients
- Analyse on the basis of allocated treatment
- Analyse common outcomes
- Analyse common patient subgroups
- Improve the overall follow-up
- Ensure equal follow –up for the randomised groups

Possible additional benefits of involving the relevant trialists in the conduct of the review

- Better identification of trials
- Better understanding of the trial intervention
- More balanced interpretation and understanding of the results of the review
- Wider endorsement
- Increased possibilities for dissemination of the results of the review
- Better clarification of the implications for future research
- Possibilities for collaboration in future research

Possible additional benefits of using IPD

- Analyse by time to event
- Increase statistical power
- More flexible analysis of patient subgroups
- More flexible analysis of outcomes
- Might be easier for trialists to supply IPD than to prepare tables
- Easier for trialists to supply small amounts of additional or new data
- Data can be checked and corrected

Possible disadvantages of IPD reviews

- May take longer and cost more
- Reviewers need a wider range of skills
- Inability to include IPD from all relevant trials

The process of meta-analysis

Meta analysis is a process that occurs in two stages:

Firstly, a summary statistic is calculated for each of the trials to be entered into the meta-analysis. Then these summary statistics are combined to form a weighted average. Most meta-analyses are carried out by computer programme that will calculate an estimate of precision (a confidence interval) and a measure of statistical significance (a P value). A test statistic (z) is given for the overall effect and P value for statistical significance.

Different types of data can be summarised (Deeks et al. 2001):

- binary data – where a 2x2 table can be constructed and odds ratios, risk ratios and risk differences calculated for the strength of association between for example exposure to an intervention or risk factor and presence of a clinical outcome or diagnosis.
- continuous data, either calculated as differences in means or, where different measurement scales have been used as standardised difference in the means. In the later case, the standardised mean difference (SMD), the size of the treatment effect in each trial is expressed relative to the variability observed in that trial.
- time-to-event analyses where hazard ratios (again an estimate of the degree of association) are summarised.

These data summaries are then analysed using either a fixed effects model or a random effects model. The choice of model is given as an option on most meta-analysis statistical software packages. The decision is largely dependent on: the type of data being analysed; the choice of summary statistics; the amount of heterogeneity that is observed between the trials and any limitations of the computational methods.

Fixed effect model – this approach assumes a single "common" effect and can use a range of possible methods: Inverse Variance method; Mantel-Haenszel method and the Peto (also known as Peto and Yusuf) method. Fixed effect models can be used to calculate study weights dependent on the contribution made by each of the trials to the meta-analysis.

Random effects model – this includes an estimate of between-study-variation (heterogeneity), sometimes considered as the "combinability" of the trials, and usually uses the DerSimonian and Laird method.

Deeks et al. describe the models in detail and considered that "There is no consensus regarding the choice of fixed or random effects models, although they differ only in the presence of heterogeneity, where the random effects model will usually be more conservative." (Deeks et al. 2001).

The same authors consider errors can arise for the fixed effect models in the following instances:-

- Inverse variance method - this is considered less robust and reliable when trials are small (and is rarely preferable to the Mantel-Haenszel method).
- Both the inverse variance and Mantel-Haenszel methods are considered less robust and reliable when the rate of events is very low.
- Peto's method is considered less robust and reliable when treatment effects are large and when there are severely unequal numbers of subjects in treatment and control groups in some or all of the trials. This last situation would be unusual when dealing with randomised trials.

None of the methods compensate for publication bias or deal with bias introduced through poor study design or execution. A table of considerations in choosing a method of meta-analysis is given in Appendix IV.

In the second stage of the meta-analysis process, the weights of each study are calculated as the contribution they make to the combined result. The weights used are often the inverse of the variance of the treatment effect i.e. the square of the standard error. This usually relates closely to sample size, with larger samples being allocated greater weight.

Considering heterogeneity

When selecting trials to enter into the meta-analysis, we should consider how consistent are treatment effects across the primary studies.

Trials may be fundamentally different in their aims, patient group, setting, other (concomitant) care or how the intervention was delivered. This "clinical" heterogeneity may lead to variability of results. A decision to include trials often depends on clinical experience and background knowledge of the patient groups, the interventions and the disease. If trial results are consistent this tends to corroborate generalisation of any treatment effect. However, Type II error (false negative) may arise where there is a small number of studies which may not detect excess variation (Mulrow & Oxman 1997).

Heterogeneity may arise within a group of trials that appear to be clinically similar. Statistical testing for heterogeneity is available in the form of the I^2 statistic. This is the percentage of variability in point estimates that is due to heterogeneity rather than sampling error (Higgins et al. 2003).

There are limitations of the χ^2 test of heterogeneity as it is sensitive to the number of studies in the meta-analysis. Where there are few studies, as is the case with most meta-analyses, it is underpowered to detect differences between the studies, yet when there are many studies it may overestimate differences and detect differences that are unimportant.

If significant or substantial heterogeneity is identified by reviewing the trials or in performing statistical tests of heterogeneity we should attempt to find a reason for it or abandon pooling the estimate and use another method. As an alternative we can consider a stratified meta-analysis or "meta-regression" in order to test potential associations between study factors and the estimated treatment effect. The important point is that we are able to estimate the amount of heterogeneity and consider how it might impact on the findings of the meta-analysis (see Table 4.2).

Table 4.2 Consideration of heterogeneity can affect:

(Deeks et al. 2001)

- whether a meta-analysis should be considered, depending on the similarity of the trial characteristics.
- whether an overall summary can have a sensible meaning, depending on the degree of disagreement observed between the trial results.
- whether a random effects method is used to account for extra between-trial variation and to modify the significance and precision of the estimate of overall effect.
- whether the impact of other factors on the treatment effect can be investigated using stratified analyses and methods of meta-regression.

The systematic review of published data on the intensity of physiotherapy after stroke.

Objective

Using some of the methods I have been discussing, I set out to review the published data on intensity of physiotherapy after stroke (most of which were described in Chapter 2). In my review I describe in a systematic manner, how I selected and critically appraised the available evidence using methods employed in a Scottish Intercollegiate Guidelines Network (SIGN) guideline review of the management of patients with stroke (SIGN 2002). The SIGN methods (SIGN 2004) largely reflect those laid out in the Cochrane Collaboration Handbook (Mulrow & Oxman 1997).

Parts of this work contributed to the publication of the national clinical guideline (SIGN 2002).

Trial selection - Inclusion / Exclusion Criteria

In order to limit the area of study and focus on the questions of interest, I wanted to develop a specific literature search strategy yet avoid missing any potentially relevant papers. I limited variations due to methodology, by only including randomised controlled trials in the review. All trials needed to satisfy the following criteria. They should:

1). be randomised controlled trials.
2). compare different intensities of "physiotherapy" or "physical therapy".
3). contain interventions that reflect current physiotherapy practice in the UK.
4). include patients in the acute and rehabilitation stages of treatment after stroke.
5). be mostly in-patient based.

Finding the relevant trials of intensity of physiotherapy

The search for relevant trials was based on the Cochrane Stroke Group Trials Register with assistance from the Stroke Therapy Evaluation Programme[1] (STEP) based at the University of Glasgow. The Stroke Group Trials Register is compiled from highly sensitive searches of databases including Medline, EMBASE, BIOSIS, Derwent Drug File, Scisearch, AMED, CINAHL, Cochrane Controlled Trials Register, Dissertation Abstracts, Healthstar, National Research Register, Psych INFO, SIGLE. This is supplemented with hand-searching of over 40 journals, over 100 textbooks and several hundred conference proceedings. It includes articles in all languages. The main search strategy is given in Appendix V.

I initially excluded obviously irrelevant studies before two reviewers independently screened relevant publications for inclusion (see review profile – Figure 4.2). We identified 34 potentially relevant trials (See Appendix V, Table A5.1). We repeated our search during the period of study (up to end of December 2002) in order to identify any new trials. Trials that were excluded and the reasons for exclusion are described in Appendix V (summarised in Table A5.2, Appendix V). We also contacted existing trialists for additional information and approached specialist groups such as The British Stroke Search Group, Society for Research and Rehabilitation, and the Chartered Society of Physiotherapy.

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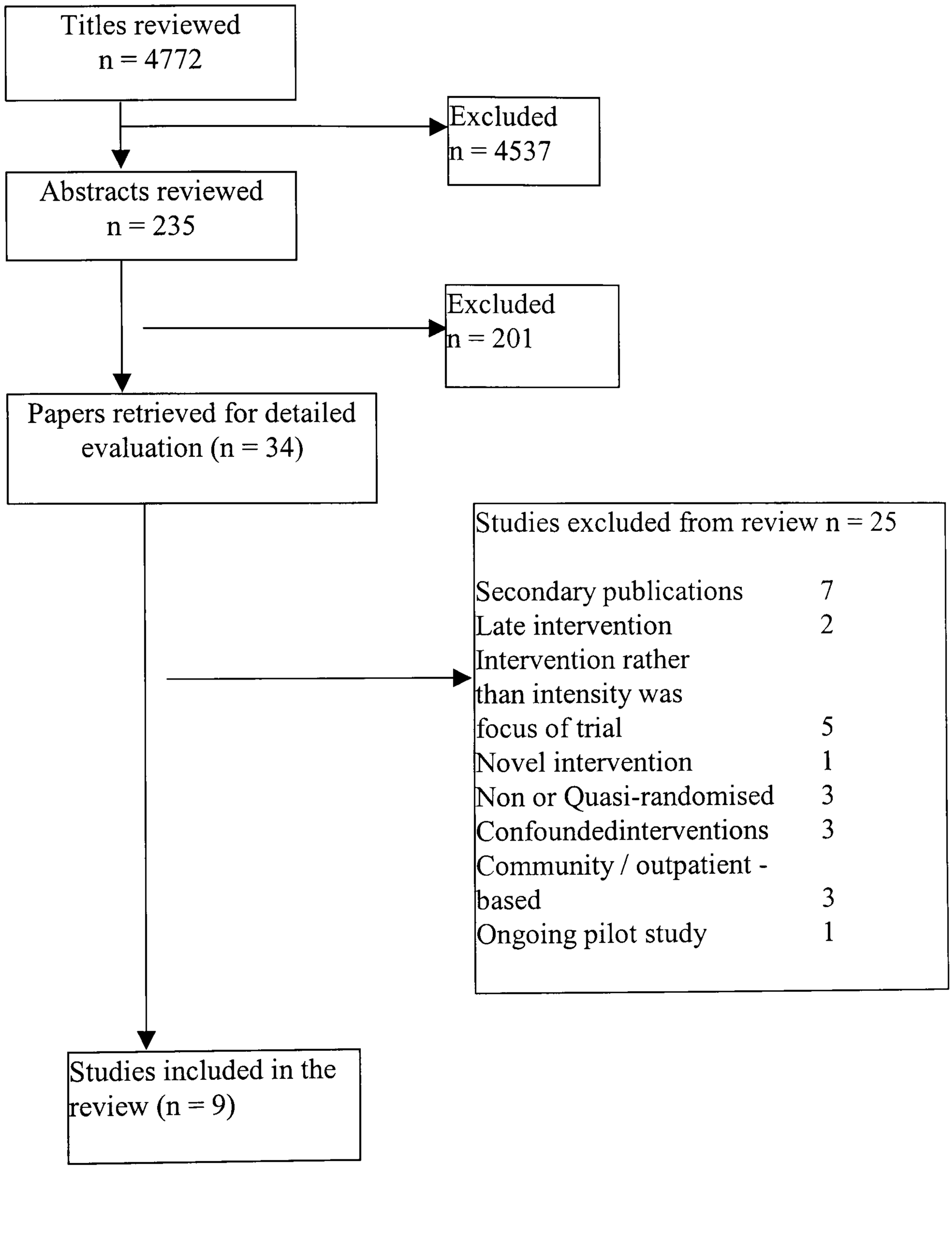
[1] STEP is a project based in Glasgow Royal Infirmary, funded by the charity Chest, Heart and Stroke (Scotland).

Figure 4.2 Review profile



There were three existing systematic reviews identified by the search (Langhorne et al. 1996, Kwakkel et al. 1997, van der Lee et al. 2001) all used slightly different methods to review their selected papers and have already been described briefly in Chapter 2.

We selected nine trials, in five cases a trial had more than one publication (Table 4.3).

Table 4.3 Trials considered to fit the inclusion criteria
Trials are grouped to indicate the main study (underlined) and secondary papers.

GAPS (unpublished)
Kwakkel et al. 1999
Kwakkel and Wagenaar 2002
Lincoln et al. 1999.
Lincoln et al. 1999.
Parry et al. 1999(a)
Parry et al. 1999(b)
Miller et al.2000 (abstract only)
Partridge et al. 2000
Rodgers et al. (paper was being prepared and was published in 2003)
Richards et al. 1993
Malouin et al. 1993
Slade et al. 1999 (abstract)
Slade et al. 2002
Sunderland et al. 1992
Sunderland et al. 1994

This group includes the results from the GAPS study from the previous chapter (subsequently published in 2004) and results from the trial by Rodgers et al. that had not been published at the time of the literature review. We were aware of this trial and considered it suitable to be included at this stage to allow comparison of data.

The trials have been described in Chapter 2 and are characterised in Table 4.4.

Table 4.4 Description of included studies

Study	Intervention	Outcome measures used	Number of patients	Scale and direction of measured effect
GAPS Published in 2004	Intervention: 30 – 45 minutes (double) more PT, 5days per week Control:Daily conventional PT only (approx 30 – 45 min)	BI Trunk control test Nottingham EADL Motricity index Mobility Milestones RMI Gait speed Euroquol Length of stay Complications	70 patients 35 intervention 35control	No difference demonstrated
Kwakkel et al. 1999	Intervention: Half an hour extra arm or leg training, 5 times a week for 20 weeks + routine rehab programme Control: Half an hour immobilisation of arm and leg by air splints, 5 times a week for 20 weeks + conventional rehab programme	BI ARAT Walking ability	33 arm training 31 leg training 37 controls Acute (< 14 days post stroke)	Small positive (significant)
Lincoln et al. 1999	Intervention: 2 hours a week additional therapy from a senior research PT or physiotherapy assistant for 5 weeks + daily routine PT Control: Daily conventional PT only	RMA arm scale ARA THPT Grip strength BI Extended ADL scale	94 + qualified PT 93 + assistant PT 95 controls Acute (1-5 weeks post stroke)	Most outcomes improved none significantly
Miller et al. 2000 (abstract)	Intervention: 3 weeks of additional PT	Motor and sensory recovery, Dexterity, Degree of use of limb	6 patients 4 intervention 2 controls	Positive effect in small pilot study
Partridge et al. 2000	Intervention:30 minutes a day additional PT Control: Conventional (approx 30 min / day)	Profile of recovery Functional reach step:time ratio timed sit to stand 5m walk speed	114 patients 54 intervention 60 controls	No difference demonstrated

Table 4.4 continued

Study	Intervention	Outcome measures used	Number of patients	Scale and direction of measured effect
Rodgers et al. Published in 2003	Intervention: additional PT + OT (mean 52 min) 5 days / week Control: (mean 38 min)	ARAT Motricity index FAT Upper limb pain BI Nottingham EADL Costs Social service use	123 patients 62 intervention 61 controls	Very small non significant positive effect
Richards et al. 1993	Intervention: 50 X 1 hour additional treatment over 5 weeks to either gait focussed or conventional focussed groups Control: Conventional programme	Gait analysis Mean gait velocity BI	10 early, gait- focussed with greater intensity 8 early, conventional-focus greater intensity 9 controls Acute (<7 days post stroke)	Small, positive
Slade et al. 2002	Intervention: Enhanced (59% more PT and OT) Control: Conventional (approx 7.5 hrs / week of PT and OT)	Length of stay Cost	161 randomised 80 intervention 81 control (75 intervention + 66 controll entered into analysis) Patients in rehabilitation unit - including some head injured and other neurological patients	Moderate (14 day) reduction in length of stay in hospital
Sunderland et al. 1992	Intervention: Enhanced physiotherapy - more than twice the amount of arm therapy per week over a longer period Control: Conventional therapy	Ext. Motricity Index Motor Club Assessment Pain FAT NHPT Sensory loss BI	65 enhanced amount 67 controls Acute (<3 weeks post stroke)	Small, positive effect

PT = physiotherapy, OT = occupational therapy, BI = Barthel Index, ARAT = Action Research Arm Test, RMA = Rivermead Mobility Assessment, NHPT = Nine Hole Peg Test, THPT = Ten Hole Peg Test, FAT = Frenchay Arm Test

Systematic review

I used existing review criteria - the Scottish Intercollegiate Guidelines Network (SIGN) criteria and rating system (see Appendix VI).

The review was considered in three sections:

1. Description of the study (where the study intervention, outcome measures, number of subjects and scale and direction of the measured effect are described).
2. Internal Validity; (where the clarity of the study, its attempts to minimise bias and rigour of its analysis are assessed).
3. Overall assessment of the study (where the study quality is rated).

Each section is shown in tables 4.4 – 4.6.

I reviewed the nine selected trials along with an experienced, expert, independent reviewer, Lynn Legg, from the related field of occupational therapy in stroke rehabilitation, based at the Stroke Therapy Evaluation Project (STEP) at the University of Glasgow. This had the advantage of reducing potential bias that may arise when reviewers of a similar professional background examine a trial. Neither of us was blinded to the authors of the papers. This would have further reduced potential bias in our review but was impractical due to the small number of papers and the fact that we were both familiar with a number of the studies due to previous work in this field. An adjudicator, Professor Peter Langhorne, was appointed, but in practice was not needed as any differences in opinion on the criteria were easily resolved by discussion.

Table 4.5 Evaluation of internal validity of selected published studies

Evaluation criterion	GAPS 2004	Kwakkel 1999	Lincoln 1999	Miller 2000	Partridge 2000	Rodgers 2003	Richards 1993	Slade 2002	Sunderland 1992
Does the study address an appropriate and clearly focused question?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the assignment of subjects to treatment groups randomised?	Yes	Yes	Yes	Unclear but confirmed verbally	Yes	Yes	Yes	Yes	Yes
Were the treatment and control groups similar at the start of the trial?	Some small differen-ces	Yes	Yes	Yes	Yes	More severe strokes in control group (non sig. difference)	Unclear	Yes	Yes
Was an adequate concealment method used?	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear not reported	Unclear	Unclear
Were subjects and investigators kept blind to treatment allocation?	Assessor was blinded	Assessor was blinded	Assessor was blinded	Unclear	Blinded follow up but unblind baseline assessment	Assessor was blinded	Assessor was blinded	Unclear	Assessor was blinded
Are all relevant outcomes measured in a standard, valid and reliable way?	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Apart from the treatment under investigation, were the groups treated equally?	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Yes
What % of the individuals or clusters recruited into the study are included in the analysis?	100%	88%	82%	100%	100%	100%	83%	88%	96%
Were all the subjects analysed in the groups to which they were randomly allocated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are the results homogeneous between sites?	Unclear	Unclear	Single site	Single site	Single site	Single site	Single site	Single site	Single site

Table 4.6 Overall assessment of selected published studies

Evaluation criterion	GAPS 2004	Kwakkel 1999	Lincoln 1999	Miller 2000	Partridge 2000	Rodgers 2003	Richards 1993	Slade 2002	Sunderland 1992
How well has the study done to minimise bias? Code ++, +, or -	++	++	++	Unknown	+	++	+	+	+
If coded + or – what is the likely direction in which bias might affect the study results?					Either direction		Either direction	Either direction	Either direction
Taking into account clinical considerations, your evaluation of the methodology used and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	No	Yes	No	No	No	No	No	No	Yes

Trials excluded from the review

The trials excluded from the review are given in Appendix V along with the reasons for their exclusion.

"Combinability" (clinical heterogeneity) of trials

Considering how suitable the selected trials are for combination in the meta-analysis raises a couple of issues. Firstly, whilst most of the trials were published within the last ten years, we need to assume that "physiotherapy" as an entity has not altered considerably within this period. Secondly, one of the trials (Kwakkel et al. 1999) suggested significant benefit from increased physiotherapy intervention while others have reported little (Sunderland et al. 1992) or no measurable benefits (Partridge et al. 2000, Lincoln et al. 1999, Rodgers et al. 2003). This discrepancy could be due to differences in trial methodology, patient selection, therapy technique, outcome measures or simply due to chance as all these trials are relatively small.

Outcomes

Returning to my original research questions (Chapter 1 page 14) I analysed the data for differences in groups in terms of reduction in upper and lower limb impairment (in the short and longer term), reduction in disability (in the short and longer term), survival and reduction in hospital length of stay.

Changes in levels of impairment and disability and timing of effect– there are mixed results from the studies. Different measures were used, particularly to measure impairment, there are trends towards reductions in both impairment and disability, but these are seldom statistically significant. Kwakkel et al. suggested benefit in the short term (Kwakkel et al. 1999), but benefits may be short lived and more readily detected in the acute phase of treatment, with other studies showing no significant differences.

Targeting of treatment The majority of the studies (5/9) focussed on treating the upper limb, whilst two focussed on treating the lower limb. The others were looking for general effects. Only Kwakkel et al. specifically split their subjects allocating additional treatment for the upper or lower limb.

Are any treatment effects greater for patients with moderate impairment and little co-morbidity.

This is inadequately addressed with a wide variety of patients being included and Sunderland et al. being the only group to report results of analyses of their "mild" and "severe" groups. There are difficulties in defining co-morbidity and a lack of standardised measures used and reported in the other trials.

Survival - analyses of rates of death are normally calculated, and although we do not expect significant differences it is important to identify potentially harmful interventions.

Reduction in hospital length of stay – Slade et al. reported a reduction in the length of hospital stay but their results may be biased as their sample included other neurologically impaired patients. The available data from their paper does not allow figures to be entered into the meta-analysis. Different studies use different points in time and interventions commenced at various times. Generally there was a lack of information about blinding of "decision makers" regarding decisions of when patients should be discharged home.

Assumptions

In order to carry out the analysis a number of assumptions were made. I needed to consider the balance between on one hand, including a small number of studies with a complete data set and on the other hand including a large number of studies but making assumptions where data were not available or explicitly reported. I decided to adopt an inclusive approach that would reduce bias associated with excluding trials. In taking this approach, it is important to make the assumptions explicit (Greener & Langhorne 2002). However, this inclusive approach means that the data should be used with caution as their quality may be called into question.

By detailing my assumptions and making conservative estimates, the limitations of the data have been made explicit (see Table 4.7). Table 4.8 describes the data selected for analyses of impairment, disability, death and length of hospital stay.

Table 4. 7 Assumptions made of the published data for all analyses

We have assumed a Normal distribution of outcomes selected.

Where interventions have been split into subgroups e.g. upper and lower limb treatment we have divided the control group evenly.

For secondary outcome measures
Where only the median is reported we have taken this value as an estimate of the mean.

Where the standard deviation (SD) was not reported, we have estimated this by 3 methods (Langhorne et al. 2005):

Where only inter quartile range (IQR)is given -
SD = (IQR ÷ 0.7) divided by 2

Where only range is given –
SD = Range x 0.25

Where only SEM is given
SD = SEM x $\sqrt{n}$ (standard error of mean times square root of no of observations)

Where means and SD have been calculated from available data rather than the original number of subjects in groups i.e. not an intention to treat analysis, figures based on available data have been used.

Table 4.8 Data selected and assumptions for analyses of death, impairment, disability and length of hospital stay.
Unless specified data, mean and standard deviation were routinely available from the text.

Trial	Impairment	Disability	Death	Length of stay
GAPS	Motricity index	Barthel index		Calculated from date of randomisation to discharge
Kwakkel	Upper limb used ARAT (mean & IQR) Lower limb used maximum gait speed	Barthel index	One death reported but group not specified – allocated to lower limb treatment	Not available
Lincoln	RMA (median &IQR)	Barthel index		Not available
Miller	No available data	None reported	None reported - assumed to be none	Not available
Partridge	6 week follow up used as 3 month. Used gait speed	Profile of recovery (POR)	Reported 21 subjects as dead or lost to follow up at 6 months no further data. Assumed no deaths.	Not available
Richards *	6 week data used as 3 month. Used gait speed 6 month data not reported	Barthel index	None reported - assumed to be none. Included all baseline patients	Not available
Rodgers		Barthel index		Not available
Slade	No data available	Barthel index	No deaths reported - assumed none	Not available
Sunderland	100 day follow up (estimated from figure in paper) 109 patients assumed to be evenly distributed - experimental 54 control 55	Barthel index	Compared at 6 months Reported 2 deaths in experimental group, 8 deaths in control group but no detail of subgroup – assumed to be evenly distributed	Reported as weeks of inpatient therapy. Reported figures are not split by mild / severe categories. Labelled "severe" for the analysis.

ARAT = Action Research Arm Test, IQR = Inter-quartile range, RMA = Rivermead Mobility Assessment,
* Richards et al.'s study was not analysed on an intention to treat basis, therefore means and SD were based on available data.

Egger and Davey Smith recommend routinely testing for bias using funnel plots and sensitivity analyses (Egger & Davey Smith 1998). Due to the small number of trials in the meta-analyses we did not formally test for publication bias.

I went on to analyse the aggregate (published and unpublished) data from the above trials using RevMan software (Version 4.2) (Review Manager 2004).

Figures 4.3 – 4.8 show the summary statistics, meta-analyses and forest plots for each of the six outcomes. These are summarised in Table 4.9 below along with heterogeneity statistics and interpreted in the following section.

Figure 4.3
PINTAS published data meta-analysis. Forrest plot showing Disability at 3 months

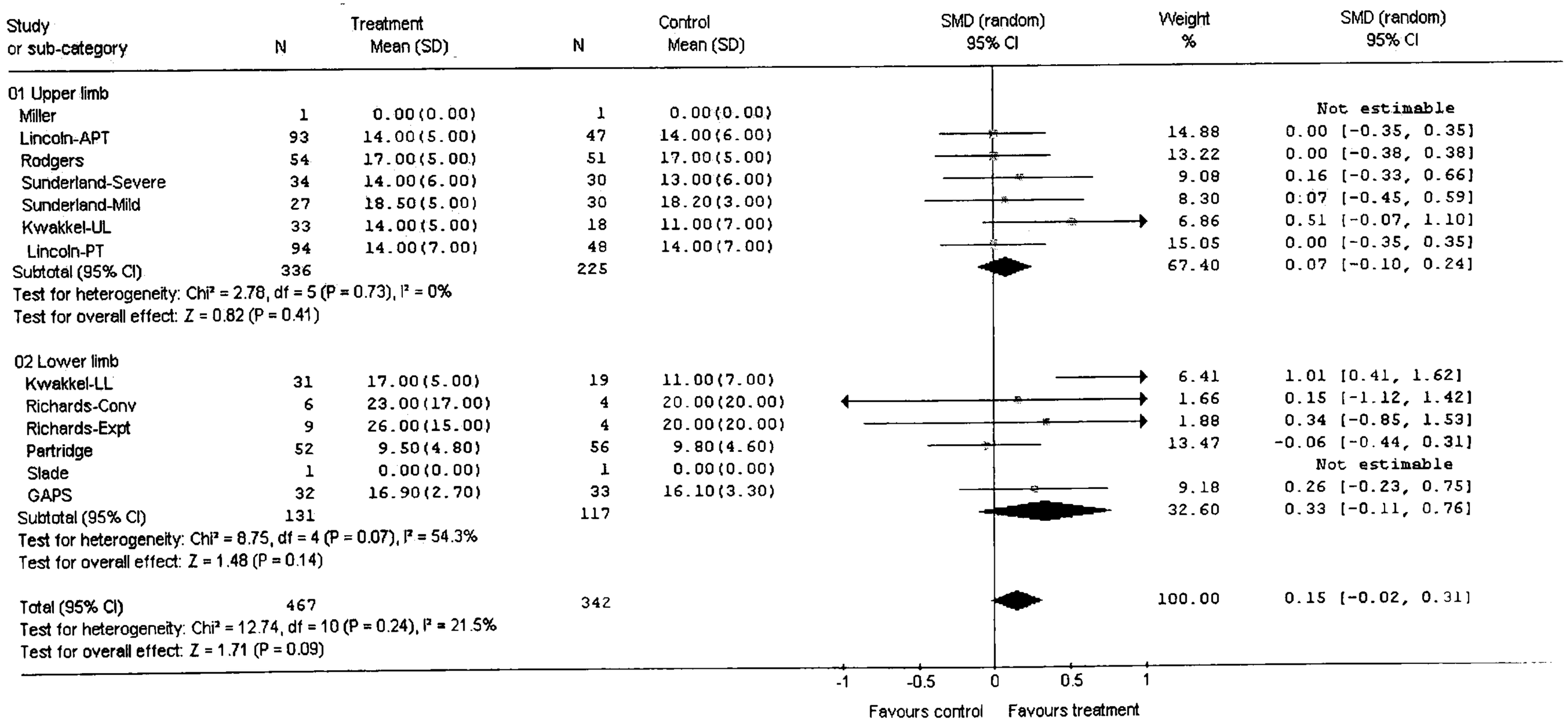


Figure 4.4
PINTAS published data meta-analysis. Forrest plot showing Disability at end of study

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
01 Upper limb							
Miller	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Lincoln-APT	93	16.00(4.00)	47	16.00(5.00)		17.00	0.00 [-0.35, 0.35]
Rodgers	48	18.00(5.00)	48	17.00(3.00)		12.97	0.24 [-0.16, 0.64]
Sunderland-Severe	34	17.00(5.00)	30	16.00(3.00)		8.62	0.24 [-0.26, 0.73]
Sunderland-Mild	27	20.00(3.00)	30	19.00(2.00)		7.58	0.39 [-0.13, 0.92]
Kwakkel-UL	33	17.00(6.00)	18	17.00(6.00)		6.34	0.00 [-0.57, 0.57]
Lincoln-PT	94	16.00(4.00)	48	16.00(5.00)		17.30	0.00 [-0.35, 0.35]
Subtotal (95% CI)	330		222			69.82	0.12 [-0.06, 0.29]
Test for heterogeneity: Chi² = 2.66, df = 5 (P = 0.75), I² = 0%							
Test for overall effect: Z = 1.32 (P = 0.19)							
02 Lower limb							
Kwakkel-LL	31	19.00(4.00)	19	17.00(6.00)		6.28	0.41 [-0.17, 0.98]
Richards-Conv	6	23.00(17.00)	4	20.00(10.00)		1.30	0.18 [-1.09, 1.45]
Richards-Expt	9	26.00(15.00)	4	20.00(10.00)		1.47	0.40 [-0.79, 1.60]
Partridge	43	9.00(4.20)	49	10.10(3.30)		12.34	-0.29 [-0.70, 0.12]
Slade	1	0.00(0.00)	1	0.00(0.00)			Not estimable
GAPS	31	16.90(2.70)	34	16.20(4.20)		8.79	0.19 [-0.29, 0.68]
Subtotal (95% CI)	121		111			30.18	0.07 [-0.23, 0.38]
Test for heterogeneity: Chi² = 4.81, df = 4 (P = 0.31), I² = 16.9%							
Test for overall effect: Z = 0.48 (P = 0.63)							
Total (95% CI)	451		333			100.00	0.10 [-0.05, 0.24]
Test for heterogeneity: Chi² = 7.64, df = 10 (P = 0.66), I² = 0%							
Test for overall effect: Z = 1.30 (P = 0.19)							

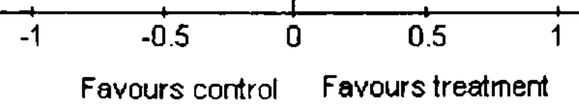


Figure 4.5
PINTAS published data meta-analysis. Forrest plot showing Impairment at 3 months

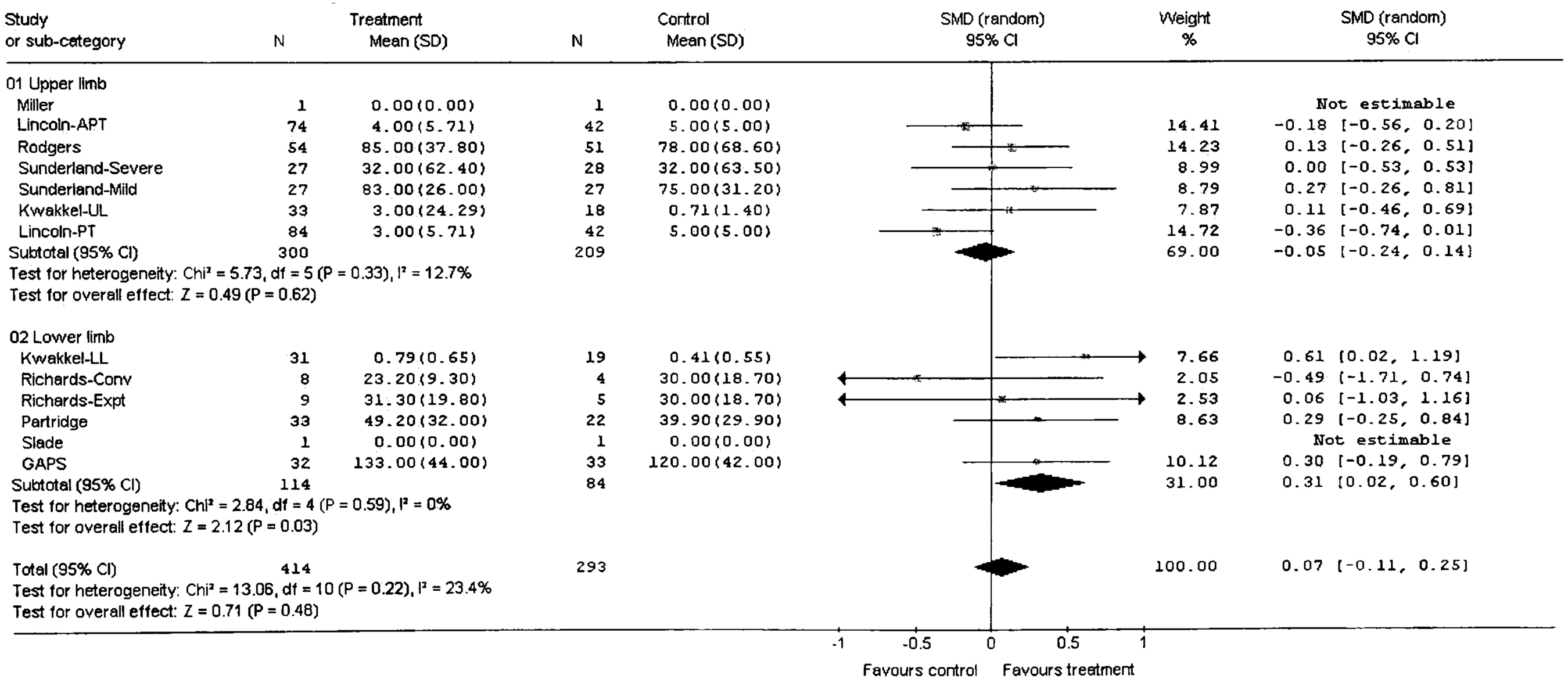


Figure 4.6
PINTAS published data meta-analysis. Forrest plot showing Impairment at end of study

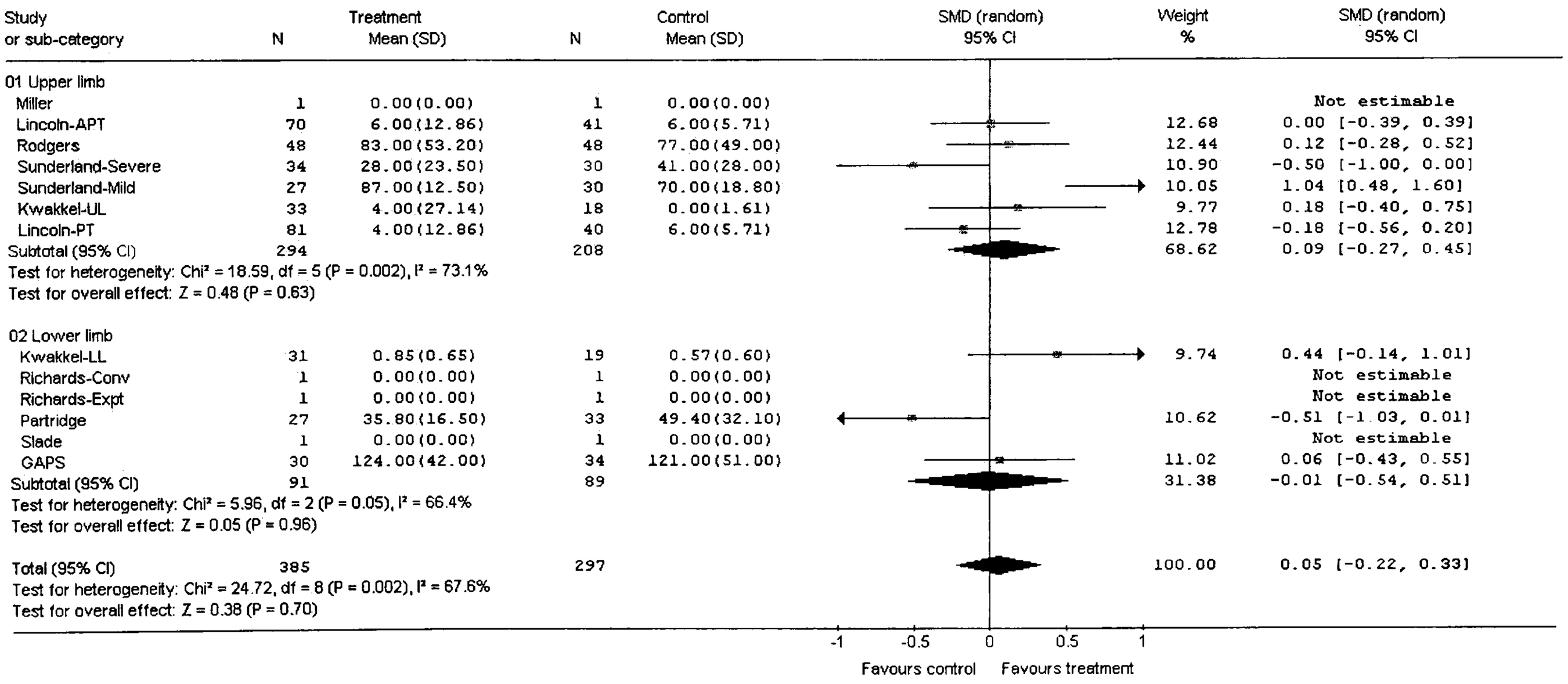


Figure 4.7
PINTAS published data meta-analysis. Forrest plot showing Death

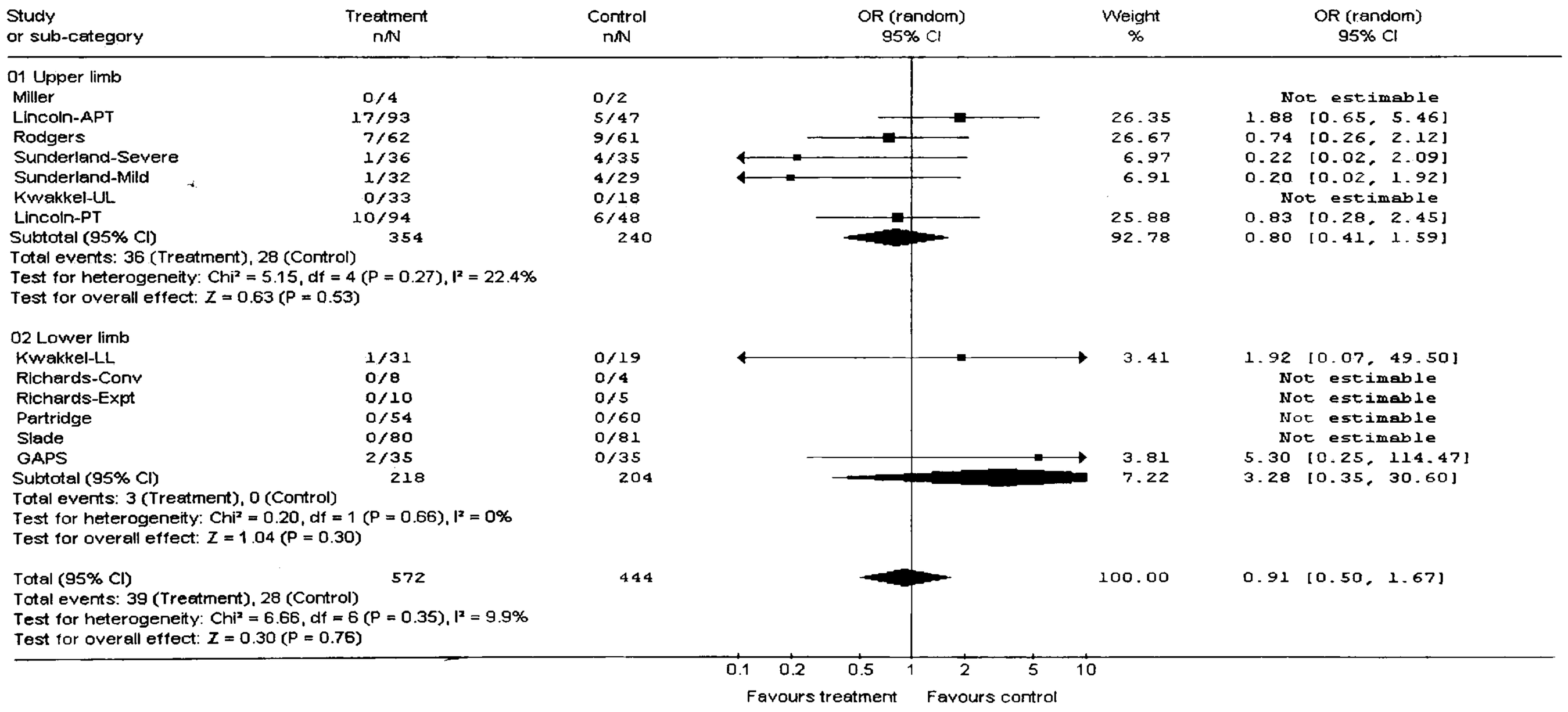


Figure 4.8
PINTAS published data meta-analysis. Forrest plot showing Length of hospital stay

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	SMD (random) 95% CI	Weight %	SMD (random) 95% CI
01 Upper limb							
Miller	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Lincoln-APT	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Rodgers	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Sunderland-Severe	67	28.00(0.00)	65	49.00(0.00)			Not estimable
Sunderland-Mild	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Kwakkel-UL	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Lincoln-PT	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
02 Lower limb							
Kwakkel-LL	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Richards-Conv	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Richards-Expt	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Partridge	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Slade	1	0.00(0.00)	1	0.00(0.00)			Not estimable
GAPS	35	45.00(0.00)	35	54.00(0.00)			Not estimable
Subtotal (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	0		0				Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

-10 -5 0 5 10

Favours control Favours treatment

Table 4.9 Summary of effects

Outcome	n	Method	Effect size (95% CI)	P value	Hetero-geneity I^2 (%)
Disability 3 months	805	SMD (random)	0.15 (-0.02 to 0.31)	0.09	21.5
Disability end of study	780	SMD (random)	0.10 (-0.05 to 0.24)	0.19	0
Impairment 3 months	703	SMD (random)	0.07 (-0.11 to 0.25)	0.48	23.4
Impairment end of study	674	SMD (random)	0.05 (-0.22 to 0.33)	0.70	67.6
Death	1016	OR (random)	0.91 0.50 to 1.67	0.76	9.9
Length of hospital stay	202	Not estimable			

SMD = Standardised Mean Difference, Random = Random effects model
OR = Odds ratio, CI = Confidence interval

Interpretation of results

We can see from Table 4.9 that there is variable heterogeneity between the studies entered into the analyses. Interpretation of results of the I^2 statistics is a matter of debate. Higgins and Thompson suggest that as a general rule I^2 values of 30% and 50% can be used as guidelines. Mild heterogeneity might account for less than 30% of the variability of point estimates and notable heterogeneity substantially more than 50%. Using this as a guide it was reasonable to combine the trials in most of our selected analyses, impairment at 6 months being the only comparison with substantial heterogeneity.

Impairment

The analyses indicate a trend towards a positive effect on impairment with most summary data being on the right hand side of the line of no effect though the confidence intervals tend to be wide.

The combined figure (diamond plot) though mostly favouring treatment, is small and crosses the line of no effect. This may reflect small numbers and the difficulties in obtaining full data collection when measuring this outcome using a variety impairment measures. These are possible reasons for the statistical tests for heterogeneity in the end-of-follow-up analysis identifying "notable" heterogeneity.

Disability

There is a trend towards positive results but not large enough to be statistically significant. This analysis had the best availability of a common outcome measure, the Barthel index, but the numbers are still limited. The outlying data from Kwakkel et al. may have arisen due to their ability to have early intervention and maintain treatment contrast by immobilising the limbs of the patients in the control group.

Survival

As expected, survival appears unaffected by the intensity of physiotherapy. This analysis acts as a check that the intervention does not appear to be producing an excess of deaths, for example by exercise induced death due to repeated physiological stress on patients. The assumptions I made may underestimate the number of deaths (by assuming no deaths where deaths were not reported and that "lost to follow up" did not necessarily mean "dead"), but without specific data we cannot be certain. The group lost to follow up in the trial of Partridge et al. are likely to include a few deaths and it might be more likely that the deaths that Sunderland et al. reported were largely in the "severe" subgroup.

Length of hospital stay

These data have problems of definition of terms and only two studies were able to contribute length of stay data. Interestingly, data from Slade et al. – the only study to have this as its primary outcome measure, could not be included as they did not include original data in their report. The meta-analysis could not be undertaken. Out of all the studies, only Slade et al. report a reduction in mean length of stay that reaches statistical significance.

Conclusion

Using our inclusion criteria and a considerable number of assumptions of the data, I could not detect differences between the groups in our overview based on combined analyses of impairment, disability, death and length of stay. Although there was a trend towards short-term advantage with increased intensity of physiotherapy the confidence intervals were wide.

With other methods of meta-analysis offering potential benefits (Table 4.1), we set about forming a collaborative group to carry out an IPD meta-analysis. We aimed to repeat the review using all available data and using IPD methods. This would give us the opportunity to carry out subgroup analyses that might address our questions. The IPD meta-analysis is described in the next chapter.

Summary

- In this chapter I outlined the process of systematic review then go on to carry out such a review based on aggregate data (published and unpublished) relating to intensity of physiotherapy after stroke.

- I determined the criteria used to select trials from the body of available evidence.

- I carried out a literature search with assistance from the STEP team and the Cochrane Stroke Group and identified 9 key studies from the 34 papers that were identified that fitted the criteria for inclusion.

- Using recognised review criteria (the SIGN review criteria) I reviewed the papers along with an independent assessor. Our appraisal of the main studies is tabulated and described.

- I discuss the review of the papers and the other available reviews in relation to the research questions.

- We made explicit assumptions about data that were not directly available. The aggregate data were then entered into the meta-analysis and forest plots generated.

- From the available results I conclude that there is still a lack of evidence of benefit, in terms of death, reductions in impairment, disability and length of hospital stay, with an increased intensity of physiotherapy after stroke. With this uncertainty in mind and potentially more useful methods of meta-analysis available, we set out to form a collaborative group to carry out an individual patient data meta-analysis.

CHAPTER 5

THE "PINTAS" INDIVIDUAL PATIENT DATA META-ANALYSIS

Introduction

The results from the previous chapter's aggregate data meta-analysis indicated a lack of evidence of benefit, in terms of death, or reductions in impairment, disability and length of hospital stay, with an increased intensity of physiotherapy after stroke. Despite some limitations, meta-analysis appears to offer a unique and efficient use of the available information gathered from physiotherapy trials at a fraction of the cost of an adequately powered new trial. Whilst a large prospective RCT would be ideal, it seems unlikely to happen in the foreseeable future due to financial and practical constraints. We therefore wanted to explore meta-analysis further and examine some of the subgroups of patients.

Given the available data and our aims, it seemed reasonable for us to select the individual patient data (IPD) method (see Table 5.1). We set out to form a collaborative group, the Physiotherapy Intensity After Stroke (PINTAS) group, to carry out an individual patient data meta-analysis.

Table 5.1 Factors that may influence the systematic review approach
(Stewart & Tierney 2002)

When IPD may be beneficial	When IPD may not be beneficial
Poor reporting of trials: information inadequate, selective or ambiguous	Detailed and clear reporting of trials (CONSORT quality (Moher et al.2001))
Long term outcomes	Short term outcomes
Time to event outcome measures	Binary outcome measures
Multivariate or other complex analyses	Univariate or simple analyses
Differently defined outcome measures	Outcome measures defined uniformly across trials
Subgroup analyses of patient-level characteristics important	Patient subgroups not important
Individual patient data available for high proportion of trials / individuals	Individual patient data available for only a limited number of trials

IPD = individual patient data

Collaborative IPD meta-analysis, by involving the primary trialists in a more thorough analysis, can greatly improve the quality of the information gathered and of the interpretation of results (Stewart et al. 1995). We successfully applied for funding from the charity Chest Heart and Stroke Scotland to carry out the meta-analysis still aiming to address the hypothesis set out in Chapter 1.

Aims

We aimed to carry out a collaborative IPD meta-analysis of randomised trials that compared standard physiotherapy with an increased amount of the same approach (intensive physiotherapy).

Design

We used standard methods (Stewart et al. 1995) to define the analysis and formed a collaborative group (comprising the contact authors of the primary trials) to permit comprehensive data collection, analysis and interpretation.

The project had three phases:

Preparation - complete trial searching; liaison with collaborators; refining the meta-analysis questions.

Database management – request for and transmission of individual datasets; creation of combined study analysis database; grooming and cleaning of data; categorising data sets; formal meeting with collaborators to finalize questions and meta-analysis strategy.

Analysis - statistical analysis and writing up; presentation of results.

1. Preparation

Literature search strategy

We used the same search strategy as in the previous chapter in order to identify all relevant trials, including studies identified up until the end of December 2002.

Trial selection - Inclusion / Exclusion Criteria

We used the same criteria as in Chapter 4, applying the same inclusion criteria to unpublished studies to determine whether they should be included in our analysis (Cook et al. 1993).

Forming the collaborative group

During the pilot phase of the study we made informal contact with potential collaborators. All the potential collaborators (primary authors of the trials) were willing to participate in the study (see Appendix VII).

Refining the meta-analysis questions

In this type of analysis it is important to pre-set the questions to be addressed and make judgments about categorising the data. This was done after categorising the data (but prior to any analysis) and further discussion at a meeting of the collaborators.

The formal meeting of the collaborating trialists was held at the headquarters of the Chartered Society of Physiotherapy in London on the 29th November 2002. The aim of the meeting was to confirm the questions and assumptions to be made in the meta-analysis, and to decide about the dissemination of the results.

At the meeting we discussed the potential analyses, considering availability of data and our original research questions. We selected activities of daily living (ADL) disability and impairment as our primary outcomes and wanted to explore subgroups in secondary analyses.

The major advantage of this study has over a meta-analysis based on published data is the availability of patient level data. This allows the potential for adjusting treatment effects for covariates of interest, and for examining treatment effects within subgroups. Additionally, fewer assumptions need to be made of the data. However, forcing data from many studies carried out in different places at different times using a variety of patients, with various outcomes and differing sets of explanatory covariates creates a challenge. Clearly such data are not identical to a very large unified study conducted at one place at one time using consistent methods.

This challenge has two complementary parts: – to create a unified database of the individual studies data, and to conduct a statistical analysis that in some sense best addresses the questions in the hypotheses, whilst accommodating the limitations of the data.

2. Database Management

Grooming and cleaning data

We developed an outline database (see Table 5.2) to provide a structure for the many variables in each of the studies.

To reduce the barriers to participation in the pooling of the data, we sought to minimise the effort required by the individual principal investigators and their research teams. We therefore allowed data to be sent in any format on any media, with the only stipulation being that the data were first anonymised before transmission. The Robertson Centre for Biostatistics at the University of Glasgow has the facility to convert data from virtually any format into a standard format allowing the meta-analysis to go ahead. This helped to minimize, the workload of the collaborating trialists.

Table 5.2 Outline database used in PINTAS meta-analysis

Component	Variable	Example
Patient	Demographic	Age, sex,
	Frailty	Pre-stroke dependency, co-morbidities
	Baseline severity – general	Barthel index at randomisation
	- upper limb	Motricity index, Action Research Arm Test (ARAT)
	- lower limb	Motricity index, Rivermead mobility index
Intervention(s)	Physiotherapy type	Philosophy / approach (qualitative description)
	" aims	Target (eg. balance, upper limb dexterity)
	" amount	Minutes per day (average)
Outcomes	Upper limb impairment	Motricity index, ARAT, peg test
	Lower limb impairment	Motricity index
	Mobility	Functional ambulation category, Rivermead
	Gait	Gait analysis
	Activities of daily living	Barthel index
	Quality of life	Euroquol
	Resources	Inpatient stay, number of contacts, treatment time

Our simple draft version of this database was, however, different in most cases to the format in which the trialists' data were stored. The heterogeneous data therefore needed to be categorized to produce a meaningful and manageable database.

Categorizing data sets

We used standard methods (Stewart & Clarke 1995, Mulrow & Oxman 1997) to define subgroups that would be clinically relevant and identify common outcome measures. We requested assistance from the collaborators to help with the interpretation of their data.

The data set needed to be simplified in order to find common denominators. These needed to reflect physiotherapists' interventions with patients with stroke in order to help clinicians and service managers alike, understand the implications of increasing the intensity of therapy. Inevitably we had to find a compromise between the high quality detail of the specific studies and the general information available to all the studies when they are combined.

For each eligible trial the principal investigator was asked to provide the following basic information for all patients randomised (see Table 5.3).

Table 5.3 Core data requested for all trials in PINTAS meta-analysis

Patient data	
Date of birth or age at randomisation	
Sex	
Baseline levels of disability and impairment	
Intervention data	
Date of randomisation	
Treatment allocation	
Quantity (intensity) of intervention	- intended
	- received (dates, durations, intensities)
Outcome(s) data	
Survival status	
Date of death (if dead)	
Date of last follow up (if alive)	
Performance status (outcomes)	
- at end of intervention	
- at medium term (e.g. 3 months)	
- at long term follow up (e.g. 6 months, one year)	
Exclusions from trial analysis	
Reason for exclusion (if applicable)	

Data checking procedures

The data centre for the project was the Robertson Centre for Biostatistics at the University of Glasgow. The collaborators' data were loaded into a new, unified analysis database. All published results for all trials on all relevant data were reproduced in so far as possible, and any anomalies or inconsistencies queried to the individual study investigators.

Further information is presented in the Statistical Appendix (Appendix VIII).

3. Analysis

Statistical Methods

All statistical analyses were approved by the Study Steering Committee and performed using SAS 8.2 for Windows on the central study analysis database and Review Manager (RevMan 4.2) (Review Manager 2004) for additional analyses.

Statistical analysis began with a general description and summary of key data. As indicated these were then checked against published data to ensure comparability and any queries directed back to the primary trialists. The primary analyses (the effect of intensive physiotherapy on disability and impairment scores) used all available data. The secondary analyses were restricted to individual patient data for which the relevant outcome information were available i.e. included only subjects with complete data on the selected groups of covariates. These analyses were adjusted for explanatory covariates. With the exception of length of hospital stay data, we did not use any missing data techniques to explore the robustness of the findings to missing data or to impute data for those subjects missing observations.

After discussion with the Collaborative group we decided on the following analyses (Table 5.4):

Primary outcome analyses: The primary outcomes were overall disability (recorded at 3 months), measured using the Barthel index (Mahoney & Barthel 1965, Wade 1992) where this was available or a comparable disability measure, and overall impairment (recorded at 3 months) measured using the Motricity index (Demeurisse et al. 1980) where this was available or a comparable impairment measure.

Secondary outcome analyses: Secondary outcomes were: death from all causes; improvement in arm impairment; improvement in leg impairment (both measured by change in the relevant sections of the Motricity index; improvement in upper limb function measured by change in the Action Research Arm Test (ARAT) (Lyle 1981); lower limb function by walking speed (Wade 1992); improvement in disability was measured by change in Barthel index score. We also examined length of hospital stay and treatment success.

We first explored the influence of each covariate in a univariate logistic regression model. Next we examined the influence of covariates on modifying the treatment effect by fitting each covariate in the presence of treatment. Finally we examined the joint influence of any covariates on the treatment effect found to be significant at $P<0.05$. The battery of covariates felt to be influential and of interest was identified prior to beginning the modelling process and was written down in an agreed statistical analysis plan.

If data were approximately normally distributed, parametric t-tests were used to compare the two treatment groups with normal linear models used to adjust the treatment differences for covariates. If data were non-normally distributed, then non-parametric rank tests (such as Wilcoxon rank sum test) were used.

We modelled mean change over baseline score using a Normal linear model. After fitting a model just with treatment (in the presence of study), we then looked at a study by treatment interaction. Then, age and gender were added, and all the interactions between treatment, age, gender and study were explored.

***Treatment success*:** The final analysis defined a treatment success as a subject who has a change over baseline Barthel index greater than or equal to the stated threshold change over baseline (or a subject who has achieved the maximum score on the measure). We defined "good recovery" as an improvement in activities of daily living (ADL) score greater than the median recovery in the control group (increase from baseline of 6 or more Barthel units). Similarly, "excellent recovery" was defined as an improvement in ADL score greater than the upper quartile of the control group (increase from baseline of 9 or more Barthel units).

Treatment success was then modelled as a binary outcome in a logistic regression using study, age, gender, and treatment group as covariates. These logistic regressions were fitted separately for the 3 months data (patterns were similar at 1 and 6 months).

Subgroup Analyses: Several pre-defined subgroups were identified (Table 5.4) and analysis carried out as outlined above. The one exception was the subgroup analysis, analysed at the level of the trial (total treatment contrast). This was analysed using RevMan 4.2 software to calculate subgroup effects and between-subgroup heterogeneity.

We were aware of the potential of finding spuriously significant relationships due to carrying out multiple subgroup analyses (Counsell et al. 1994, Mulrow & Oxman 1997). We therefore kept the number of subgroups small and clearly recorded them in the analysis plan. Any other analyses would be considered exploratory, and any significant results treated with caution.

Table 5.4 PINTAS meta-analysis - Outline of analysis plan.

Outcome	Measure	Timing	Subgroups
Primary analyses			
Disability	Activities of daily living score (Barthel index or comparable score)	3 months	Target of therapy
Impairment	Impairment score (Morticity index or comparable score)	3 months	Target of therapy
Secondary analyses			
Death	All cause death	End of follow up	Target of therapy
Improvement in arm impairment	Change in arm Motricity index	From randomisation to point of follow up	Target of therapy, age, initial stroke severity, initial arm impairment, total treatment contrast
Improvement in leg impairment	Change in leg Motricity index	From randomisation to point of follow up	As above
Improvement in arm function	Change in Action Research Arm Test	From randomisation to point of follow up	As above
Improvement in leg function (gait)	Walking speed	From randomisation to point of follow up	As above
Improvement in disability	Change in Barthel index	From randomisation to point of follow up	As above
Good recovery	Change in Barthel index greater than the trial median	From randomisation to point of follow up	None
Excellent recovery	Change in Barthel index greater than trial upper quartile	From randomisation to point of follow up	None
Length of stay	Length of stay	Duration after randomisation	Target of therapy

Definitions of the subgroups are given in Table 5.5.

Table 5.5 Subgroup definitions used in PINTAS meta-analysis

Domain	Subgroup	Definition	Status
Patient characteristics			
Patient age	Younger	Age <70 years	Pre-specified
	Older	Age ≥70 years	
Stroke severity	Moderate	Baseline Barthel >10	Pre-specified
	Severe	Baseline Barthel ≤10	
Arm impairment	Moderate	MI arm score > 15 or ARAT score > 0	Pre-specified
	Severe	Severe = MI arm ≤ 15 or ARAT = 0	
Co-morbidity	Minor	Proved difficult to define -	Dropped from analysis
	Major		
Treatment characteristics			
Physiotherapy target	Upper limb	Upper limb	Pre-specified
	Mixed	Lower limb ± upper limb	
Total treatment contrast	Lower	Lower contrast trials: 10 (7-12) hours	Pre-planned but not pre-specified
	Higher	Higher contrast trials: 32 (15-44) hours	

MI = Motricity index, ARAT = Action Research Arm Test

Treatment contrast: The treatment contrast subgroup was defined according to whether the mean difference in physiotherapy contact time between intervention and control patients was above or below the median for all included trials. Lower treatment contrast trials had a physiotherapy treatment contrast ranging from 7-12 hours per trial; higher contrast trials ranged from 15-44 hours per trial. These two subgroups of trial tended to cluster by other characteristics. The lower treatment contrast subgroup also tended to contain the trials with a later treatment onset (12-47 days post-stroke), lower daily treatment contrasts (30-45 minutes per patient, and shorter treatment duration (5-6 weeks). The higher contrast subgroup tended to cluster as earlier onset trials (7-10 days post-stroke), with higher daily treatment contrasts (53 – 70 minutes) and longer treatment duration (10 – 20 weeks).

"Clinically" significant improvement

In order to aid interpretation of the results, before undertaking the analyses, we sent out a questionnaire to the Collaborators. We asked for their opinions on what might be regarded as a "clinically" significant change in Barthel index score for patients with stroke (see Appendix VIII). The Collaborative group's responses varied widely and were difficult to interpret. We therefore did not pursue this category.

Testing for heterogeneity: As before, we tested the data set for heterogeneity, testing the level of inconsistency in the results from the studies to determine whether it was reasonable to combine the trials. The I^2 statistics were calculated for overall disability, overall impairment, survival and length of hospital stay outcomes.

Results

Trial selection

Essentially we had the same set of trials as in Chapter 4 but with much more detailed data.

Study characteristics

Table 5.6 shows the key characteristics of the included studies which are described further in Table 5.7. These included 9 randomised trials with 951 participants (Figure 5.1). The average participant age was 69 years and there was a relatively equal split of males and females (ranging from 43% to 62% men). Three studies contained more than one treatment group, which resulted in slightly more subjects receiving augmented physiotherapy than standard physiotherapy. The upper limb was targeted for 62% of participants with a lower limb target in 6% and a mixed target for 33%.

All the studies demonstrated a recovery curve in relation to mean levels of disability (measured by Barthel index). The change in mean Barthel index score over time is shown in Figure 5.2.

The treatment approach in the trials was broadly similar, with physiotherapists aiming to restore normal movement and function through regular exercise, with or without physical assistance or adaptive equipment.

Table 5.6 Characteristics of studies included in PINTAS meta-analysis

STUDY → / ↓CHARACTERISTIC		GAPS	KWAKKEL	LINCOLN	MILLER	PARTRIDGE	RICHARDS	RODGERS	SLADE	SUNDER-LAND	TOTAL
Number Subjects		70	101	282	21	114	22	123	83	135	951
Age	Mean (SD)	67(10)	66(11)	72(12)	58(17)	77(8)	68(8)	74(11)	54(11)	68(10)	69(12)
	Range	39-96	30-86	37-97	27-80	61-94	48-84	34-94	23-68	32-92	23-97
Gender n (%)	Male	41(59%)	43(43%)	144(51%)	13(62%)	52(46%)	11(50%)	58(47%)	51(61%)	62(46%)	475(50%)
Treatment n (%)	Enhanced	35(50%)	64(63%)	187(66%)	12(57%)	54(47%)	9(68%)	62(50%)	43(52%)	67(50%)	533(56%)
Target n (%) –	Arm	-	33(33%)	282(100%)	21(100%)	-	-	123(100%)	-	135(100%)	594(62%)
	Leg	-	31(31%)	-	-	-	22(100%)	-	-	-	53(6%)
	Mixed	70(100%)	37(37%)	-	-	114(100%)	-	-	83(100%)	-	304(32%)
Baseline Barthel	n	70	101	282	Not measured	-	133	118	83	133	809
	Mean (SD)	11.0(3.3)	5.2(3.0)	6.6(3.8)			4.2(2.2)	9.7(4.7)	9.8(5.0)	10.2(4.6)	8.1(4.6)
	Range	4-18	0-14	0-18			0.6-8.4	1-20	0.4-20	2-20	0-20
Baseline ARAT	n	Measured at 1, 3, 6 months, not baseline	101	282	Not measured directly	-	-	123	-	-	506
	Mean(SD)		3.05(8.32)	6.36(12.8)				18.8(22.3)			8.73(16.1)
	Range		0-45	0-51				4-57			0-57

Table 5.7 Characteristics of randomised trials investigating the effect of intensive physiotherapy on outcome after acute stroke

Author, Year	Setting	Comparison of groups	Follow-up	Primary outcome measures	Authors conclusions
GAPS 2004	Admitted to rehabilitation hospital	Intervention: Double the amount of PT 5/7 week Control: conventional PT (30 – 45 mins 5/7 week)	1 month 3 months 6 months	Motricity index BI ARAT Gait speed Rivermead Mobility Length of stay	Small non-significant improvement with increased intensity
Kwakkel et al. 1999	Acute (< 14 days post stroke)	Intervention: Half an hour extra arm or leg training, 5 times a week for 20 weeks + routine rehab programme Control: Half an hour immobilisation of arm and leg by air splints, 5 times a week for 20 weeks + conventional rehab programme	6 weeks 12 weeks 20 weeks 26 weeks *	BI ARAT Walking ability	Small but significant improvements with greater intensity
Lincoln et al. 1999	Acute (1-5 weeks post stroke)	Intervention: 2 hours a week additional therapy from a senior research PT or physiotherapy assistant for 5 weeks + daily routine PT Control: Daily conventional PT only	3 months 6 months	RMA arm scale ARA THPT Grip strength BI Extended ADL scale	No significant effect on arm function
Miller et al. 2000 (abstract)	Acute Data, included subjects not reported in interim results in abstract	Intervention: Additional task-related practise, facilitation of muscles Control: Standard rehabilitation programme	Pre / post intervention 3 months	Motor and sensory recovery, dexterity, use of arm, MAS, Chedoke-McMaster, Grip & pinch strength, SA – SIP30	Ongoing pilot study when reported
Partridge et al. 2000	Acute stroke unit setting	Intervention: intensive PT (60 mins. 5/7 week) Control: conventional PT (30 mins. 5/7 week)	6 weeks 6 months	Profile of recovery, gait speed, functional reach, step:time ratio, timed sit to stand, HAD, Locus of control	No difference demonstrated between the groups

Table 5.7 continued.

Author, Year	Setting	Comparison of groups	Follow-up	Primary outcome measures	Authors conclusions
Richards et al. 1993	Acute (<7 days post stroke)	Intervention: 50 X 1 hour additional treatment over 5 weeks to either gait focused or conventional focused groups Control: Conventional programme	6 weeks 3 months 6 months	Gait analysis Mean gait velocity BI	Small positive effect with greater intensity
Rodgers et al. 2003	Acute (intervention from day 10)	Intervention: additional 30 minutes PT + OT 5/7 days week Control: Conventional programme	3 months 6 months	ARAT at 3 months BI OHS FAT Nottingham E-ADL	No improvement with increased interdisciplinary therapy
Slade et al. 2002	Patients in rehabilitation unit - Trial including some head injured patients. Only data for patients with stroke were used	Intervention: Enhanced (59% more PT and OT) Control: Conventional (approx 7.5 hrs / week of PT and OT)	At discharge	Length of stay Cost	Shorter stay and cost saving with enhanced therapy
Sunderland et al. 1992 1994	Acute (<3 weeks post stroke)	Intervention: Enhanced physiotherapy - more than twice the amount of arm therapy per week over a longer period Control: Conventional therapy	6 months Sunderland 1994; follow-up until 1 year	Ext. Motricity Index Motor Club Assessment Pain FAT NHPT Sensory loss BI	Small but statistically significant difference in intervention group after 6 months; effect lost at follow up

* Kwakkel et al. have follow up data at 1 year on this group.

OT = occupational therapy, PT = physiotherapy. ARAT = Action Research Arm Test, BI = Barthel Index, FAT = Frenchay Arm Test, HAD = Hospital Anxiety and Depression scale, MAS = Motor Assessment Scale, NHPT = Nine Hole Peg Test, Nottingham E-ADL = Nottingham Extended Activities of Daily Living scale, OHS = Oxford Handicap Scale, RMA = Rivermead Mobility Assessment, SA-SPI30 = Stroke adapted SPI (30 item), THPT = Ten Hole Peg Test.

Figure 5.1 Number of patients in trials in PINTAS meta-analysis

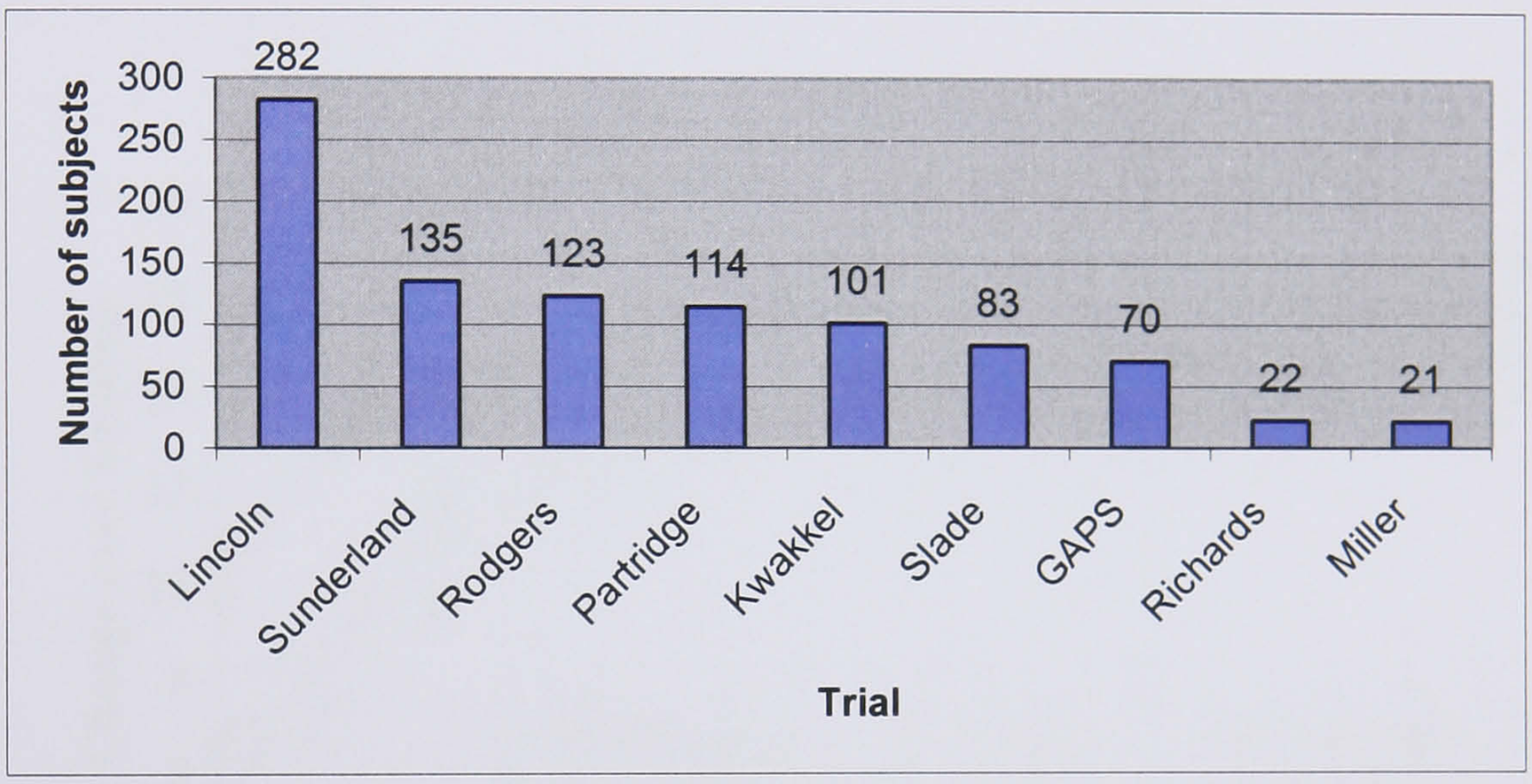
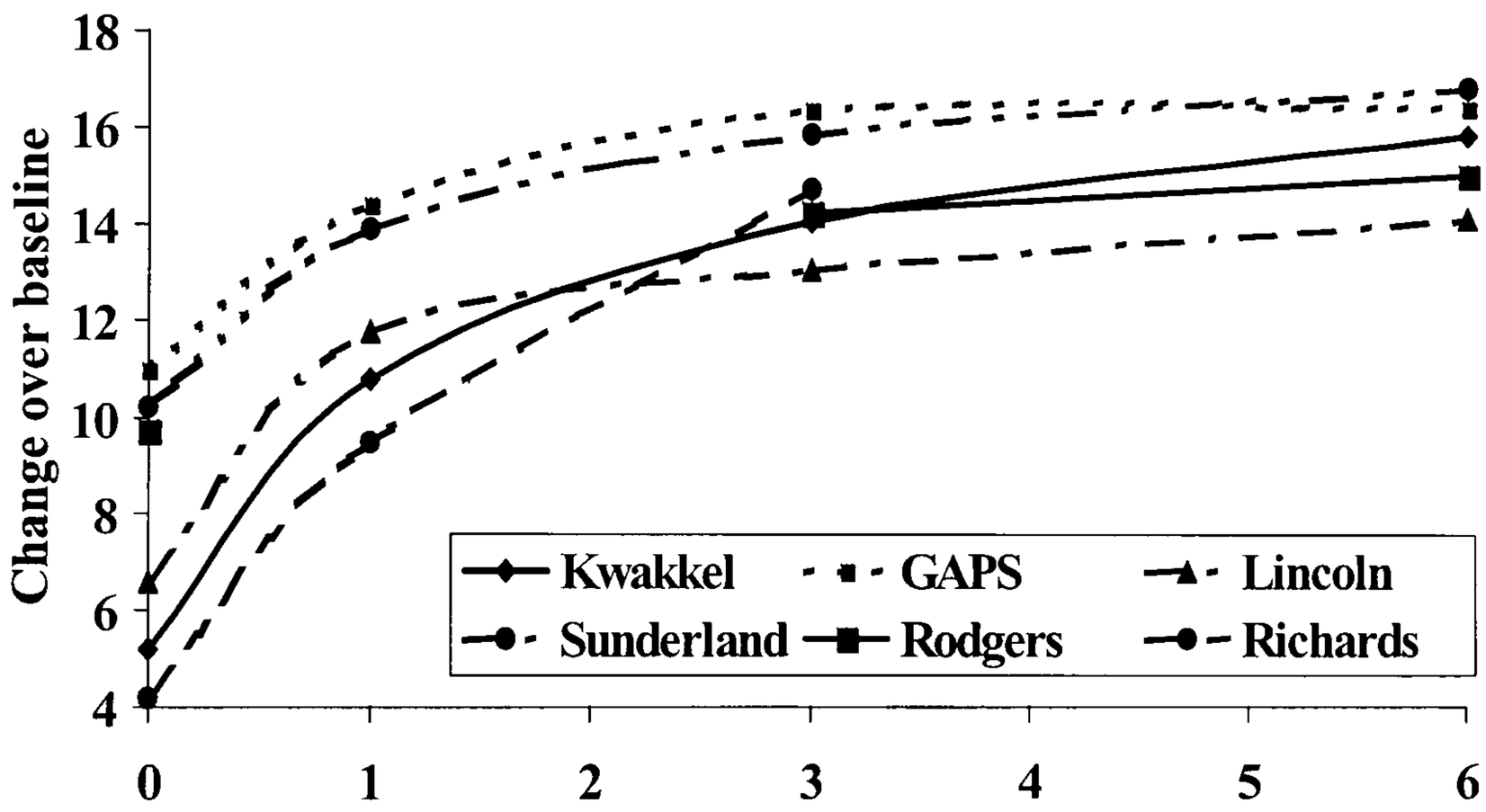


Figure 5.2 Change in mean Barthel index score over time in trials in PINTAS meta-analysis



Primary Analyses

Disability: The primary analyses included all identifiable data addressing disability within the first 3 months after stroke (median 3 months, range 6 weeks – 3 months). Seven of the nine trials used an ADL score providing the largest group of pooled data (805 patients at 3 months).

Overall there was no significant difference in ADL score at 3 months (Standardised Mean Difference (SMD) 0.15; 95% Confidence Interval (CI) -0.02 to 0.31; P = 0.09) or at end of follow up (SMD 0.10; 95% CI–0.05, 0.24; P=0.19). These conclusions were confirmed if the analysis was restricted to the Barthel index only or used the change in Barthel index between baseline and follow up.

RevMan analyses (Review Manager 2004), carried out at the level of the trial and stratified by the target of the physiotherapy are shown in Figures 5.3 and 5.4.

Impairment : Four of the nine trials used the Arm Motricity Index (maximum 393 subjects at 3 months, 373 subjects at end of follow up), and two of these in addition measured Leg Motricity Index (maximum 153 subjects at 3 months, 151 subjects at end of follow up). Four studies used the Action Research Arm Test (ARAT). (maximum of 447 patients available at 3 months, 437 at end of follow up). Five studies used gait speed (maximum 398 subjects at 3 months, 354 subjects at end of follow up).

Forest plots show summary data from each group at 3 months and end of follow up. This shows a statistically significant difference (6.6; 95% CI 0.71 to 12.5;P = 0.03) in the upper limb subgroup as measured by Motricity index (arm section)(see Figure 5.5) and in the lower limb subgroup (11.7; 95%CI 3.79 to 19.54;P = 0.004) as measured by the Motricity index (leg section) at 3 month follow up (see Figure 5.6), with benefit with additional physiotherapy intervention.

At the end of follow up analysis for Motricity index (Arm) and Motricity index (Leg), though still in favour of the intervention, the effect size has decreased (MI Arm 3.03; 95%CI –3.31 to 9.36; P = 0.3. MI Leg 5.86; 95% CI –1.96 to 13.67; P = 0.14), and the pooled result crosses the line of no effect (see Figures 5.7 and Figure 5.8 respectively).

The ARAT analysis, though with greater numbers of subjects does not demonstrate statistically significant differences between the groups at either time point (Figures 5.9 and 5.10) ARAT 3 months 3.41; 95% CI –0.85 to 7.67; P = 0.12. ARAT end of study 1.66; 95% CI –2.73 to 6.04; P = 0.5.

Similarly, the gait speed analysis does not demonstrate statistically significant differences between the groups at either time point (Figures 5.11 and 5.12) Gait speed 3 months 0.02; 95% CI –0.04 to 0.07; P = 0.6. Gait speed end of study 0.02; 95% CI –0.04 to 0.08; P = 0.5.

We can consider impairment "overall" i.e. when measured using data from all available outcome measures including the upper and lower limb. RevMan analysis, carried out at the level of the trial for overall impairment at 3 months and stratified by the target of the physiotherapy is shown in Figure 5.13. Overall impairment (SMD 0.07; 95% CI –0.11 to 0.25;P = 0.48).

Figure 5.3 PINTAS IPD meta-analysis – Forrest plot showing "Overall" Disability at 3 months follow up (stratified by the target of physiotherapy)

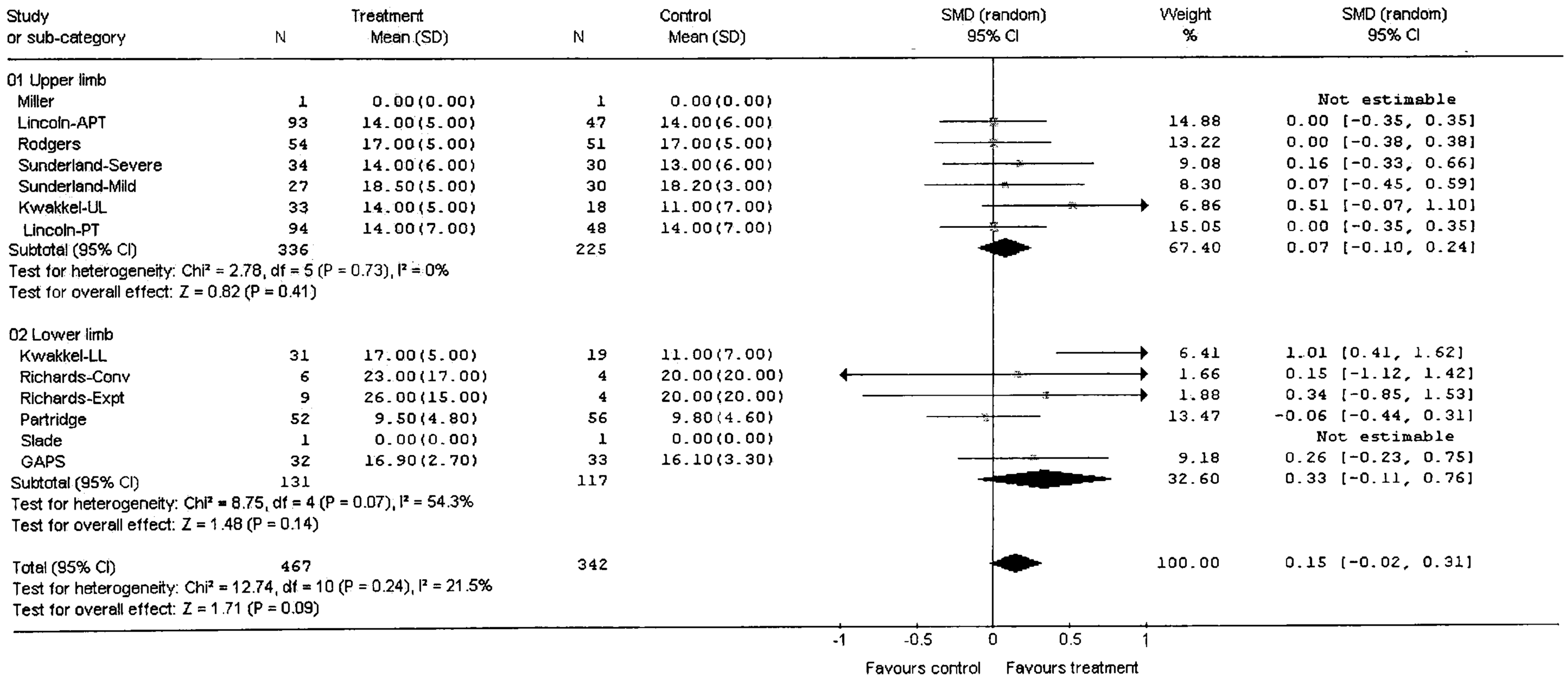


Figure 5.4 PINTAS IPD meta-analysis – Forrest plot showing Disability end of study (stratified by the target of physiotherapy)

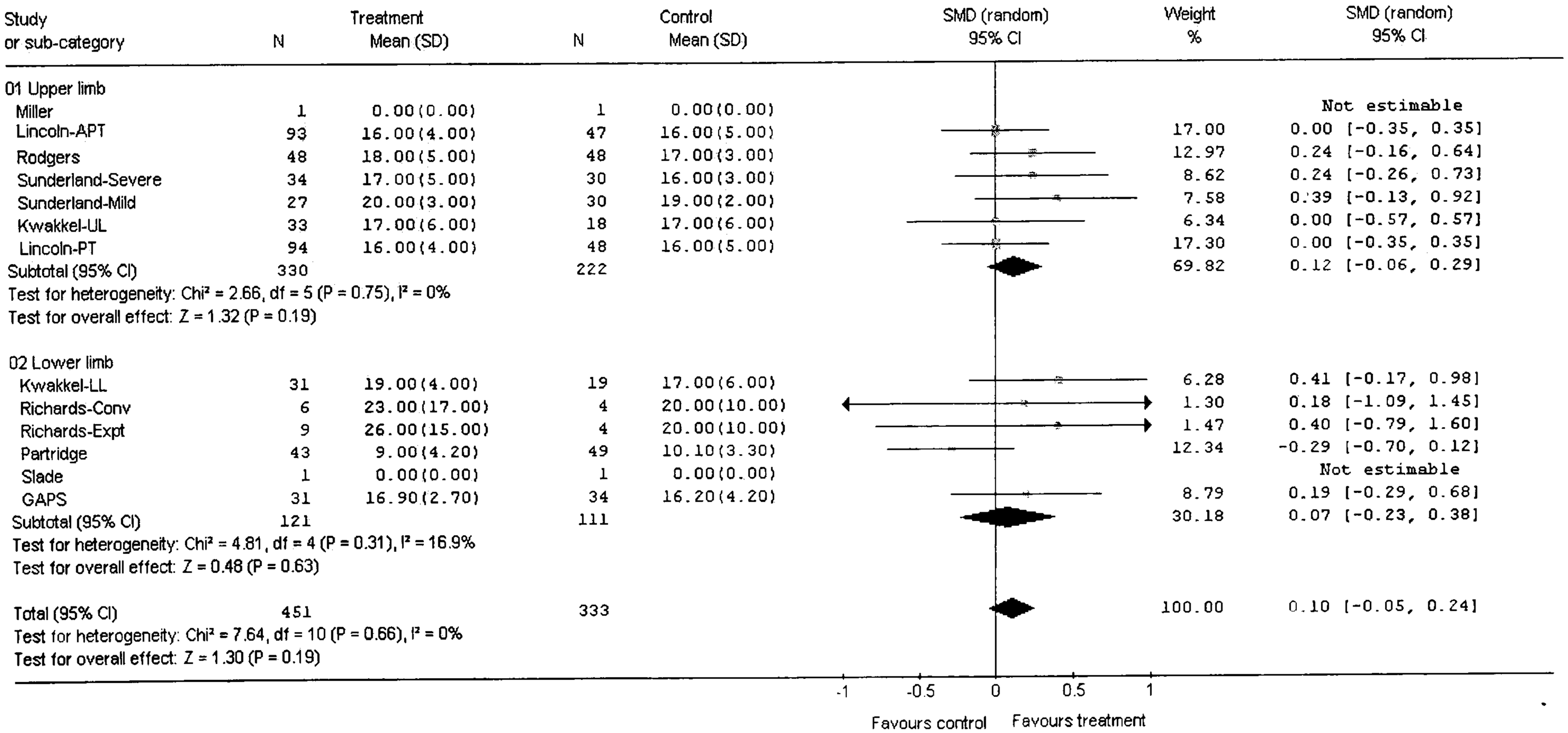


Figure 5.5 PINTAS IPD meta-analysis – Forrest plot showing Motricity Index (Arm) scores at 3 month follow up

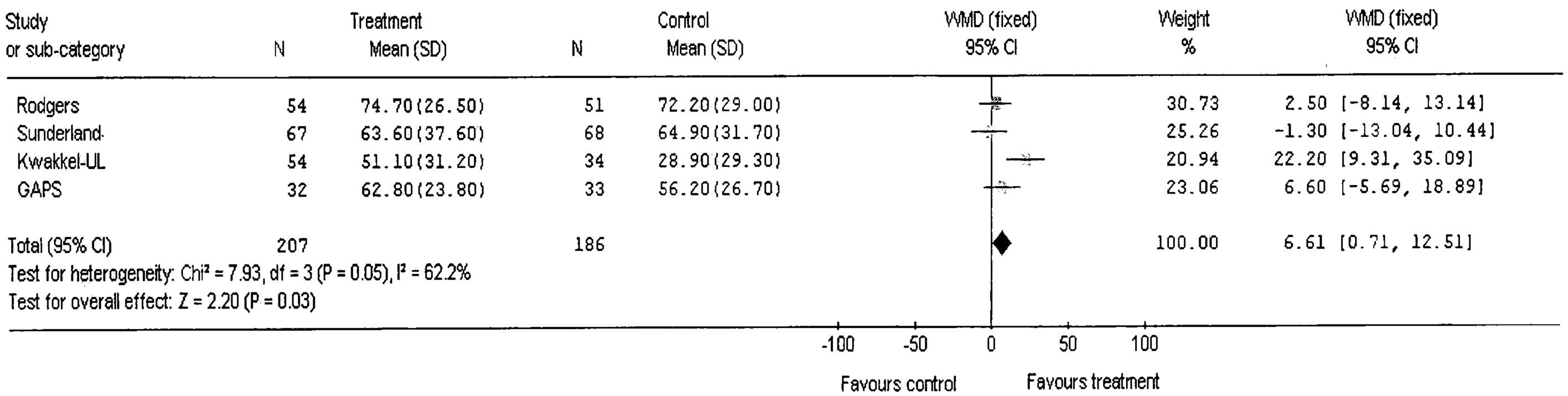


Figure 5.6 PINTAS IPD meta-analysis – Forrest plot showing Motricity Index (Arm) scores at end of study

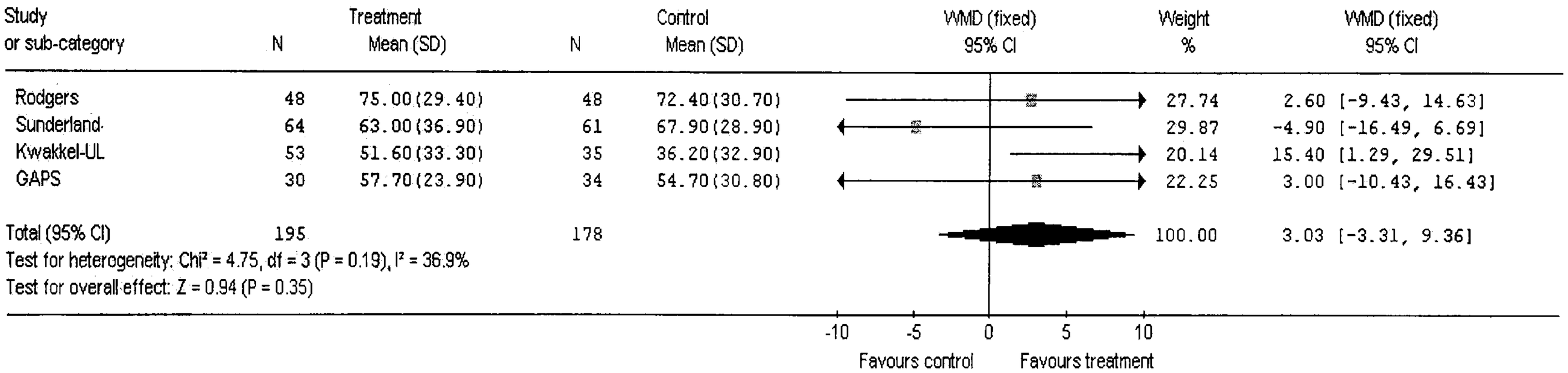


Figure 5.7 PINTAS IPD meta-analysis – Forrest plot showing Motricity Index (Leg) scores at 3 month follow up

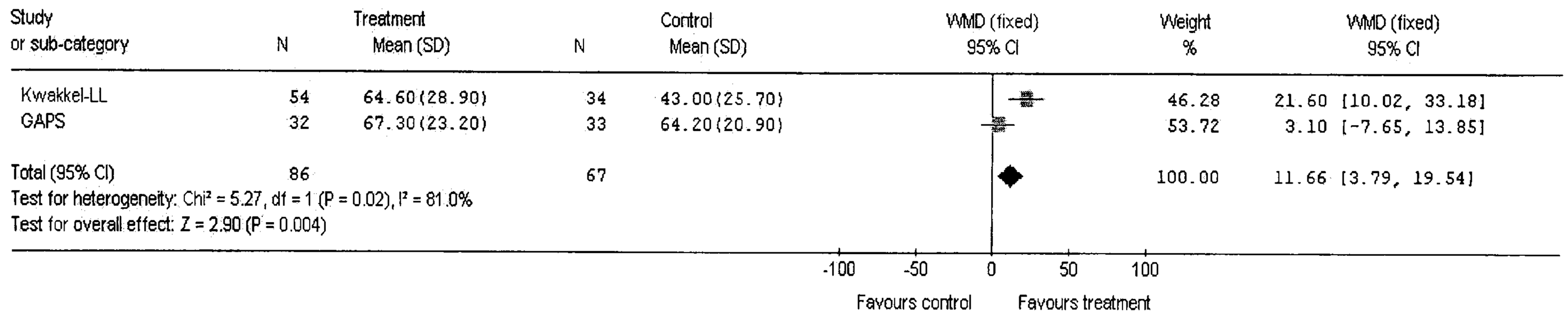


Figure 5.8 PINTAS IPD meta-analysis – Forrest plot showing Motricity Index (Leg) scores at end of study

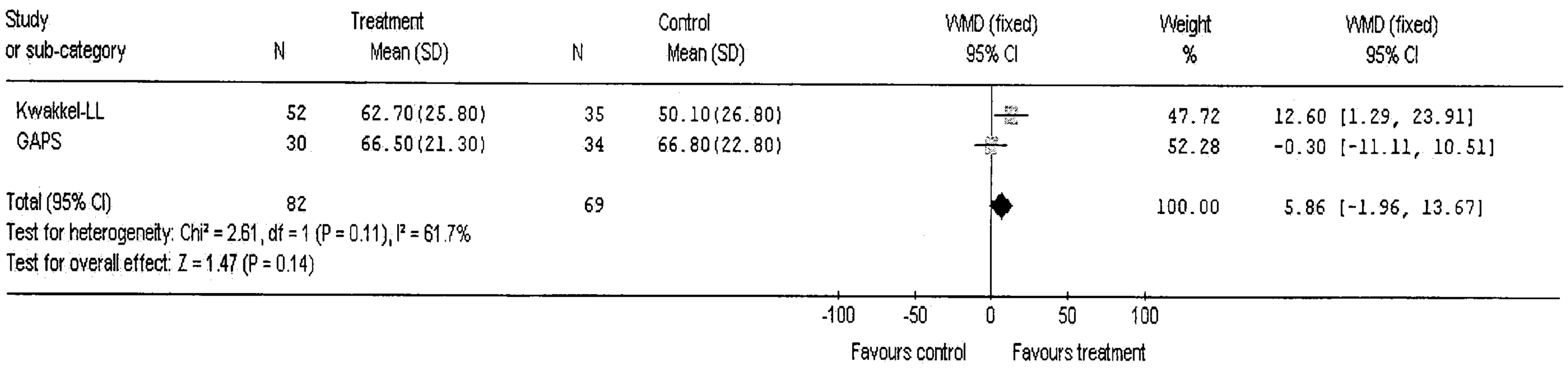


Figure 5.9 PINTAS IPD meta-analysis – Forrest plot showing Action Research Arm Test (ARAT) scores at 3-month follow up

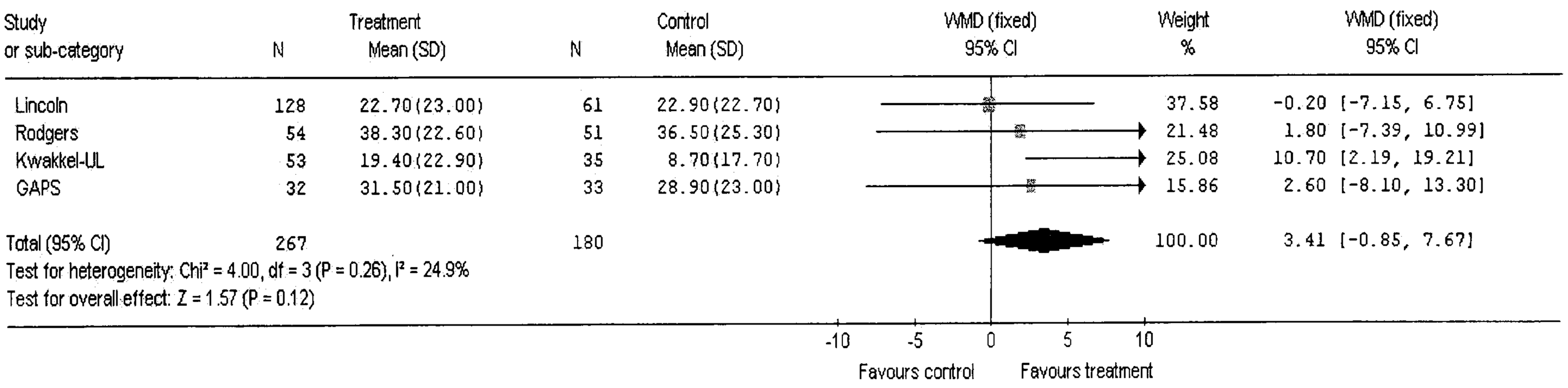


Figure 5.10 PINTAS IPD meta-analysis – Forrest plot showing Action Research Arm Test scores at end of study

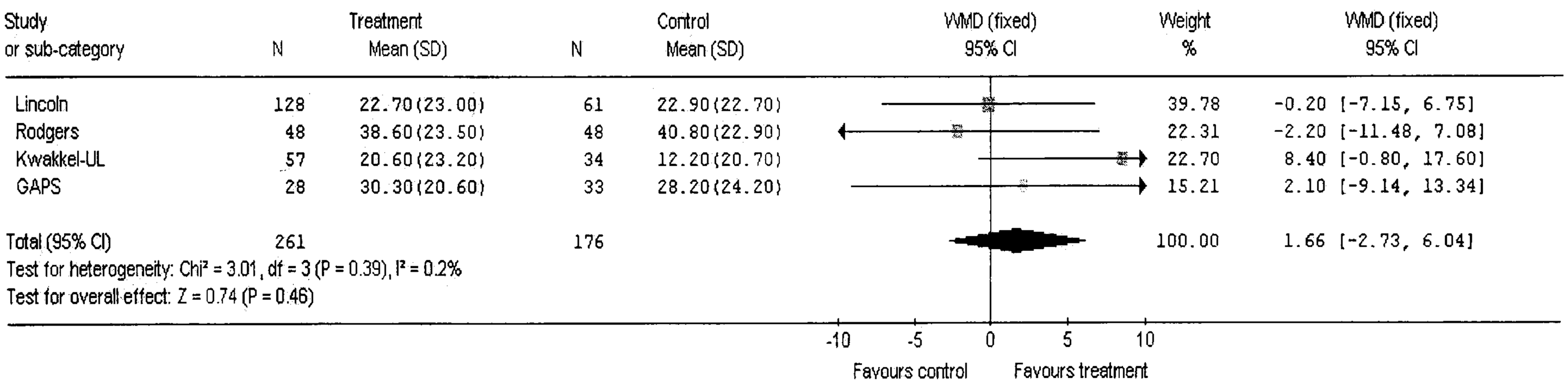


Figure 5.11 PINTAS IPD meta-analysis – Forrest plot showing Gait speed at 3-month follow up

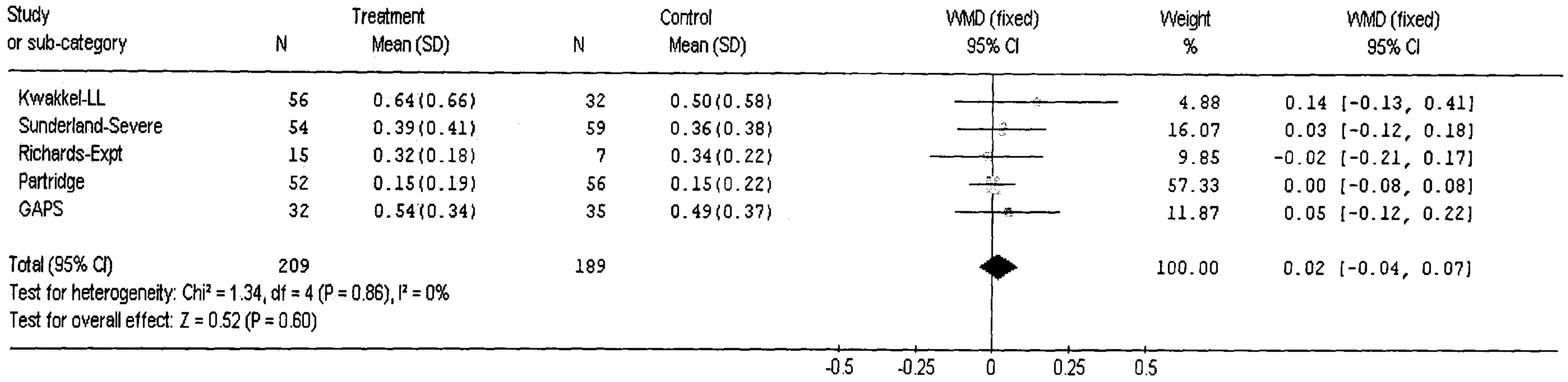


Figure 5.12 PINTAS IPD meta-analysis – Forrest plot showing Gait speed at end of study

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Kwakkel-LL	53	0.81(0.67)	33	0.70(0.58)		5.26	0.11 [-0.16, 0.38]
Sunderland-Severe	36	0.50(0.48)	39	0.44(0.41)		9.16	0.06 [-0.14, 0.26]
Richards-Expt	15	0.32(0.18)	7	0.32(0.22)		10.81	0.00 [-0.19, 0.19]
Partridge	52	0.15(0.19)	56	0.15(0.22)		62.93	0.00 [-0.08, 0.08]
GAPS	29	0.59(0.36)	34	0.48(0.36)		11.84	0.11 [-0.07, 0.29]
Total (95% CI)	185		169			100.00	0.02 [-0.04, 0.09]

Test for heterogeneity: $Chi^2 = 1.84$, df = 4 (P = 0.76), $I^2 = 0\%$

Test for overall effect: Z = 0.78 (P = 0.44)

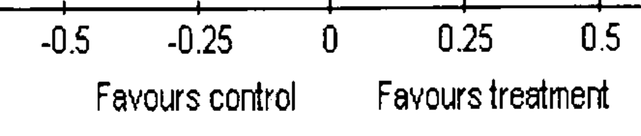
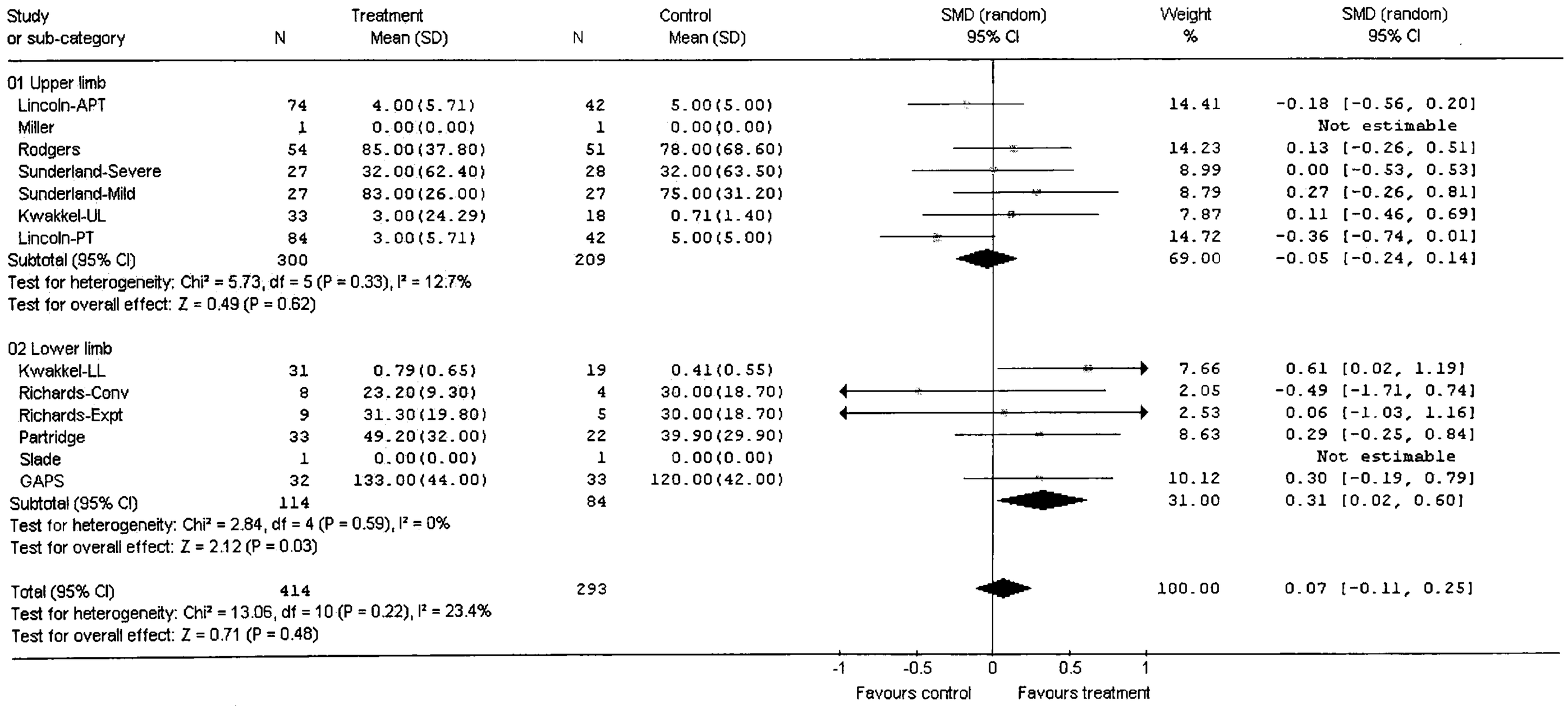


Figure 5.13 PINTAS IPD meta-analysis –

"Overall" impairment at 3-month follow up (stratified by the target of physiotherapy)



Secondary analyses

We carried out analyses for measures of death, change in impairment and disability scores (across the period of the study), treatment success and heterogeneity.

Death

Case fatality: There were 32 deaths in 418 subjects who received standard physiotherapy (crude death proportion 7.7%) compared with 44 deaths in 533 subjects who were randomised to augmented physiotherapy (8.3%) giving an odds ratio for death of 0.92 (95% CI 0.55 to 1.52; P=0.81). (See Table 5.8).

Table 5.8 PINTAS IPD meta-analysis - Case Fatality

Study	n Standard	n Augmented
GAPS	0/35	2/35
Kwakkel	1/37	0/64
Lincoln	12/95	29/187
Miller	0/9	0/12
Partridge	4/60	2/54
Richards	0/13	0/9
Rodgers	7/61	6/62
Slade	0/40	0/43
Sunderland	8/68	5/67
TOTAL	32/418	44/533

Note that we have not conducted a time-to-event analysis (it proved too difficult to establish with certainty at what point every subject in every study died in terms of days post randomisation), and note further that 41 of the 76 deaths (over 50%) occurred in one study, and that there were no deaths reported in three of the (smaller, shorter duration) studies.

Secondary analyses – Change in impairment

Improvement in arm impairment (Motricity Index Arm): Table 5.9 summarises the main arm impairment data. The main effects model estimated the difference in arm Motricity index due to augmented physiotherapy as 5.2 (95% confidence interval 1.5 to 8.8, P=0.0058) with an identical estimate returned after adjusting for age and gender. There was no evidence of a significant change in the treatment effect of augmented over standard physiotherapy over time (P=0.27).

Subgroup analysis: Subgroup analyses (Table 5.10) indicated that improvement in arm Motricity Index score was significantly greater (P=0.02) in higher treatment contrast trials 9.6 (95% CI 3.7 to 15.5; P=0.001) than in lower contrast trials -0.2 (95% CI –5.4 to 5.0; P=0.90).

**Table 5.9 PINTAS IPD meta-analysis –
Motricity index scores and change from baseline**

	Month	n	Control Motricity Index	Change from baseline	n	Augmented Motricity Index	Change from baseline	Difference (augmented – control) in change from baseline	P for change difference
Arm total	0	201	38.7(33.1)	-	228	36.8(34.2)	-	-	-
	1	136	46.0(33.4)	11.7(18.1)	158	50.2(33.4)	19.2(20.1)	6.7(2.3, 11.1)	0.0030
	3	186	58.8(33.1)	20.2(20.4)	207	63.1(32.3)	25.8(22.9)	5.1(0.8, 9.4)	0.021
	6	180	59.2(33.6)	20.8(22.7)	201	61.8(33.1)	27.9(24.1)	6.2 (1.5, 10.9)	0.0097
	12	35	36.2(32.4)	27.1(23.0)	53	51.6(33.3)	35.0(25.0)	8.0(-2.5, 18.5)	0.14

Table 5.10 PINTAS IPD meta-analysis –
Change in arm impairment (Motricity Index arm) – subgroup analysis

Subgroup	Level	Augmented-Standard (95% CI)	P-value	Subgroup interaction
Total	All groups	5.2 (1.5, 8.8)	0.006	--
Treatment target	Arm Only	3.4 (-1.7, 8.6)	0.67	P=0.54
	Leg or Mixed	4.7 (-0.7, 10.1)	0.090	
Age	<70	6.6 (1.6, 11.6)	0.0097	P=0.44
	>70	4.8 (-0.5, 10.0)	0.075	
Baseline dependency	Barthel >10	-0.4 (-5.3, 4.6)	0.89	P=0.21
	Barthel ≤10	6.8 (2.2, 11.4)	0.004	
Baseline arm impairment	Moderate	3.2 (-0.1, 6.5)	0.056	P=0.40
	Severe	6.9 (-0.3, 14.0)	0.061	
Total treatment contrast	Lower	-0.2 (–5.4, 5.0)	0.90	P=0.02
	Higher	9.6 (3.7, 15.5)	0.001	

Improvement in leg impairment (Motricity Index Leg): The overall advantage of augmented compared with standard physiotherapy was estimated as 6.8 units of leg Motricity Index (95% CI 2.2- 11.4, P=0.0042) from a repeated measures model that adjusted for age, sex, and baseline leg Motricity Index score (Table 5.11). There was no statistically significant evidence of an interaction between treatment and time (P=0.087).

Subgroup analysis: For the pre-specified subgroups of age and disability severity there was no evidence of any treatment by time interactions, nor of any formally significant differences in treatment effect between the levels of the subgroups. The higher treatment contrast trials tended to observe greater improvements (higher contrast 12.1; 4.8-19.4; P=0.004 compared with lower treatment contrast 3.3; -3.4-10.0; P=0.33) but subgroup interaction was not quite statistically significant (P=0.08) (Table 5.12).

**Table 5.11 PINTAS IPD meta-analysis –
Motricity index scores and change from baseline**

	Month	n	Control Motricity Index	Change from baseline	n	Augmented Motricity Index	Change from baseline	Difference (augmented – control) in change from baseline	P for change difference
Leg total	0	71	37.2(30.6)	-	99	36.5(29.2)	-	-	-
	1	70	46.0(28.5)	9.1(18.1)	92	57.7(28.2)	21.3(21.3)	9.1(3.9,14.3)	0.0007
	3	67	53.5(25.6)	16.4(19.4)	86	65.6(26.8)	28.3(22.6)	8.2(3.0,13.5)	0.0022
	6	71	56.6(26.8)	19.8(22.3)	89	65.4(25.0)	29.4(24.6)	5.1(-0.7,10.9)	0.086
	12	35	50.1(26.8)	33.7(20.6)	52	62.7(25.8)	38.6(15.6)	4.8(-2.9,12.6)	0.22

Table 5.12 PINTAS IPD meta-analysis –
Change in leg impairment (Motricity Index) from baseline – subgroup analysis

Subgroup	Level	Augmented-Standard (95% CI)	P-value	Subgroup interaction
Total	All groups	6.8 (2.2, 11.4)	0.004	--
Treatment target	Arm Only	Insufficient data	----	---
	Leg or Mixed			
Age	<70	7.2 (1.2 to 13.1)	0.018	P>0.1
	>70	6.7 (-1.1 to 14.5)	0.091	
Baseline dependency	Barthel >10	-0.7 (-9.2 to 7.7)	0.86	P>0.1
	Barthel ≤10	7.3 (1.8 to 12.8)	0.010	
Baseline arm impairment	Moderate	13.5 (1.7, 25.3)	0.024	P=0.87
	Severe	7.2 (-1.4, 15.6)	0.097	
Total treatment contrast	Lower	3.3 (–3.4, 10.0)	0.33	P=0.08
	Higher	12.1 (4.8, 19.4)	0.004	

Change in arm function (Action Research Arm Test (ARAT) scores): Four studies reported ARAT scores (Table 5.13)(Full summary in Appendix VIII). The estimated effect of augmented physiotherapy compared with standard physiotherapy in change over baseline ARAT score was 1.8 (95% confidence interval -1.2 to 4.8, P=0.25) There was no evidence that the effect of augmented physiotherapy in comparison with standard physiotherapy changed over time (P=0.87). On subgroup analysis (Table 5.14) significant interactions were seen with age and baseline severity. Improvements in ARAT scores were significantly (P=0.02 for subgroup interaction) greater in younger patients (8.9; 95% CI 3.3-14.5; P=0.002) compared with older patients (1.5; 95%CI -2.7- 5.7; P=0.49). Improvements were also greater (P=0.04) in patients with a baseline Barthel index >10 (5.5; 95% CI -1.5 - 12.4; P=0.12) compared with those with baseline Barthel index of <11 (0.6; 95% CI -2.8 - 3.9; P=0.74).

Table 5.13 PINTAS IPD meta-analysis - Mean (SD) ARAT scores

For 4 Studies	Time	Standard		Augmented		Total	
		N	Mean(SD)	N	Mean(SD)	N	Mean(SD)
	0	193	9.6(17.2)	313	8.2(15.4)	506	8.7(16.1)
	1	159	16.9(20.7)	259	18.0(21.0)	418	17.6(20.9)
	3	119	26.2(25.4)	139	29.5(23.7)	258	28.0(24.5)
	6	179	26.1(24.7)	263	26.2(23.8)	442	26.2(24.1)
	12	34	12.2(20.7)	57	20.6(23.3)	91	17.5(22.6)

(SD = standard deviation)

Table 5.14 PINTAS IPD meta-analysis - Change in arm function (ARAT score): subgroup analysis

Subgroup	Level	Augmented-Standard (95% CI)	P-value	Subgroup interaction
Total	All groups	1.78 (-1.25, 4.81)	0.25	--
Treatment target	Arm Only	0.93 (-2.58, 4.45)	0.52	P=0.30
	Leg or Mixed	1.85 (-4.51, 8.21)	0.58	
Age	<70	8.91 (3.32, 14.5)	0.002	P=0.02
	>70	1.49 (-2.71, 5.70)	0.49	
Baseline dependency	Barthel >10	5.45 (-1.52, 12.4)	0.12	P=0.04
	Barthel ≤10	0.57 (-2.81, 3.94)	0.74	
Baseline arm impairment	Moderate	-1.23 (-6.26, 3.81)	0.63	P=0.22
	Severe	3.44 (0.29, 6.59)	0.032	
Total treatment contrast	Lower	0.5 (-5.0, 6.1)	0.90	P=0.26
	Higher	7.6 (0.9, 14.2)	0.03	

(CI = confidence interval)

Lower limb function (walking speed):

Five of the nine trials had used walking speed. Available data were converted to metres per second for a 10m walk. Some trials used ten metre, six metre or five metre walking times. We excluded any measurements that were not a simple walk in a straight line – for example, a 3m "there and back" walk which involved a turn (See Table 5.15)(Full summary in Appendix VIII).

There was no evidence that any difference in walking speeds attributable to the intensity of physiotherapy changed over time (P=0.51). The estimated magnitude of augmented compared with standard physiotherapy in walking speed was an increase of 0.056 m/s (95% confidence interval -0.018 to 0.130, P=0.14) in a repeated measures model that adjusted for age and gender. The estimated effect of augmented compared with standard physiotherapy on walking speed excluding subjects who never walked during the study was 0.07 ms-1 (95% confidence interval –0.02 to 0.16, P=0.12).

Table 5.15 PINTAS IPD meta-analysis - Mean walking speed

Study	Time (month)	Standard		Augmented		Difference (Aug. – Std)	
		n	Mean(SD)	n	Mean(SD)	Mean(95% CI)	P-value
TOTAL	0	97	0.02(0.14)	118	0.02(0.11)	-	-
	1	188	0.27(0.38)	215	0.33(0.44)	0.05 (-0.03, 0.13)	0.23
	3	133	0.42(0.43)	157	0.50(0.56)	0.07 (-0.04, 0.17)	0.23
	6	124	0.48(0.47)	143	0.59(0.54)	0.09 (-0.03, 0.21)	0.13
	12	72	0.56(0.51)	89	0.69(0.62)	0.09 (-0.09, 0.26)	0.32

SD = Standard deviation, CI = Confidence interval

Subgroup analysis: For the pre-specified subgroups of age, disability severity, target of treatment, and baseline severity of arm impairment there was no evidence of any treatment by time interactions, nor of any formally significant differences in treatment effect between the levels of the subgroups (see Table 5.16). The most marked degree of subgroup interaction (P=0.21) was with the target of therapy where the improvement in walking speed for leg/mixed target trials was 0.09 m/sec (0.00 to 0.18; P=0.047) compared with -0.02 (-0.16 to 0.13; P=0.83) for upper limb trials.

Table 5.16 PINTAS IPD meta-analysis - Change in lower limb function (walking speed)

Subgroup	Level	Augmented-Standard (95% CI)	P-value	Subgroup interaction
Total	All groups	0.07 (-0.02, 0.16)	0.12	--
Treatment target	Arm Only	-0.02 (-0.16 to 0.13)	0.83	P=0.21
	Leg or Mixed	0.09 (0.00 to 0.18)	0.047	
Age	<70	0.07 (-0.05 to 0.19)	0.25	P=0.75
	>70	0.05 (-0.04 to 0.13)	0.28	
Baseline dependency	Barthel >10	0.01 (-0.14 to 0.16)	0.93	P=0.62
	Barthel ≤10	0.09 (-0.03 to 0.20)	0.14	
Baseline arm impairment	Moderate	0.06 (-0.07 to 0.19)	0.37	P=0.80
	Severe	0.11 (-0.02 to 0.25)	0.10	
Total treatment contrast	Lower	0.01 –0.06, 0.08	0.80	P>0.50
	Higher	0.06 (-0.07, 0.18)	0.41	

CI = Confidence interval

It should be noted that in the comparison of leg function subgroups for target (mixed / lower v arm) the only trial with upper limb focus that provided data for comparison was Sunderland (unpublished data). Most data were available for early outcomes, i.e. 1 month and 3 months outcome data, for comparison.

Further information on walking speed is provided in the Statistical Appendix (Appendix VIII).

Secondary analysis – Change in disability

Change in disability measured by Barthel index: Table 5.17 shows the mean change in Barthel index score by treatment group and compares the differences in the groups (Full summary in Appendix VIII). The estimated constant across time effect of augmented in comparison to standard physiotherapy was 0.15 units of change in Barthel index score (95% confidence interval of –0.38 to 0.67, P=0.58).

Table 5.17 PINTAS IPD meta-analysis - Change over baseline in Barthel index score: By randomised treatment group, and difference in change over baseline between randomised treatment groups.

For 8 studies*	Time (month)	Standard		Augmented		Augmented – Standard*	
		n	Mean(SD)	n	Mean(SD)	Difference	P-value
	1	270	4.1(3.9)	381	4.6(4.0)	0.2(-0.4, 0.8)	0.55
	3	305	5.6(4.4)	411	6.1(4.6)	0.3(-0.3,0.9)	0.40
	6	266	6.6(4.7)	355	7.2(4.8)	0.3(-0.4,1.0)	0.47
	12	80	7.9(4.1)	89	9.6(4.6)	1.0(-0.3,2.2)	0.12

SD = Standard deviation

* From a separate linear model for each time point that adjusts for study. Otherwise, for each individual study, from a separate linear model for each time point.

Subgroup analyses: These are shown in Table 5.18. Significant subgroup interactions were seen for treatment contrast (P=0.04).

Table 5.18 PINTAS IPD meta-analysis - Improvement in disability (Barthel index): subgroup analysis

Subgroup	Level	Augmented-Standard (95% CI)	P-value	Subgroup interaction
Total	All groups	0.15 (-0.38, 0.67)	0.58	--
Treatment target	Arm Only	0.10 (-0.60, 0.81)	0.77	P>0.1
	Leg or Mixed	0.67 (-0.10, 1.43)	0.086	
Age	<70	-0.16 (-0.82, 0.50)	0.83	P=0.26
	>70	0.62 (-0.22, 1.46)	0.15	
Baseline dependency	Barthel >10	-0.11 (-0.84, 0.62)	0.77	P>0.1
	Barthel ≤10	0.25 (-0.40, 0.91)	0.44	
Baseline arm impairment	Moderate	0.08 (-0.78, 0.93)	0.86	P=0.91
	Severe	0.18 (-0.61, 0.97)	0.66	
Total treatment contrast	Lower	0.00 (-0.70, 0.70)	0.99	P=0.04
	Higher	1.37 (0.30, 2.45)	0.01	

CI = Confidence interval

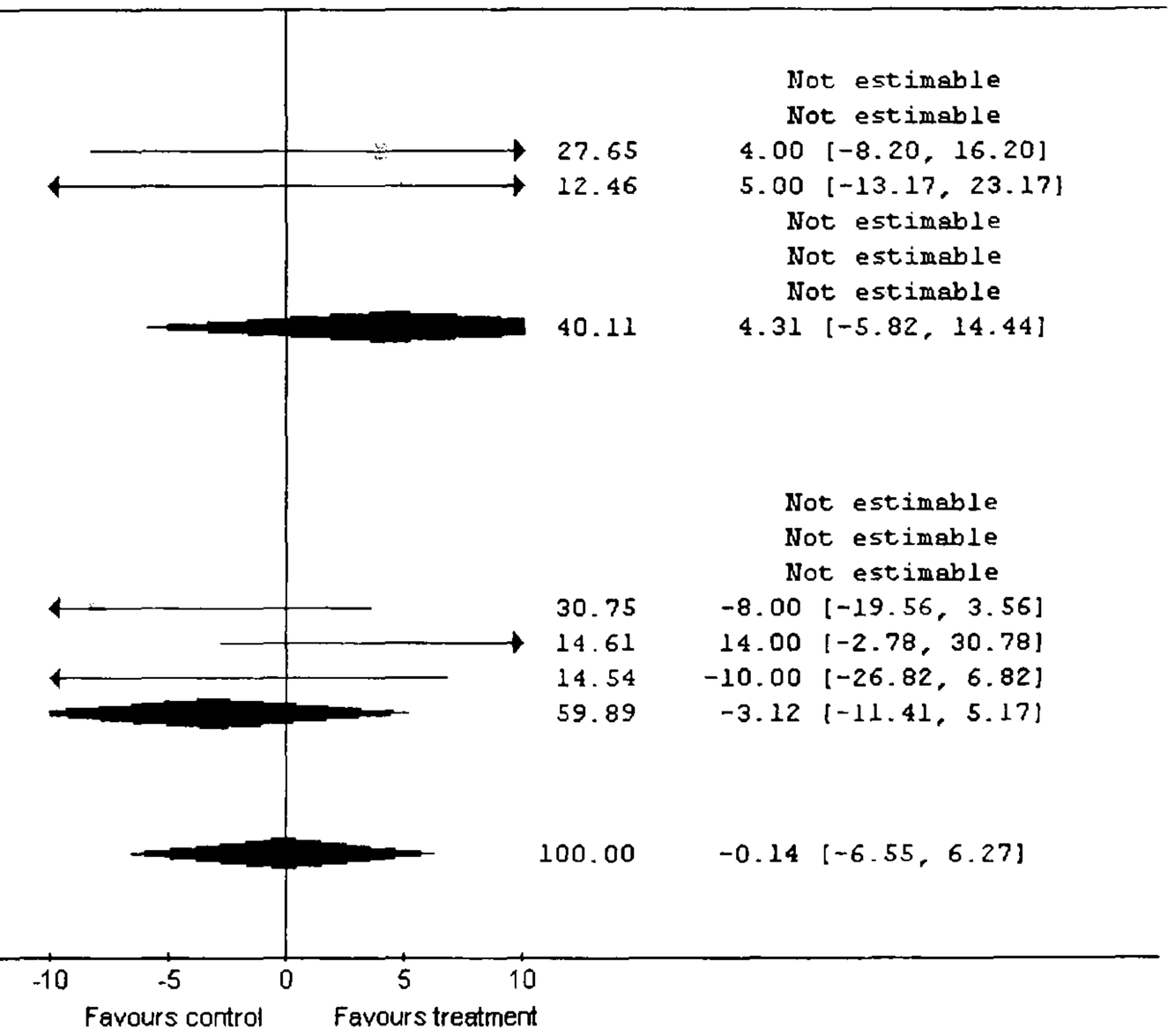
Secondary analysis – Length of hospital stay

We compared the two randomised groups (augmented and standard) for the length of hospital stay from five trials (522 patients). Of these, data on the length of stay post randomisation were available in 391 (75%) patients. In the 131 (25%) cases where this was not available, we used the total length of hospital stay, which would include a period from admission for acute stroke to the beginning of physiotherapy (or randomisation, which may be strictly speaking slightly before initiation of therapy).
For the effect of treatment alone (in a normal linear model with study fitted as a fixed effect) we found that augmented physiotherapy resulted in a non-significant increase of 1.4 days (95% CI -5.6 to 8.3, P=0.70). This result did not alter substantially in multivariate models that adjusted for study, gender, age, baseline stroke severity and treatment target. There were no significant subgroup interactions.

RevMan analysis, carried out at the level of the trial and stratified by the target of physiotherapy is shown in Figure 5.14.

Figure 5.14 PINTAS IPD meta-analysis – Forrest plot showing Length of hospital stay (stratified by the target of physiotherapy)

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Upper limb							
Lincoln-APT	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Miller	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Rodgers	62	42.00(34.00)	61	38.00(35.00)		27.65	4.00 [-8.20, 16.20]
Sunderland-Severe	63	58.00(58.00)	65	53.00(46.00)		12.46	5.00 [-13.17, 23.17]
Sunderland-Mild	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Kwakkel-UL	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Lincoln-PT	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Subtotal (95% CI)	130		131			40.11	4.31 [-5.82, 14.44]
Test for heterogeneity: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%							
Test for overall effect: Z = 0.83 (P = 0.40)							
02 Lower limb							
Kwakkel-LL	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Richards-Conv	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Richards-Expt	1	0.00(0.00)	1	0.00(0.00)			Not estimable
Partridge	54	60.00(30.00)	60	68.00(33.00)		30.75	-8.00 [-19.56, 3.56]
Slade	43	86.00(40.00)	40	72.00(38.00)		14.61	14.00 [-2.78, 30.78]
GAPS	35	45.00(27.00)	35	55.00(43.00)		14.54	-10.00 [-26.82, 6.82]
Subtotal (95% CI)	135		138			59.89	-3.12 [-11.41, 5.17]
Test for heterogeneity: Chi² = 5.32, df = 2 (P = 0.07), I² = 62.4%							
Test for overall effect: Z = 0.74 (P = 0.46)							
Total (95% CI)	265		269			100.00	-0.14 [-6.55, 6.27]
Test for heterogeneity: Chi² = 6.57, df = 4 (P = 0.16), I² = 39.1%							
Test for overall effect: Z = 0.04 (P = 0.97)							



Secondary outcome - Treatment success:

The final analysis defined a treatment success as a subject who has a change over baseline Barthel index greater than or equal to the stated threshold change over baseline (or a subject who has achieved the maximum score on the measure). Treatment success was then modelled as a binary outcome in a logistic regression using study, age, gender, and treatment group as covariates. These logistic regressions were fitted separately for the 3 months data (patterns were similar at 1 and 6 months).

We first focussed on treatment effects greater than the median recovery in the control group (increase from baseline of 6 or more Barthel units). There was an increased odds of an improved recovery in the augmented therapy group which did not reach statistical significance (odds ratio 1.33; 95% CI 0.96 – 1.85; P=0.09).

The second analysis focussed on treatment effects greater than the upper inter-quartile level of the control group (increase from baseline of 9 or more Barthel units). There was a statistically significant increased odds of an improved recovery in the augmented therapy group (odds ratio 1.47; 95% CI 1.03 – 2.05; P=0.04).

Heterogeneity of studies

With the same trials included in the meta-analysis, we expect the I^2 results to be the same or very similar to those obtained in Chapter 4. Results are given in Table 5.19. The exception is length of stay which was impossible to analyse in the aggregate data meta-analysis. This showed I^2 to be 39.1%.

Comparing published data to IPD meta-analyses

To examine the differences in the methods depending on whether data are gathered from published evidence, aggregate data or from individual patient data we carried out a published data meta-analysis with just the data that were available in print up to the end of as at December 2002 (see Table 5.19).

Although this is an academic exercise (as clearly we knew about our own and Rodgers et al.'s unpublished trials) it was designed to reflect "real life" meta-analysis. The results are bound to be different as there will be fewer data in the published data analysis. However a comparison should demonstrate the difference between the

methods if not actually demonstrate the amount of effort involved in undertaking the IPD meta-analysis (Stewart & Parmar 1993)(Stewart & Teirney 2002).

In carrying out this comparison I did not use independent data extraction by two authors but simply looked at the effect of removing those trials that were unpublished.

Table 5.19 Comparing results from meta-analyses based on published data to those based on individual patient data (IPD)

Outcome		Published data only	Individual patient data
Overall Disability (at 3 months)	No. of trials (n patients)	6 n = 637	8 n = 805
	SMD	0.17	0.15
	95% CI	-0.04 to 0.38	-0.02 to 0.31
	P	0.11	0.09
	Heterogeneity I^2 (%)	33.4	21.5
Overall Impairment (at 3 months)	No. of trials (n patients)	6 n = 535	8 n = 703
	SMD	0.03	0.07
	95% CI	-0.19 to 0.25	-0.11 to 0.25
	P	0.78	0.48
	Heterogeneity I^2 (%)	30.9	23.4
Death	No. of trials (n patients)	7 n = 823	9 n = 951
	OR	0.85	0.92
	95% CI	0.37 to 1.95	0.55 to 1.52
	P	0.69	0.81
	Heterogeneity I^2 (%)	23.9	0
Length of stay	No. of trials (n patients)	2 n = 202	5 n = 518
	SMD	Not estimable	-0.14
	95% CI		-6.55 to 6.27
	P		1
	Heterogeneity I^2 (%)		39.1

SMD = Standardised men difference, OR = odds ratio, CI = Confidence interval

Interpretation of results

We found no statistically significant differences in the patient groups receiving standard or augmented intensity of physiotherapy, in terms of our primary outcomes: overall disability or impairment or of our secondary outcomes; length of hospital stay and case fatality.

There is a statistically significant difference between the groups in impairment outcome (as measured by the Motricity Index Arm and Leg sections) in the short term (3 months).

It is perhaps not surprising that the improvements seen in the Barthel index are modest, as the scale has recognised limitations in its measurement properties. However, we were attracted by the ready availability of data when testing for a treatment effect. Most physiotherapy intervention trials have impairment as their primary outcome but standardised outcome measures have not been universally adopted.

While being wary of the problems of multiple subgroup comparisons (Counsell et al. 1994, Mulrow & Oxman 1997) the real benefit of IPD meta-analysis is the ability to carry out subgroup and exploratory analyses. We have highlighted subgroups of patients with stroke that may benefit from increased intensity of treatment:

a). Patients who might show a major decrease in disability (measured by BI).
Those making large gains in Barthel index score over the short term (3 months) i.e. making a rapid functional recovery ("good" and "excellent" recovery) may benefit from more intensive physiotherapy treatment. This may be due to additional physiotherapy treatment enhancing natural recovery in the short term.

b). Patients who might show a decrease in impairment.
Benefit in terms of upper and lower limb impairment (measured by the Motricity Index Arm and Leg sections) can be seen in those patients receiving more intensive therapy in the high contrast trials. There are also benefits in terms of impairment assessed by change in ARAT score for younger (< 70 years) patients and those with less initial disability (a baseline Barthel index score > 10).

However the evidence from the subgroup analyses is not consistent, nor is there a consistent effect with targeting of therapy although for some outcomes e.g. walking speed there was a non statistically-significant trend indicating a targeting effect.

What was more convincing was the pattern of higher treatment contrast trials observing greater effects of augmented physiotherapy.

There were little demonstrable differences in length of hospital stay and therefore inpatient costs are unlikely to be significantly reduced.

Our survival analysis did not show significant differences but at least demonstrated additional physiotherapy (as delivered in our selected trials) to be a reasonably safe intervention when used to improve patients' mobility.

In some of the plots, outlying data from Kwakkel et al. may be explained by their ability to provide early intervention and maintain treatment contrast by immobilising the limbs of the patients in the control group.

When considering our results we need to be able to make judgements as to whether benefits have clinical significance not just statistical significance. We investigated this by exploring the use of abridged versions of the Barthel index. Changes in scores at the level most collaborators might consider to be "clinically significant" did not appear to reach statistically significance. This analysis is made more complex by variable baseline scores and a measure with an acknowledged "ceiling" effect that may not be sensitive to the intervention.

We can see from Table 5.20 that there is variable heterogeneity between the studies entered into the analyses. (Higgins et al. 2003). Using this as a guide most of our selected analyses would be considered to have "mild" or "moderate" heterogeneity.

Discussion

By carrying out this IPD meta-analysis, using clearly defined methods, we have been able to thoroughly explore the available data from the trials of intensity of physiotherapy. To do so required a considerable amount of data handling and interpretation in order to guide the analyses. Despite our inclusive methods the available data were still limited. One major limitation is that key variables may cluster at the level of the trial resulting in co-variance of results.

We are also limited by not having recognized measures of co-morbidity and at present we would not look to convert available data into a recognized co-morbidity score. Age could be used as a proxy measure along with any available data on pre-stroke disability or handicap e.g. Pre-stroke Rankin score – though few trials had these data or excluded patients with previous disability.

By performing published and individual patient data meta-analyses we were able to compare the results obtained by both methods. At this point there was little difference in any conclusion one might draw from the results from the main outcome measures. The accuracy of the estimate has improved with smaller P values and narrower confidence intervals but this may partly reflect the additional number of studies available for the IPD meta-analysis. However, the main benefit of the IPD method in our case is that it allows the exploration of the subgroups. Without this we would not have the results that indicate there may be particular benefit to certain groups of patients with stroke. We should however remain cautious of generalizing from results based on exploratory analyses of secondary outcomes (Counsell et al. 1994).

Trials in the future in this area should carefully select their outcome measures especially those sensitive to impairment. This may help to accurately target those groups we identified as benefiting from increased treatment, and allow further pooling of data in meta-analysis.

Conclusions

Bearing in mind our initial hypotheses, a number of conclusions can be drawn:

1) We found no statistically significant impact of augmented physiotherapy on our primary outcome of disability.
2) We did not identify any consistent effect with targeting of therapy although for some outcomes (e.g. walking speed) there was a trend indicating a targeting effect.
3) There was no consistent evidence that any subgroup of patients would gain a greater or lesser benefit from augmented physiotherapy.
4) There were no significant differences in length of stay or case fatality.

Additionally,

5) For those trials that recorded the Motricity Index, there was a statistically significant improvement in impairment (both in the Arm and Leg scores).
6) There was a consistent pattern of higher treatment contrast trials observing greater effects of augmented physiotherapy.
7) Our IPD estimate improved on information that was available had we only relied on published data up to the end of 2002.

Summary

- We set out to carry out an IPD meta-analysis and set up a collaborative group of primary authors.

- We searched the literature as before, obtaining data from the authors. These were entered into a combined database and the analysis strategy and questions were discussed and agreed at the Collaborators meeting.

- With availability of data in mind, we selected overall disability as our primary outcome and overall impairment, death and length of stay as secondary outcomes. We had the opportunity to explore the subgroups of patients derived from our original questions.

- No statistically significant difference was seen between the augmented and standard groups, in overall disability as measured by ADL scale, length of stay or case fatality.

- There was a lack of consistency between the results obtained from different outcome measures used in the subgroup analyses.

- Generally, effects were most notable in those trials that started early and featured a high contrast between the groups. Effects were more marked in the short-term than the long-term.

- There was only mild heterogeneity between the included trials for most of the analyses.

- Comparing the type of meta-analysis highlighted some benefits of undertaking the IPD meta-analysis.

CHAPTER 6
CONCLUSION

Introduction

In this chapter I look back on the components of the thesis and return to my original hypothesis. I have attempted to address this using a variety of methods, exploring the benefits and limitations of each, before progressing to the next method. The results at each stage have helped to build up information on the intensity of physiotherapy after stroke.

Aims

In this chapter I aim to:

1). Reflect on the available results in relation to my original research questions.

2). Consider the lessons learned from carrying out the work.

3). Identify areas for development in the future.

4). Make recommendations.

1) The results

I put forward the hypothesis that intensive physiotherapy after stroke will produce benefits that would:

a). speed recovery in terms of impairment and disability.

Neither the GAPS study randomised controlled trial nor the PINTAS IPD meta-analysis identified statistically significant benefits in terms of overall disability (see Figure 5.3, page 143), overall impairment (see Figure 5.13, page 153), death (see Table 5.8, page 154) or length of hospital stay (see Figure 5.14, page 166) with increased intensity of physiotherapy. Perhaps the disability and death results are to be expected, given that physiotherapy may not always be directed at reducing disability or preventing death. The Barthel index was widely used, but may not be sensitive to physiotherapy intervention. Even if the intervention was shown to be effective, the scale of the improvement looks likely to be, at best, modest. Although this may be of some significance to individual patients, the "clinically relevance" remains unclear.

Impairment on the other hand, is often the focus of physiotherapy treatment, yet taken overall, we could not show clear benefit with increased intensity. This may reflect the ability of the available outcome measures to detect modest treatment effects.

When we studied subgroups in our meta-analysis, patients receiving more intensive treatment in the high contrast trials showed greater improvements in upper and lower limb impairment when it was measured by the Motricity index. Younger patients who were less disabled at baseline also demonstrated greater improvements in upper limb impairment when measured on the ARAT. Increased intensity may also assist rapid recovery in the subgroup of patients making large improvements in their ADL scores (>9 points on the BI). There was however, a lack of consistent benefit across the subgroup analyses.

b). are greater when targeted (e.g. on upper limb recovery).

Similarly, there was a lack of consistency in the effects of targeting augmented physiotherapy. The trend is positive (but not statistically significant) for some areas such as walking, but is not clear for the others.

c). are greater for patients with moderate impairment and little co-morbidity.

In our subgroup analyses there were no statistically significant subgroup interactions for those patients considered to have moderate baseline arm impairment (categorized by Motricity index (Arm) or ARAT).

There is a lack of accepted measures of co-morbidity that are routinely collected and obtaining accurate data about pre-morbid states can be difficult. Consequently, we were unable to carry out analyses based on co-morbidity.

d). are greater in the shorter (3 months) than longer term (6 – 12 months).

In our selected trials, long-term follow up is the exception, with just two of our studies following patients to 12 months. Available data for these analyses were therefore limited. Differences in impairment between groups, though still in favour of the augmented group, appeared to diminish over time and lost any statistical significance. Although some acute intervention studies of stroke have followed-up subjects for up to ten years after intervention (Indredavik et al. 1999), they require sizable treatment effects for them to be worthwhile. The longer-term effects (> 12 months) of acute physiotherapy interventions remain unclear.

e). result in a reduced duration of inpatient rehabilitation.

Although the GAPS study showed a non-significant reduction in length of hospital stay, and Slade et al. (Slade et al. 2002) found a reduction in hospital stay, overall there was little sign of benefit. Consequently, there was no consistent evidence of economic benefits arising from shorter admissions.

The overall direction of benefit with increased intensity fits with the picture developing from other studies: the late intervention studies (e.g. Duncan et al. 2003, Green et al. 2004); suggestions of benefit from repeated practice of functional tasks in the motor relearning programme (Langhammer & Stanghelle 2000) and possible benefits with constraint-induced therapy (forced use) (Taub et al. 2002). Benefit was also seen in a recent published-data meta-analysis of "exercise therapy" i.e. physiotherapy and occupational therapy (Kwakkel et al. 2004). This meta-analysis, with broad inclusion criteria (including most of the trials in our meta-analysis), demonstrated benefit overall and suggested greater benefit in trials with at least 16 hours of contrast between groups.

Whilst our results show promise for selected subgroups of patients with stroke, the results cannot yet be generalized.

There may be a critical threshold above which we start to see benefit – this is suggested by the subgroups with greater contrast showing greater benefit. This may be relevant to any "some versus none" trials. Although the contrast may be high, the trial may not be able to demonstrate benefit as the intervention group may not reach a threshold of treatment effect.

Heterogeneity of our studies

Some authors recommend routinely carrying out sensitivity analysis and creating a funnel plot when undertaking meta-analyses (Egger & Davey Smith 1998). We did not do this as the number of trials was small and we found only mild and moderate heterogeneity when considering most of our outcomes.

2) Lessons from our randomised controlled trial

To sustain a robust and complex trial with sound methodology over three sites for a period of 18 months, with limited resources, required considerable effort and enthusiasm from the research group and the staff members involved.

Despite having carried out feasibility studies, our recruitment rate was lower than anticipated. To try to address this we extended the period of the trial as much as funding allowed. Though we would have liked to extend the recruitment further it seemed unlikely that this would alter our sample size significantly. Although attempting to run the trial over a larger number of centres with more staff members might have allowed more rapid recruitment, this would have been costly and more complex to organize and sustain. The lesson is that recruitment rates do not always reach the levels expected or required, despite best efforts.

Recognising that our one trial would be unlikely to influence clinical decision-making or to be generalized to the majority of patients, we gathered a broad range of data from our subjects. Planning in this way allowed us the opportunity to examine a large number of outcomes in the meta-analysis.

Lessons from Meta-analysis

Size

Our meta-analyses had limitations in terms of the numbers of subjects, number of trials and the size of the subgroups, along with heterogeneous outcome measures and interventions. Clearly we would have preferred to have a larger number of subjects from more homogeneous trials.

The need for collaboration

With the IPD meta-analysis we were fortunate to secure the co-operation of all of the trialists. This strengthened the data set and allowed the group to be involved in the interpretation, dissemination and publication of results and planning of further studies. Our collaborative group's formal meeting helped to focus our analysis and agree the limitations of the data. Unfortunately, we did not budget for holding a second meeting. This might have been a useful forum in which to discuss the interpretation and dissemination of the results, the future of the group and further work. It may have also been useful in helping to keep the project running to timetable.

Managing the data was a challenge, requiring considerable communication and interpretation of the data, as IPD was a new venture for most of the collaborative group members. As noted by Stewart and Clarke (Stewart & Clarke 1995), it is important not to underestimate the length of time required for IPD meta-analysis. Our project was time-consuming and may have benefited from the availability of full-time dedicated staff members for data management in order to maintain consistency and momentum. Such resources are, of course, expensive.

Treatment contrast

We want to direct future research to target specific groups, with as much treatment contrast as possible. Yet, there are definite challenges in delivering and maintaining a strict treatment protocol in a clinical setting. In the trial by Rodgers et al. "competitive therapy" bias was encountered (Rodgers et al. 2003). Therapists involved in delivering treatment to their control group provided additional therapy as "compensation" to those patients allocated to receive standard amounts of treatment. Unfortunately this resulted in a significantly reduced treatment contrast ratio. The ability to maintain this contrast may be the reason we saw such an outstanding treatment effect in the trial of Kwakkel et al. that featured both early intervention and the maintenance of a high treatment contrast with the use of splints to immobilize the control group (Kwakkel et al. 1999).

Importance of pre-determined analysis plan

It was important to have a clearly determined and recorded analysis plan at the start of each phase and prior to the analysis. This reduces the risk of significant results being discovered by chance and helps to keep the focus of the question during, often complex, analyses. While it is tempting to perform further analyses in the light of available results, these should be regarded as exploratory and treated with caution.

Limitations of available data

One advantage of IPD meta-analysis is the potential to perform "time to event" analyses. The difficulty we encountered was the lack of consistent outcome gathering across the trials e.g. we could have selected the Mobility Milestones, discharge from hospital, first recorded ability to perform 10-metre walk. This made selecting outcomes difficult and the number of missing data considerable.

Similarly, we would have liked to carry out a "dose response" analysis, however the data were so limited that this proved impossible. This highlighted the lack of standard methods of describing and recording physiotherapy interventions in trials. This sort of level of detail, if available, is not often published and trialists need to be contacted to obtain information.

Ultimately, the quality of the data will be reflected in the analysis, results and conclusions.

The real benefit of IPD meta-analysis

Having carried out an IPD meta-analysis, we wanted to assess whether it was worth the considerable additional resources (Stewart & Parmar 1993). We compared results from the different methods on our selected outcomes. Whilst this showed some benefit in terms of the accuracy of the estimates, the obvious point is that without carrying out the IPD meta-analysis, none of the subgroup analyses would be possible with just published data. Our conclusions are likely to have been the same or similar, but the real benefit was the ability to explore and examine these subgroups.

3) Identifying areas for development in the future

Maintaining the database

Although a definitive large-scale multi-centre RCT of intensity might be possible, it seems unlikely to happen in the near future. We will therefore consider maintaining the database and updating it on a regular basis. This may be useful, but it is important not to underestimate the complexity of the data management and analysis.

Stewart and Tierney describe IPD as having a number of benefits but also raise the issue of "price tags" on data sets and possible difficulties of sharing data due to data protection legislation (Stewart & Tierney 2002). These were not a problem for our group but could alter the direction and possibilities offered by this method.

Recent publications

We repeated our literature search up to the start of May 2005 but failed to find trials that fit our inclusion criteria or look to significantly alter our results. We are not aware of any current large-scale randomized trials of physiotherapy intensity after stroke.

Of the trials that have been published, one small study (n = 30), using additional physiotherapy sessions delivered to inpatients in a circuit class format, showed variable results dependent on the focus of the intervention (Blennerhassett & Dite 2004). While preliminary results from another small study (n = 22) in acute stroke patients (Kreisel et al. 2005) suggest similar results to our meta-analysis with modest non-statistically significant improvements in motor scores when measured by the Motricity index.

In a larger, Chinese trial with 156 participants, Fang et al. set out to carry out a RCT but their comparison has a number of difficulties (Fang et al.2003). Their control group appears to receive no therapy, which though it increases their treatment contrast, may be unusual for many acute stroke patients in Western countries. In addition, their intervention group lost large numbers of subjects to follow up. This reflects that these trials are not easy to deliver, though with a highly-selected group and high loss to follow up (36% of intervention group lost at 3 months and 85% lost at 6 months) their results are difficult to analyse and generalize.

Other trials may not necessarily have been focused on intensity of physiotherapy e.g. Martinsson et al. (Martinsson et al. 2003), investigating the combination of intensive physiotherapy and amphetamine in severely disabled patients.

Further data extraction

Until further relevant trials are available we could attempt to maximise the use of existing data by using missing data techniques (such as multiple imputation or last observation carry forward) to explore the robustness of the findings to missing data. We could also consider converting data from the trials by Partridge et al. and Miller et al. to obtain estimated Barthel index scores.

Developing standard methods of describing and defining physiotherapy interventions in trials

We could investigate the properties of the record of physiotherapy input (Appendix I) used in the GAPS study. At the start of the study there did not appear to be recognised measures of physiotherapy input available. Though we gathered considerable detail of treatment, we utilised only a small component of this (the amount of time spent by the therapist). It would be useful to establish the reliability and validity of this method of data collection. If it proved to be a valid measure it might be useful in studies examining content of treatment as well as dosage.

Tyson and Selley have recently developed an intervention recording tool for use with stroke (Tyson & Selley 2004) and further work is expected from an international comparison of physiotherapy practice in stroke rehabilitation (CERISE 2005). Meanwhile a study in Sweden has looked at the characteristics of physiotherapy intervention from both therapists' and patients' perspectives (Wottrich et al. 2004).

Exploring predictors of recovery

We could further explore the data by examining predictors of recovery and exploring the features of patients who make a very good or very poor recovery. Having the IPD database puts us in a good position to carry out what can be a complex analysis (Thompson & Higgins 2005). However, we must be cautious of carrying out multiple subgroup analyses (Counsell et al. 1994) and recognise that numbers of available data

are likely to be small. These exploratory analyses, though likely to have limited conclusions, might be useful in generating new hypotheses.

Disseminating our recommendations

Our results have been made available to a wide audience (see Appendix IX) and further dissemination is planned through presentations and publication in a variety of media. The PINTAS Collaborative group could consider registering the meta-analysis as a Cochrane Review in order to help disseminate our findings and stimulate continued interest in this area of stroke rehabilitation.

Future research

In the larger research context, in order to obtain a better understanding of the "black box" of rehabilitation, we may have to adopt several different strategies in order to describe and test what is happening e.g. Campbell et al.'s framework for complex interventions (Campbell et al. 2000).

Optimum delivery of treatment

While none of the trials in our analyses reported serious adverse events attributable to the intervention or raised concerns about safety, one of the reasons treatment contrast cannot be maintained is poor tolerance of the intervention. We should consider methods of optimal delivery of interventions.

We have just looked at intensity, but other treatment factors should be considered such as: the method in which the additional therapy is delivered e.g. by one longer treatment session or a number of shorter sessions; the timing of the intervention e.g. the early intervention trials appear to demonstrate benefits but timing could be further explored, along with the content of intervention (Page 2003)(Van Peppen et al. 2004).

Such studies might be aided by the development of technical equipment. For example the activity monitor used in the GAPS study continues to be developed and may help to provide objective outcome data.

General v specific questions

We need to maintain a balance between questions addressing "the big picture" of rehabilitation and small specific questions.

Although a recent, published-data meta-analysis (Kwakkel et al. 2004) reported a positive treatment effect with increased "exercise therapy" we believe our trial selection was more specific and representative of "physiotherapy" intervention. Although our meta-analysis is smaller it allows us to be more specific when defining the intervention and generalising our results. Other rehabilitation interventions, e.g. occupational therapy, face similar difficulties, with a diverse group of patients and heterogeneous interventions that are poorly defined and understood. However, pooling studies across the interventions may limit the extent to which specific questions can be addressed.

There may be less incentive to examine physiotherapy intensity in terms of length of hospital stay with co-ordinated early supported discharge (ESD) services proven to be an effective intervention (Langhorne et al. 2005). However, all of the trials included in this IPD meta-analysis of ESD, featured physiotherapy, and it is still worth investigating the effective components of ESD.

In other chronic diseases e.g. head injury, researchers are attempting to tackle the intensity question and are likely to come across similar difficulties and challenges to those mentioned in Chapter 2 (Sheil et al. 2001). Slade et al. had carried out a trial with a mixed patient group, though we only included data from stroke patients. Although this method may reflect service delivery in some rehabilitation settings it is obviously less specific and results may be difficult to generalize.

Despite our focus being intervention delivered by a physiotherapist, it may be activity (regardless of how it is delivered), that is the beneficial factor that should be investigated. Current and future levels of patient contact with physiotherapists are likely to be limited. Therefore, there has been recent interest in early mobilization trials that involve interventions with a rehabilitation approach that encourages activity and repeated practise of mobility, whether delivered by physiotherapists or others (Berhardt et al., Kwakkel et al. – personal communication). Such broad treatment approaches may be complex to investigate as increasing the number of components of the intervention

may lead to contamination. Consequently, strict monitoring and large numbers of subjects are likely to be required.

4) Recommendations

Finally, I want to make some recommendations based on the work in the thesis:

The results of our investigations should not lead to a change in clinical practice or service delivery, though our findings support a general pattern in results towards benefit to patients with stroke with increased physiotherapy input.

The main impact of the work is likely to be in informing future research in this area. Recommendations could be made to encourage researchers to use a core standard of methods and outcomes that would facilitate further meta-analyses.

Although we must be cautious when interpreting results based on subgroup analyses of secondary outcomes, there are several recommendations that can be made:

a) Future trials should carefully select their outcome measures to reflect the aims of physiotherapy.
b) The greatest impact is likely to be at the level of impairment.
c) The greatest impact is likely to be seen at higher treatment contrasts (more than 15 hours difference between groups).
d) There may be value in targeting some aspects of therapy (e.g. lower limb focus to improve walking speed) but our data are inconclusive.

We would encourage registration of new trials in trials registers to allow access to data and inclusion in collaborative efforts (Egger & Davey Smith 1998).

Conclusion

In conclusion, I consider I have addressed my research questions as completely as possible. Using sound methods, the analyses have provided some answers and raised a number of issues around the methods and available data.

The GAPS study, though inconclusive, had many methodological strengths. It was a logical progression to pool the data we obtained with the other studies in order to pursue our questions. This also provided the opportunity to examine the benefits of the different methods of meta-analysis.

There appears to be justification in considering IPD meta-analysis as the "gold standard" as it maximizes the use of available data. However, although IPD meta-analysis is a strong method, it will not compensate for poor quality data or lack of data.

We have produced useful results and recommendations that will contribute to the design of physiotherapy research in the future and been able to direct further work based on the project. Considered in these terms, the project has been a success, tackling a complex issue and providing information to further this area of rehabilitation research.

Summary

- I return to the questions in my hypothesis to consider to what extent they have been addressed by the results from the RCT and IPD meta-analysis.

- Our results should not lead to changes in clinical practice or service delivery. However, they provide estimates of the modest treatment effect likely in the domains we examined. Modest increases in the intensity of physiotherapy after stroke did not produce substantial changes in any of the primary outcomes in my hypothesis.

- Targeted additional therapy in selected patients may lead to some improvement in limb impairment and walking speed. Treatment effects were greater in those trials with higher treatment contrast (> 15 hours) that started intervention at an earlier stage after stroke.

- I discuss issues arising from the randomised controlled trial and the meta-analyses

- Individual patient data meta-analyses, maximize the use of available data and provide the opportunity to explore subgroups in order to address clinically relevant questions and guide further research.

- Large numbers of subjects are required for randomised controlled trials (RCTs) of intensity of physiotherapy. I make recommendations to those designing such trials to use higher treatment contrasts in order to detect modest treatment effects and similar outcome measures in order to facilitate future meta-analysis.

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APPENDIX I
GAPS study, Physiotherapy input data collection form

GAPS Study

Description of Physiotherapy

Version 1.0

Random No [ ][ ][ ][ ] 01 | Initials [ ][ ][ ] 02 | Date of Session [D][D] / [M][M] / [Y][Y] 03

NB RETURN ONE FORM FOR EACH INTERVENTION

A. PATIENT'S NAME _____ 04

B. WHICH PHYSIOTHERAPY SESSION OF THE DAY? (1=1st, 2=2nd, etc.) [ ] 05

C. TREATMENT ALLOCATION Standard [1] Augmented [2] 06

D. AMOUNT OF PHYSIOTHERAPY TIME THIS SESSION (minutes)

1. Total indirect contact time [ ][ ][ ] 07 mins
2. Total direct contact time [ ][ ][ ] 08 mins
3. Combined physiotherapy time [ ][ ][ ] 09 mins

E. TOTAL TIME SPENT ON (minutes)

1. Gait re-education [ ][ ][ ] 10 mins
2. Upper limb re-education [ ][ ][ ] 11 mins
3. Discussion / Explanation / Reassurance [ ][ ][ ] 12 mins
4. Postural set (minutes)

Lying	Side Lying	Sitting	Standing	Other
[ ][ ][ ] 13	[ ][ ][ ] 14	[ ][ ][ ] 15	[ ][ ][ ] 16	[ ][ ][ ] 17

5. Focus of Treatment (Yes/No)
   Circle as appropriate

	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Initial assessment	1	2 18	1	2 19	1	2 20	1	2 21	1	2 22
Tone	1	2 23	1	2 24	1	2 25	1	2 26	1	2 27
Posture	1	2 28	1	2 29	1	2 30	1	2 31	1	2 32
Balance	1	2 33	1	2 34	1	2 35	1	2 36	1	2 37
U/L function	1	2 38	1	2 39	1	2 40	1	2 41	1	2 42
L/L function	1	2 43	1	2 44	1	2 45	1	2 46	1	2 47
Transfers	1	2 48	1	2 49	1	2 50	1	2 51	1	2 52
Other	1	2 53	1	2 54	1	2 55	1	2 56	1	2 57

F. TREATMENTS USED

1. Which of the following were used?
   (a) Trunk mobilisations — Yes [1] No [2] 58
   (b) Wheelchair education/use — Yes [1] No [2] 59
   (c) Splints for the upper limb — Yes [1] No [2] 60
   (d) Splints for the lower limb — Yes [1] No [2] 61
   (e) Education (patient, relatives, staff) — Yes [1] No [2] 62

GAPS Study

Description of Physiotherapy continued...

Version 1.0

Random No [ ][ ][ ][ ] 01

Initials [ ][ ][ ] 02

Date of Session [D][D] / [M][M] / [Y][Y] 03

G. PHYSIOTHERAPIST DETAILS

1. Who completed this form? _____ 04
2. Lead Physiotherapist _____ 05
3. Number of physiotherapists involved [ ] 06

H. TYPE OF PHYSIOTHERAPISTS INVOLVED

1. Lead therapist — Yes [1] No [2] 07
2. Senior therapist — Yes [1] No [2] 08
3. Junior grade therapist — Yes [1] No [2] 09
4. Assistant therapist — Yes [1] No [2] 10
5. Student therapist — Yes [1] No [2] 11

I. COMMENTS

1. Any comments/problems/complications? _____

For Office Use Only

Signature: _____ Date: _____

APPENDIX II
GAPS study, Outcome assessment forms (example of 3 month form)

GAPS Study — 3 Month Assessment, Page 1

Resource Use Since Hospital Discharge

Draft 01

Random No ☐☐☐☐ 01 | Initials ☐☐☐☐ 02 | Assessor Code ☐☐ 03 | Date of Visit ☐☐/☐☐/☐☐ (D D / M M / Y Y) 04

A. PLACE OF RESIDENCE

Private address alone	1
Private address not alone	2
Sheltered housing	3
Residential care	4
Nursing home	5
Other	6

06

If Other, specify _____ 07

B. AIDS AND APPLIANCES

1. Are any aids or appliances required? Yes [1] No [2] 08

If Yes, specify which

(a) Standing/walking support

Zimmer frame	Yes [1] No [2]	09
Rollator	Yes [1] No [2]	10
Tripod/quad stick	Yes [1] No [2]	11
Delta frame	Yes [1] No [2]	12
Two sticks	Yes [1] No [2]	13
Crutches	Yes [1] No [2]	14
One stick	Yes [1] No [2]	15
Other	Yes [1] No [2]	16

If Other, specify _____ 17

(b) Splints/Slings

AFO	Yes [1] No [2]	09
Knee splint	Yes [1] No [2]	10
Hand splint	Yes [1] No [2]	11
Shoulder Sling	Yes [1] No [2]	12
Other	Yes [1] No [2]	13

If Other, specify _____ 17

(c) Adaptive equipment and alterations to property? Yes [1] No [2] 15

If Yes, specify which

Bathing aids	Yes [1] No [2]	15
Kitchen aids	Yes [1] No [2]	16
Grab rails	Yes [1] No [2]	12
Kitchen trolley	Yes [1] No [2]	13
Stair rail	Yes [1] No [2]	14
Stair lift	Yes [1] No [2]	15
Other	Yes [1] No [2]	16

If Other, specify _____ 17

(d) Wheelchair, or waiting for a wheelchair? Yes [1] No [2] 15

(i) If Yes, specify

For outdoor use only	1
Sometimes use indoors	2
Always use/unable to walk	3

(ii) Type of wheelchair

Electric	1
Attendant propelled	2
Self-propelled	3

C. CARER INFORMATION

1. Has anyone had to stop work to look after the patient? Yes [1] No [2] 18

If Yes, what job did they do?

_____

Signature: _____ Date: _____

GAPS Study

3 Month Assessment, Page 2

Resource Use Since Hospital Discharge

Draft 01

Random No [01] | Initials [02] | Assessor Code [03] | Date of Visit D D M M Y Y [04]

A. SERVICES

	No	Once or twice	Weekly	2 times per week	>2 times per week
(a) Home help	1	2	3	4	5
(b) District nursing	1	2	3	4	5
(c) Day hospital	1	2	3	4	5
(d) Outpatient physiotherapy	1	2	3	4	5
(e) Outpatient occupational therapy	1	2	3	4	5
(f) Outpatient S&LT	1	2	3	4	5
(g) Physiotherapy home visit	1	2	3	4	5
(h) Occupational therapy home visit	1	2	3	4	5
(i) Social work	1	2	3	4	5
(j) Health visitor	1	2	3	4	5
(k) GP	1	2	3	4	5
(l) Stroke Clinic	1	2	3	4	5
(m) Day Centre	1	2	3	4	5
(n) Meals on wheels	1	2	3	4	5
(o) Living with a stroke/Disability resource centre	1	2	3	4	5
(p) Other	1	2	3	4	5

specify _____

Signature: _____ Date: _____

GAPS Study

3 Month Assessment, Page 3

Adverse Outcomes

Draft 01

Random No [ ][ ][ ][ ] (01) Initials [ ][ ][ ][ ] (02) Assessor Code [ ][ ] (03) Date of Visit [D D]/[M M]/[Y Y] (04)

A. FALLS

1. Since discharge from hospital, has the patient suffered any falls? Yes [1] No [2] (05)

If Yes, give details

	Fall Severity Code	Date of Fall
(a)	[ ]	[D D]/[M M]/[Y Y] (06)
(b)	[ ]	[D D]/[M M]/[Y Y] (07)
(c)	[ ]	[D D]/[M M]/[Y Y] (08)
(d)	[ ]	[D D]/[M M]/[Y Y] (09)
(e)	[ ]	[D D]/[M M]/[Y Y] (10)

Fall Severity Code Box

No injury	1
Minor injury	2
Major injury	3

B. OTHER PROBLEMS/ILLNESSES

1. Any other problems or illnesses since hospital discharge? Yes [1] No [2] (11)

If Yes, give details

	Description	Event Code	Date of Event
(a)	_____	[ ][ ]	[D D]/[M M]/[Y Y] (12)
(b)	_____	[ ][ ]	[D D]/[M M]/[Y Y] (13)
(c)	_____	[ ][ ]	[D D]/[M M]/[Y Y] (14)
(d)	_____	[ ][ ]	[D D]/[M M]/[Y Y] (15)
(e)	_____	[ ][ ]	[D D]/[M M]/[Y Y] (16)
(f)	_____	[ ][ ]	[D D]/[M M]/[Y Y] (17)
(g)	_____	[ ][ ]	[D D]/[M M]/[Y Y] (18)
(h)	_____	[ ][ ]	[D D]/[M M]/[Y Y] (19)

Code Box

DVT	1
PTE	2
UTI	3
Chest infection	4
Other infection	5
Fracture	6
Depression	7
Anxiety	8
Confusion	9
Pressure sore	10
Painful shoulder	11
Other pain	12
Recurrence/extension of stroke	13
Other pain	14

Signature: _____ **Date:** _____

GAPS Study — 3 Month Assessment, Page 4

Current Disability: Rankin Scale, Mobility and Barthel Index

Draft 01

Random No [01] | Initials [02] | Assessor Code [03] | Date of Visit D D M M Y Y [04]

A. CURRENT RANKIN OXFORD HANDICAP SCALE

1. 'Rankin' Oxford Handicap Scale

- Well, no symptoms — 0
- Minor symptoms affecting lifestyle — 1
- Minor handicap but independent in self care — 2
- Moderate handicap, needing a little help with ADL — 3
- Needing a lot of help with ADL — 4
- Needing constant attention day and night — 5 [05]

B. POST-STROKE MOBILITY

- Able to walk 200m outside — 1
- Able to walk indoors — 2
- Unable to without help — 3 [10]

C. BARTHEL INDEX

1. Bowels

- Incontinent or needs to be given enema — 0
- Occasional accident (once a week) — 1
- Continent — 2 [06]

2. Bladder

- Incontinent or catheterised and unable to manage alone — 0
- Occasional accident (maximum once per week) — 1
- Continent — 2 [07]

3. Grooming

- Needs help with personal care — 0
- Independant face/hair/teeth/shaving (implements provided) — 1 [08]

4. Toilet use

- Dependent — 0
- Needs some help, but can do something alone — 1
- Independent (on and off, dressing and wiping) — 2 [09]

5. Feeding

- Unable — 0
- Needs help cutting, spreading butter, etc. — 1
- Independent — 2 [10]

6. Transfer (bed to chair and back)

- Unable, no sitting balance — 0
- Major help (one or two people, physical), can sit — 1
- Minor help (verbal or physical) — 2
- Independent — 3 [11]

7. Mobility

- Immobile — 0
- Wheelchair independent including corners — 1
- Walks with help of one person (verbal or physical) — 2
- Independent (but may use any aid, eg. stick) — 3 [12]

8. Dressing

- Dependent — 0
- Needs help but can do about half unaided — 1
- Independent (including buttons, zips, laces, etc) — 2 [13]

9. Stairs

- Unable — 0
- Needs help (verbal, physical, carrying aid) — 1
- Independent — 2 [14]

10. Bathing

- Dependent — 0
- Independent (or in shower) — 1 [15]

TOTAL SCORE [16]

Signature: _____ Date: _____

GAPS Study

3 Month Assessment, Page 5

Current Disability: Rivermead Mobility Index

Draft 01

Random No [ ][ ][ ][ ] 01 | Initials [ ][ ][ ][ ] 02 | Assessor Code [ ][ ] 03 | Date of Visit [D][D]/[M][M]/[Y][Y] 04

A. RIVERMEAD MOBILITY INDEX

Instructions

The patient is asked the following 15 questions, and observed (for item 5). A score of 1 is given for each 'yes' answer.

1. Turning over in bed

Do you turn over from your back to your side without help? Yes [1] No [0] 06

2. Lying to sitting

From lying in bed, do you get up to sit on the edge of bed on your own? Yes [1] No [0] 07

3. Sitting balance

Do you sit on the edge of the bed without holding on for 10 seconds? Yes [1] No [0] 08

4. Sitting to standing

Do you stand up (from any chair) in less than 15 seconds, and stand there for 15 seconds (using hands, and with an aid if necessary)? Yes [1] No [0] 09

5. Standing unsupported

Observe standing for 10 seconds without any aid. Yes [1] No [0] 10

6. Transfer

Do you manage to move from bed to chair and back without any help? Yes [1] No [0] 11

7. Walking inside, with an aid if needed

Do you walk 10 metres, with an aid if necessary, but with no standby help? Yes [1] No [0] 12

8. Stairs

Do you manage a flight of stairs without help? Yes [1] No [0] 13

9. Walking outside (even ground)

Do you walk around outside, on pavements without help? Yes [1] No [0] 14

10. Walking inside, with no aid

Do you walk 10 metres inside with no caliper, splint, or aid, and no standby help? Yes [1] No [0] 15

11. Picking off floor

If you drop something on the floor, do you manage to walk 5 metres, pick it up and then walk back? Yes [1] No [0] 16

12. Walking outside (uneven ground)

Do you walk over uneven ground (grass, gravel, dirt, snow, ice, etc.) without help? Yes [1] No [0] 17

13. Bathing

Do you get in/out of bath or shower unsupervised and wash self? Yes [1] No [0] 18

14. Up and down four steps

Do you manage to go up and down four steps with no rail, but using an aid if necessary? Yes [1] No [0] 19

15. Running

Do you run 10 metres without limping in four seconds (fast walk is acceptable)? Yes [1] No [0] 20

Signature: _____ Date: _____

GAPS Study

3 Month Assessment, Page 6

Current Disability: Motricity Index

Draft 01

Random No [ ][ ][ ][ ] 01 | Initials [ ][ ][ ][ ] 02 | Assessor Code [ ][ ] 03 | Date of Visit [D D] / [M M] / [Y Y]

A. MOTRICITY INDEX

(i) Tests

ARM

1. Pinch grip; 2.5cm cube between thumb and forefinger

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

2. Elbow flexion; from 90 degrees, voluntary contraction/movement

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

3. Shoulder abduction; from against chest

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

LEG

4. Ankle dorsiflexion; from plantar flexed position

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

5. Knee extension; from 90 degrees, voluntary contraction/movement

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

6. Hip flexion; usually from 90 degrees

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

Signature: _____ Date: _____

GAPS Study — 3 Month Assessment, Page 7

Trunk Control Test, Walking Test, Mobility Milestones & Functional Reach

Draft 01

Random No [ ][ ][ ][ ] 01 | Initials [ ][ ][ ][ ] 02 | Assessor Code [ ][ ] 03 | Date of Visit [D D]/[M M]/[Y Y] 04

A. TRUNK CONTROL TEST

(i) Tests

1. Rolling to weak side

Unable to do on own	0
Able to do, but only with non-muscular help-for example, pulling on bed clothes, using arms to steady self when sitting, pulling up on rope or monkey pole, etc.	12
Able to complete normally	25

2. Rolling to strong side

Unable to do on own	0
Able to do, but only with non-muscular help-for example, pulling on bed clothes, using arms to steady self when sitting, pulling up on rope or monkey pole, etc.	12
Able to complete normally	25

3. Sitting up from lying down

Unable to do on own	0
Able to do, but only with non-muscular help-for example, pulling on bed clothes, using arms to steady self when sitting, pulling up on rope or monkey pole, etc.	12
Able to complete normally	25

4. Balance in sitting position (on side of bed)

Unable to do on own	0
Able to do, but only with non-muscular help-for example, pulling on bed clothes, using arms to steady self when sitting, pulling up on rope or monkey pole, etc.	12
Able to complete normally	25

B. MOBILITY MILESTONES

1. Independent standing balance Yes [1] No [2]

2. Able to walk 10 paces Yes [1] No [2]

3. Able to walk 10 metres Yes [1] No [2]

C. FUNCTIONAL REACH

1. Able to perform functional reach? Yes [1] No [2]

If Yes, specify [ ][ ][ ].[ ] cm

D. RMI-confirmation of question 5.

<u>Standing unsupported</u>

1. Can the patient stand unsupported for 10 seconds without any aid? (Observe) Yes [1] No [2]

E. TIMED 10 METRE WALKING TEST

1. Was the patient able to perform the test? Yes [1] No [2]

If Yes, specify the time in seconds [ ][ ][ ] secs

2. Aid used

None	0
One stick	1
Two sticks	2
Quad or tripod stick	3
Zimmer frame	4
Rollator	5
Other	6

If Other, specify _____

_____

Signature: _____ Date: _____

GAPS Study — 3 Month Assessment, Page 8

Current Disability: Nottingham Extended Activities of Daily Living Index

Draft 01

Random No [ ][ ][ ][ ] 01 | Initials [ ][ ][ ][ ] 02 | Assessor Code [ ][ ] 03 | Date of Visit [D D][M M][Y Y] 04

DO YOU...

	Not at all	With help	Alone with difficulty	Alone easily
A. MOBILITY				
- walk around outside?	0	1	2	3
- climb stairs?	0	1	2	3
- get in and out of the car?	0	1	2	3
- walk over uneven ground?	0	1	2	3
- cross roads?	0	1	2	3
- travel on public transport?	0	1	2	3
B. IN THE KITCHEN				
- manage to feed yourself?	0	1	2	3
- make yourself a hot drink?	0	1	2	3
- take hot drinks from one room to another?	0	1	2	3
- do the washing up?	0	1	2	3
- make yourself a hot snack?	0	1	2	3
C. DOMESTIC TASKS				
- manage your own money when out?	0	1	2	3
- wash small items of clothing?	0	1	2	3
- do your own shopping?	0	1	2	3
- do a full clothes wash?	0	1	2	3
D. MOBILITY				
- read newspaper and books?	0	1	2	3
- use the telephone?	0	1	2	3
- write letters?	0	1	2	3
- go out socially?	0	1	2	3
- manage your own garden?	0	1	2	3
- drive a car?	0	1	2	3

Signature: _____ Date: _____

GAPS Study — 3 Month Assessment, Page 9

Current Disability: Rivermead Visual Gait Assessment

Draft 01

Random No [ ][ ][ ][ ] Initials [ ][ ][ ][ ] Assessor Code [ ][ ] Date of Visit [D D] [M M] [Y Y]

Scoring: 0 = normal **Deviations:** 1 = mild 2 = moderate 3 = severe (please cirle)

Upper Limb Position

1. Shoulder Depressed/Retracted/Elevated 0 1 2 3

2. Elbow flexed ≤ 45° (=0) 45° to 90° (=1) >90° (=2) 0 1 2

Stance Phase

For trunk deviations, 0 = midline

3. Trunk flexed/extended 3 2 1 0 1 2 3

Inclinded: backward ← → forward

4. Trunk side flexed 3 2 1 0 1 2 3

Direction: left ← → right

5. Trunk and pelvis: lateral displacement 3 2 1 0 1 2 3

Amount: excessive ← → reduced

6. Contralateral drop pelvis 0 1 2 3

7. Hip extension decreased 0 1 2 3

8. *with backward rotation* 0 1 2 3

9A. Knee <u>flexion</u> excessive: *at initial contact* 0 1 2 3

10A. *throughout range* 0 1 2 3

<u>OR</u>

9B. Knee <u>extension</u> excessive: *at initial contact* 0 1 2 3

10B. *throughout range* 0 1 2 3

11A. Ankle in excess <u>plantar</u> flexion 0 1 2 3

<u>OR</u>

11B. Ankle in excess <u>dorsi</u> flexion 0 1 2 3

12. Inversion excessive 0 1 2 3

13. Plantar flexion decreased at toe-off 0 1 2 3

Signature: _____ Date: _____

GAPS Study — 3 Month Assessment, Page 10

Current Disability: Rivermead Visual Gait Assessment continued...

Draft 01

Random No [ ][ ][ ][ ] Initials [ ][ ][ ][ ] Assessor Code [ ][ ] Date of Visit [D][D]/[M][M]/[Y][Y]

Swing Phase

For trunk deviations, 0 = midline

14. Trunk flexed [3] [2] [1] [0] [1] [2] [3]

Direction: backward ← → forward

15. Trunk side flexed [3] [2] [1] [0] [1] [2] [3]

Direction: left ← → right

16. Hike pelvis (elevation) [0] [1] [2] [3]

17. Backward rotation pelvis [0] [1] [2] [3]

18. Decreased hip flexion [0] [1] [2] [3]

19. Decreased knee flexion [0] [1] [2] [3]

20. Ankle in excess plantar flexion [0] [1] [2] [3]

Any other deviations noted _____ [0] [1] [2] [3]

_____ [0] [1] [2] [3]

21. Support required

AFO Yes [1] No [2]

Knee splint Yes [1] No [2]

Signature: _____ Date: _____

GAPS Study — 3 Month Assessment, Page 11

Current Disability: Body Worn Gait Analysis and Nine Hole Peg Test

Draft 01

Random No [ ][ ][ ][ ] 01 | Initials [ ][ ][ ][ ] 02 | Assessor Code [ ][ ] 03 | Date of Visit [D D]/[M M]/[Y Y] 04

A. SIDE AFFECTED Left [1] Right [2] 06

B. ABILITY TO UNDERGO GAIT ANALYSIS

1. Was the patient able to undergo gait analysis? Yes [1] No [2] 05

If No, specify reason

- Patient unfit to undergo gait analysis [1]
- Patient refused to undergo gait analysis [2]
- Unable to walk 10 metres [3]
- Equipment failure [4]
- Other [5] 07

If Other, specify _____

_____ 08

C. RESULTS OF TEST

1. Number of scuffs (fast contact during swing)

(a) Affected side [ ][ ][ ] 09

(b) Unaffected side [ ][ ][ ] 10

2. Heel Strike (% of total foot contact time)

(a) Affected side [ ][ ] % 11

(b) Unaffected side [ ][ ] % 12

3. Inversion (% of metatarsal head contact time with only 5th head in contact)

(a) Affected side [ ][ ][ ][ ] % 13

(b) Unaffected side [ ][ ][ ][ ] % 14

4. Average Stride Length (Average speed x Average time for stride) [ ][ ][ ] cm 15

5. Symmetry (Ratio of swing phase) [ ][ ][ ] % 16

6. Speed [ ].[ ][ ] m/sec 17

D. AID USED

- None [0]
- One stick [1]
- Two sticks [2]
- Quad or tripod stick [3]
- Zimmer frame [4]
- Rollator [5]
- Other [6] 18

If Other, specify _____

_____ 19

E. NINE HOLE PEG TEST

1. Time of test [ ][ ]:[ ][ ] (24 hour clock) 07

2. Results for unaffected side

Able to attempt test? Yes [1] No [2] 08

If Yes, either
Time to place all pegs [ ][ ] secs 09

or

If > 50 seconds, number of pegs placed in 50 seconds [ ] pegs 10

3. Results for affected side

Able to attempt test? Yes [1] No [2] 11

If Yes, either
Time to place all pegs [ ][ ] secs 12

or

If > 50 seconds, number of pegs placed in 50 seconds [ ] pegs 13

Signature: _____ Date: _____

GAPS Study — 3 Month Assessment, Page 12

Current Disability: Action Research Arm Test (Unaffected Side)

Draft 01

Random No [01] | Initials [02] | Assessor Code [03] | Date of Visit D D M M Y Y [04]

A. RESULTS FOR UNAFFECTED SIDE

Grasp

1. Pick up 10cm cube, block of wood (If score = 3, total = 18 and go to GRIP) [06]
2. Pick up 2.5cm cube, block of wood (if score = 0, total = 0 and go to GRIP) [06]
3. Pick up 5cm cube, block of wood [06]
4. Pick up 7.5cm cube, block of wood [06]
5. Pick up cricket ball, 7.5cm diameter [06]
6. Pick up sharpening stone 10 x 2.5 x 1cm [06]

TOTAL SCORE [12]

Grip

1. Pour water from glass to glass (plastic tumbler half full (100 mls of water)) (if score = 3, total = 12 and go to PINCH) [06]
2. Lift tube 2.25cm from one peg to another peg on shelf (if score = 0, total = 0 and go to PINCH) [06]
3. Lift tube 1 cm from one peg to another peg on shelf [06]
4. Lift washer 3.5cm in diameter from table and place over bolt on table [06]

TOTAL SCORE [17]

Pinch

1. Pick up 6mm ball bearing between 3rd finger and thumb from 10cm dish on table to 10cm dish on shelf (if score = 3, total = 18 and go to GROSSMT) [06]
2. Pick up 1.5cm marble between first finger and thumb from dish to dish (if score = 0, total = 0 and go to GROSSMT) [06]
3. Pick up ball bearing between 2nd finger and thumb [06]
4. Pick up ball bearing between 1st finger and thumb [06]
5. Pick up marble between 3rd finger and thumb [06]
6. Pick up marble between 2nd finger and thumb [06]

TOTAL SCORE [17]

Gross Movement

1. Place hand behind head (if score = 3, total = 9 and finish) (if score = 0, total = 0 and finish) [06]
2. Place hand on top of head [06]
3. Lift hand to mouth [06]

TOTAL SCORE [18]

SCORING CODE BOX

Performs test normally	3
Completes test, but long time or great difficulty	2
Performs test partially	1
Can perform no part of test	0

Signature: _____ Date: _____

GAPS Study — 3 Month Assessment, Page 13

Current Disability: Action Research Arm Test (Affected Side)

Draft 01

Random No [01] | Initials [02] | Assessor Code [03] | Date of Visit (D D / M M / Y Y) [04]

B. RESULTS FOR AFFECTED SIDE

Grasp

1. Pick up 10cm cube, block of wood (If score = 3, total = 18 and go to GRIP) [05]
2. Pick up 2.5cm cube, block of wood (if score = 0, total = 0 and go to GRIP) [05]
3. Pick up 5cm cube, block of wood [05]
4. Pick up 7.5cm cube, block of wood [05]
5. Pick up cricket ball, 7.5cm diameter [05]
6. Pick up sharpening stone 10 x 2.5 x 1cm [05]

TOTAL SCORE [12]

Grip

1. Pour water from glass to glass (plastic tumbler half full (100 mls of water)) (if score = 3, total = 12 and go to PINCH) [06]
2. Lift tube 2.25cm from one peg to another peg on shelf (if score = 0, total = 0 and go to PINCH) [06]
3. Lift tube 1 cm from one peg to another peg on shelf [06]
4. Lift washer 3.5cm in diameter from table and place over bolt on table [06]

TOTAL SCORE [17]

Pinch

1. Pick up 6mm ball bearing between 3rd finger and thumb from 10cm dish on table to 10cm dish on shelf (if score = 3, total = 18 and go to GROSSMT) [06]
2. Pick up 1.5cm marble between first finger and thumb from dish to dish (if score = 0, total = 0 and go to GROSSMT) [06]
3. Pick up ball bearing between 2nd finger and thumb [06]
4. Pick up ball bearing between 1st finger and thumb [06]
5. Pick up marble between 3rd finger and thumb [06]
6. Pick up marble between 2nd finger and thumb [06]

TOTAL SCORE [17]

Gross Movement

1. Place hand behind head (if score = 3, total = 9 and finish) (if score = 0, total = 0 and finish) [06]
2. Place hand on top of head [06]
3. Lift hand to mouth [06]

TOTAL SCORE [18]

SCORING CODE BOX

Performs test normally	3
Completes test, but long time or great difficulty	2
Performs test partially	1
Can perform no part of test	0

Signature: _____ Date: _____

GAPS Study

3 Month Assessment, Page 14

Draft 01

Random No [01] | Initials [02] | Assessor Code [03] | Date of Visit D D M M Y Y [04]

Coding Difficulties

1. Have there been any problems coding the data for this visit? Yes [1] No [2] [05]

If Yes, specify

Patient no longer at the rehabilitation centre	0
Patient unable to attend assessment	1
Patient refused for part of the assessment	2
Patient refused for all of the assessment	3
Assessor unavailable	4
Assessor unblinded	5
Equipment problem	6
Other	7

[10]

specify _____

_____

[10]

Signature: _____ Date: _____

Rationale for selection of outcome measures used in the GAPS study (listed alphabetically)

Action Research Arm Test (ARAT) (Lyle 1981)

This is a measure of upper limb disability with 4 sections (grasp, grip, pinch and gross movement), scored 0 – 57 (0 = no arm function, 57 = normal arm function).

It is a detailed and sensitive measure of a variety of upper limb functions over a broad spectrum of functional levels. Although it is relatively complex and requires special equipment, we included it because it provides more information than the 9 Hole Peg Test and has been used in other intensity trials.

Activity Monitoring (Suckalingham 1993)

We measured patient activity using a "high-tech" monitor (Figure 3.1, page 49) that attached a sensor to the patient's unaffected leg and recorded the frequency of changes in posture. We had hoped that the equipment would measure the proportion of time spent lying, sitting, standing and walking. It records the amount of time spent in an upright position and the number of changes of the patient's position from sitting to standing. The monitor was worn on a single occasion (for a day, 3 weeks after randomisation). Data were downloaded from the data logger onto a portable computer for analysis.

It was able to provided limited information in terms of the percentage of the patients' "waking day" that is spent in an "upright position" e.g. standing or walking. More time spent upright was assumed to be more active. The monitor allowed us to analyse levels of activity at specific periods during the day e.g. to examine how active are patients in the evening when there are no therapists on duty?

Adverse Effects

The patients were monitored for falls, fatigue, shoulder pain and other pain on a weekly basis until discharge (maximum of 10 weeks) by interview. The patient was also interviewed at the 3 and 6 month assessments regarding hospital admissions, falls and other illnesses or problems. Similar information was gathered at the casenote review when the patient was discharge from inpatient rehabilitation. We could not confirm this information with the patients' General Practitioners due to limited resources.

Barthel Index (Mahoney & Barthel 1965)

This is a 20-point scale over 10 items (bowel, bladder, grooming, toilet use, feeding, transfers, mobility, dressing, stairs and bathing) (0 = dependent, 20 = independent) measuring dependency in activities of daily living (ADL). It is probably the most commonly used measure of "disability" or "dependency" in both clinical practice and research.

Originally designed to measure "dependency" this frequently used questionnaire is used as an indication of activity limitation in activities if daily living. It has been adapted, but we used its original version. It has well recognised limitations in its floor and ceiling effects and that it does not address the domains of communication or cognitive function. It is simple, quick and, if necessary, could be administered over the telephone for limited follow up with non-compliant patients or patients in institutional care (proxy answers by a member of staff).

Body-worn gait analysis (Granat et al. 1995)

This was used to measure impairment of quality of gait. The patients wear their normal footwear with a pressure sensitive insole fitted inside. Information from the insole is recorded on a data logger. The test was performed in the fourth week, three months and six months after randomisation. The patients walked 8m with a 2m acceleration and deceleration period at each end. They were assessed on the same carpeted surface on each site. Data were gathered on average stride length, speed, symmetry of gait, degree of excessive inversion or eversion, and the duration of heel contact.

Elderly Mobility Scale (EMS) (Smith 1994)

This is a 7-item measure of functional mobility disability, scored 0 – 20 (0 = poor mobility, 20 = independent mobility). It is increasingly used, both clinically and in research. It is simple to administer, the majority of its items being covered by the other scales we used. It has been validated for elderly patients but not yet specifically for stroke patients. The functional reach test within the scale has been shown to be indicative of dynamic balance and is predictive of falls.

EuroQol (Dorman et al. 1997)

This measure of health related quality of life contains 6 items and a vertical visual analogue scale (scored 0 – 100, 0 = "worst imaginable" health state, 100 = "best imaginable" health state). It is relatively short and has acceptable validity with patients after stroke. It was completed at interview in order to assist any patients with motor or visual deficits to complete the form.

Functional Reach Test (Duncan et al. 1990)

The patients' ability to reach forward whilst standing without support, was measured in centimetres, then categorised (under 8cm or unable, 8 – 16cm, over 16cm). This is a valid test of the patients' balance in the standing position. Balance had not specifically been addressed in the other measures used. The test is included within the Elderly Mobility Scale (see above) and has been shown to be indicative of dynamic balance and predictive of falls in elderly patients (Smith 1994).

Mobility Milestones (Smith & Baer 1999) (Baer et al. 2003)

This is a measure of functional mobility based on recognised patterns of recovery. The hierarchical scale gives clearly defined criteria for the assessment of each "milestone" – ability to sit unsupported for a minute; ability to stand unsupported for 10 seconds; ability to take 10 steps and the ability to walk 10 metres. It has face validity and has been investigated for reliability. It is used in a number of clinical settings. The items seem to form an obvious hierarchy, however the definitions first published prevented subjects using a walking aid in their attempts at 10 paces though an aid was permitted for the 10 metre walk. This resulted in some patients being scored as "able to walk 10 m but not able to take 10 independent steps". We kept the original definitions throughout our study. The scale is reliable and valid but has a ceiling effect. All our patients were required to have sitting balance before being considered eligible for the study.

Motricity Index (Demeurisse et al. 1980)

This index combines scores from 3 tests each in the arm and leg to give a score for the left and right side of the body (0 = no movement, 100 = normal). The arm score is derived from scores (0 – 33) for 3 tasks, + 1 = score out of maximum 100, similarly, the leg has 3 scores (0 – 33), +1 = score out of maximum 100.

Side score = (arm score + leg score) / 2. The patients are scored for both their sides.

It is a measure of impairment, taking into account general upper and lower limb function. It is quick to administer and has been tested for validity and reliability and is sensitive to change in stroke recovery (Wade 1992).

Nine Hole Peg Test (9HPT) (Mathiowetz et al. 1985)

This measure of disability, specifically of the upper limb, requires the patient to place nine wooden pegs in holes in a small board under standard conditions. We timed the placing of the pegs. The patients were allowed a maximum of 50 seconds to complete the task. If the test was not completed in 50 seconds, the number of pegs placed was scored. The number of seconds taken to place each peg was calculated. Both hands were tested. It is a quick and easy assessment, frequently used in clinical practice and research.

Nottingham Extended Activities of Daily Living (NEADL) Index (Nouri & Lincoln 1987)

This is a 22-item measure of handicap (participation limitation) in 4 sections (mobility, in the kitchen, domestic tasks and leisure activities) scored 0 – 66 (0 = inactive, 66 = very active). The sections form a hierarchy with stroke patients (Wade 1992) and the scoring dichotomises responses into those items the patient can participate in alone and those items with which they need help or are unable to perform.

Patient Satisfaction Questionnaire (Pound et al. 1994)

This is a 13 item questionnaire measuring patient satisfaction with "hospital care and treatment" and "discharge and after". The patients were sent the questionnaire by post, four weeks after being discharged as inpatients from the rehabilitation hospital. It has proven reliability and validity and contains specific items on the type and amount of "therapy" the patient received. Relatives or carers were able to help the patient complete the questionnaire but the views expressed should have been those of the patient. Patients that were discharged from rehabilitation hospital to institutional care were not sent the questionnaire.

'Rankin' Oxford Handicap Scale (Rankin 1957)

This is a 6-point scale (0 = no symptoms, 5 = severe handicap) that measures "handicap". We used the cut off point of 3 and above to indicate dependence on others. Many consider it to be more of a measure of impairment and disability (especially mobility disability). The Rankin score is, however, quick to administer and is widely used in stroke research. It was included to compare pre- and post-stroke handicap.

Resource Use

Information regarding use of health and social services was gathered by patient interview at the 3 and 6 month assessments. We also recorded follow up that was planned at the point of discharge from inpatient rehabilitation in a review of the patients' hospital records. This information could not confirmed with the patients' General Practitioners or the services concerned due to limited resources.

Rivermead Mobility Index (RMI) (Collen et al. 1991)

This is a 15-item measure, scored 0 – 15 (0 = poor mobility, 15 = good mobility). It includes one directly observed item. It measures disability (activity impairment). specifically mobility disability. It is frequently used in research and clinical practice. It has established measurement properties and is simple to administer, providing a hierarchy of mobility that covers a broad range of abilities from turning in bed to running.

Rivermead Visual Gait Analysis (Lord et al. 1998)

This is a 20 item measure of gait impairment scored from 0 – 59 (0 = normal gait, 59 = grossly abnormal gait). It was a recently developed tool and has not been widely used in other studies, however it is valid, reliable and sensitive to change in mobility. We used it as a back-up measure for the high-tech assessment of the quality of gait though in practice it was difficult to use with very disabled patients. The amount of data we gathered and our analyses were limited and results are not presented in this thesis.

Trunk Control Test (In Wade 1992)

This is a 4-item measure of impairment of (proximal) trunk stability, scored out of 100 (0 = unable to move, 100 = normal). It is commonly administered in conjunction with the Motricity Index (above) and is simple and quick.

Walking speed (Bradstater et al 1983)

We measured the patients' walking speed several different ways. They are quoted in metres per second. We measured the patients "preferred" walking speed as opposed to their maximum walking speed. We took the measurement using a stopwatch and also by electronic timing in the form of the gait analysis equipment. We used standardised instructions for the patients and carried out the assessment on different surfaces both "normal" hospital floor (linoleum or wooden) or on carpet. Measures of gait speed have been shown to be valid and reliable and are widely used in clinical practice and research.

APPENDIX III

Glasgow Augmented Physiotherapy After Stroke (GAPS) study Collaborative group and staff members

Steering group

Professor Peter Langhorne (principal grant holder), Academic Section of Geriatric Medicine, Royal Infirmary, Glasgow.

Dr Jon Macdonald, Consultant in geriatric medicine, Drumchapel Hospital, Glasgow.

Dr Christine McAlpine, Consultant in geriatric medicine, Stobhill Hospital, Glasgow.

Dr Malcolm Granat, Senior lecturer, Department of Bioengineering, University of Strathclyde.

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Mrs Gisela Creed, Superintendent physiotherapist, Royal Infirmary, Glasgow.

Miss Margaret Nutter, Superintendent physiotherapist, Drumchapel Hospital, Glasgow.

Mrs June Lawrie, Superintendent physiotherapist, Stobhill Hospital, Glasgow.

Mr Ian Wellwood, research physiotherapist, (study co-ordinator).

Ms Thorlene Egerton, research physiotherapist, (principal assessor).

Staff members

Mrs Fiona Moffat, research physiotherapist, Drumchapel Hospital, Glasgow.

Miss Patricia Hagen, research physiotherapist, Stobhill Hospital, Glasgow.

Support from Strathclyde University

Dr Douglas Maxwell

Support from Robertson Centre for Biostatistics

Miss Heather Bailley

Dr Janet Love

APPENDIX IV

Table A4.1 Considerations in choosing a method of meta-analysis.

(Deeks et al. 2001)

Choice of summary statistic depends upon:

- the type of data being analysed (binary, continuous, time-to-event)
- the consistence of estimates of the treatment effect across trials and subgroups
- the ease of interpretation of the summary statistic

Choice of weighted method depend upon:

- the reliability of the method when sample sizes are small (may exclude inverse variance method).
- the reliability of the method if the events are very rare (may exclude inverse variance and Mantel-Haenszel methods).
- the degree of imbalance in allocation ratios in the trials (may exclude the Peto method).
- the reliability of the method when treatment effects are large (may exclude the Peto method).

APPENDIX V
Literature search

Main search strategy (MEDLINE database) used for PINTAS meta-analysis

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or cerebrovascular accident/ or exp brain infarction/ or exp cerebrovascular trauma/ or exp hypoxia-ischemia, brain/ or exp intracranial arterial diseases/ or intracranial arteriovenous malformations/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or vasospasm, intracranial/ or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or cerebral vasc$ or cva$ or apoplexy).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj10 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or subarachnoid) adj10 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. ((brain or intracranial) adj10 (vascular adj5 (disease$ or disorder or accident or injur$ or insult or event or attack))).tw.
6. ((isch?emic or apoplectic) adj5 (event or events or insult or attack$)).tw.
7. hemiplegia/ or exp paresis/
8. (hemipleg$ or hemipar$ or paresis or paretic or acquired brain injur$).tw.
9. or/1-8
10. exp Physical Therapy Techniques/
11. "Physical Therapy (Specialty)"/
12. Physical Therapy Department, Hospital/
13. exp Exercise Movement Techniques/
14. rehabilitation/ or "activities of daily living"/ or early ambulation/
15. Motor Activity/
16. "Recovery of Function"/
17. (physiotherap$ or physical therap$ or exercise or rehabilitation or physical activity).tw.
18. or/10-17
19. 9 and 18
20. cerebrovascular disorders/rh or exp basal ganglia cerebrovascular disease/rh or exp brain ischemia/rh or exp carotid artery diseases/rh or cerebrovascular accident/rh or exp brain infarction/rh or exp cerebrovascular trauma/rh or exp hypoxia-ischemia, brain/rh or exp intracranial arterial diseases/rh or intracranial arteriovenous malformations/rh or exp "intracranial embolism and thrombosis"/rh or exp intracranial hemorrhages/rh or vasospasm, intracranial/rh or vertebral artery dissection/rh or (hemiplegia/rh or exp paresis/rh)
21. 19 or 20
22. (intensive or intensity or augment$ or accelerate$ or additional or dosage or dose-response or frequency or amount or quantity).tw.
23. 21 and 22
24. Randomized Controlled Trials/
25. random allocation/

26. Controlled Clinical Trials/
27. control groups/
28. clinical trials/ or clinical trials, phase i/ or clinical trials, phase ii/ or clinical trials, phase iii/ or clinical trials, phase iv/
29. Placebos/
30. placebo effect/
31. Research Design/
32. Program Evaluation/
33. evaluation studies/
34. randomized controlled trial.pt.
35. controlled clinical trial.pt.
36. clinical trial.pt.
37. evaluation studies.pt.
38. meta analysis.pt.
39. meta-analysis/
40. random$.tw.
41. (controlled adj5 (trial$ or stud$)).tw.
42. (clinical$ adj5 trial$).tw.
43. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
44. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
45. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
46. (coin adj5 (flip or flipped or toss$)).tw.
47. latin square.tw.
48. versus.tw.
49. placebo$.tw.
50. sham.tw.
51. (assign$ or alternate or allocat$ or counterbalance$ or multiple baseline).tw.
52. controls.tw.
53. (meta-analy$ or metaanaly$ or meta analy$ or systematic review or systematic overview).tw.
54. or/24-53
55. 21 and 54
56. 55 not 23
57. limit 23 to human
58. limit 56 to human

DOWNLOAD SETS 57 AND 58

We searched the following databases up until the end of 2002:
Medline 1966 onwards; EMBASE 1980 onwards; BIOSIS 1969 onwards; Psych INFO 1967 onwards; Derwent Drug File 1964 onwards; Scisearch 1974 onwards; AMED 1985 onwards; CINAHL 1982 onwards and Cochrane Stroke Group Trials Register to last quarter of 2002.

Table A5.1 Trials retrieved for detailed evaluation

Altschuler et al. 1999
Carey 1990
Duncan et al. 1998
Feys et al. 1998
GAPS 2000 (abstract)
Green et al. 2002
Kwakkel et al. 1999
Kwakkel and Wagenar 2002
Lincoln et al. 1999
Logigian et al. 1983
Malouin 1993
Miller et al. 2000 (abstract)
Nugent et al. 1994
Parry et al. 1999(a)
Parry et al. 1999(b)
Partridge et al. 2000
Peacock et al. 1972
Pollock et al. 2002
Rodgers et al. (in press, subsequently published 2003)
Rapoport & Judd-van Eerd 1989
Richards et al. 1993
Ruff et al.1999
Sivenius et al. 1985
Slade et al. 1999 (abstract)
Slade et al. 2002
Smith et al. 1981
Stern et al. 1970
Sunderland et al. 1992
Sunderland et al. 1994
Wade et al. 1992
Walker et al. 2000
Werner and Kessler 1996

Ongoing

Ng & Williams (pilot)

Trials excluded from the PINTAS meta-analysis

We excluded a number of trials because they focused only on outpatient interventions (Smith et al. 1981)(Duncan et al. 1998) and (Werner and Kessler 1996) or were examining late interventions outwith the hospital setting (Green et al. 2002) (Wade et al. 1992). Two studies were excluded because they were quasi-randomised (Rappaport & Judd van Eerd 1989)(Ruff et al. 1999).

Some studies were confounded because they compared stroke unit care to some other form of care (usually general medical ward care)(Peacock et al. 1972)(Stern et al. 1970)(Sivenius et al. 1985). Evidence from the Stroke Unit Trialists Collaboration Overview (Stroke Unit Trialists 2003) suggests that any treatment effect in these studies might reasonably be attributed to the effect of Stroke Unit care rather than the effect of increased intensity of physical therapy.

Some studies had unusual interventions that we did not consider to reflect physiotherapy practice in the UK healthcare system: using a rocking-chair and a splint to give sensory-motor stimulation (Feys et al. 1998); patients practising arm movement on their own with the use of a mirror (Altschuller et al. 1999) and self-practise of rising from the chair (Pollock et al. 2000).

The others identified by our search were excluded as they appeared to be more focused on investigating the intervention rather than the intensity of the intervention (Logigian et al. 1983)(Carey 1990)(Altschuller et al. 1999)(Walker et al. 2000).

Table A5.2 Reasons for excluding studies from PINTAS systematic review

Study	Reason for exclusion
Altschuler et al. (1999)	Late intervention, focus was intervention, not intensity
Carey (1990)	Focus was intervention not intensity
Duncan et al. (1998)	Home based intervention
Feys et al. (1998)	Novel intervention
Green et al. 2002	Late intervention, community based
Logigian et al. (1983)	Focus was intervention, not intensity
Ng & Williams	Ongoing exploratory pilot study
Nugent et al. (1994)	Non randomised
Peacock et al. (1972)	Confounded – different settings (no record of intensity)
Pollock et al. (2002)	Focus was novel intervention not intensity
Rapoport & Judd-van Eerd (1989)	Quasi-randomised
Ruff et al. (1999)	Quasi-randomised
Sivenius et al. (1985)	Methodological problems, confounded - different settings
Smith et al. (1981)	Part of intervention was outpatient based and data were not available
Stern et al. (1970)	Confounded, difficulties with randomisation, incomparable treatments
Wade et al. (1992)	Late intervention, community based
Walker et al. (2000)	Focus was intervention not intensity.
Werner & Kessler (1996)	Intervention was outpatient based

APPENDIX VI
Review criteria used by Scottish Intercollegiate Guidelines Network (SIGN 2004)

Table A6.1
SIGN Review Criteria - Evaluation of internal validity of selected studies

Evaluation criterion
Does the study address an appropriate and clearly focused question?
Was the assignment of subjects to treatment groups randomised?
Were the treatment and control groups similar at the start of the trial?
Was an adequate concealment method used?
Were subjects and investigators kept blind to treatment allocation?
Are all relevant outcomes measured in a standard, valid and reliable way?
Apart from the treatment under investigation, were the groups treated equally?
What % of the individuals or clusters recruited into the study are included in the analysis?
Were all the subjects analysed in the groups to which they were randomly allocated?
Are the results homogeneous between sites?

Table A6.2 Overall assessment of selected studies

Evaluation criterion
How well has the study done to minimise bias? Code ++, +, or -
If coded + or – what is the likely direction in which bias might affect the study results?
Taking into account clinical considerations, your evaluation of the methodology used and the statistical power of the study, are you certain that the overall effect is due to the study intervention?

Gradings for overall assessment of selected studies (meta-analyses)

Well covered

Adequately addressed

Poorly addressed

Not addressed (i.e. not mentioned, or indicates that this aspect of study design was ignored)

Not reported (i.e. mentioned , but insufficient detail to allow assessment to be made)

Not applicable

Internal Validity

Does the review address an appropriate and clearly focused question?

Does the review include a description of the methodology used?

Was the literature search sufficiently rigourous to identify all relevant studies?

Was study quality assessed and taken into account?

Does the review include all the potential benefits and harms of the intervention?

Was it reasonable to combine the studies?

Do the conclusions flow from the evidence reviewed?

Overall assessment of the study

How well has the study done to minimise bias?

Code ++, +, or –

If coded as +, or – what is the likely direction in which bias might affect the study results?

Are the results of the study directly applicable to the patient group targeted by this guideline?

Selected studies are described and tabulated with the following headings

Study

Intervention

Outcome measures used

Number of patients

Scale and direction of measured effect

Table A6.3 Key to the Evidence Statements

Levels of Evidence	Inclusion criteria
1++	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Non-analytic studies, case reports, case series.
4	Expert opinion.

APPENDIX VII

The PINTAS Collaborative group

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Professor Peter Langhorne, Professor of Stroke Care, University of Glasgow

Professor Nadina Lincoln, Professor of Clinical Psychology, University of Nottingham

Ms Kimberley Miller, Lecturer, University of Melbourne, Australia

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Prof. Carol Richards, Professor and Holder of Canada Research Chair in Rehabilitation, Laval University, Quebec, Canada

Dr Helen Rodgers (Reader in Stroke Medicine) & Dr Christopher Price, Centre for Health Services Research, University of Newcastle upon Tyne

Dr Anita Slade, Rheumatology and Rehabilitation Research Unit University of Leeds

Dr Alan Sunderland, Reader in Clinical Neuropsychology, University of Nottingham

Mr Ian Wellwood, Research Physiotherapist, University of Glasgow

APPENDIX VIII

PINTAS meta-analysis - Additional data and statistical comments

This appendix contains information on database management and reports on additional analyses carried out on the Barthel index data and walking speed data that are not covered in the main report.

Forming the database and database management

Collaborators provided data which we cleaned to form a workable database with information on field structure, labelling, data assumptions and handling / coding of missing values.

We incorporated data from the 9 studies, totalling 951 subjects. The data were read into a master datafile containing data on:

- Patient identification (ID) number (both the original study ID and an assigned PINTAS ID)
- Gender
- Age
- Randomised treatment group
- Treatment target
- Date of onset of stroke
- Barthel at baseline, 1, 3, 6, and 12 months
- ARAT at baseline, 1, 3, 6 and 12 months
- Motricity Arm Index at baseline, 1, 3, 6, and 12 months
- Motricity Leg Index at baseline, 1, 3, 6, and 12 months
- Motricity Total Index at baseline, 1, 3, 6, and 12 months

Standardisation of visits

For the Barthel index, ARAT and Motricity Index measurements, although most studies measured at common times, we chose to standardise the measurement times at 1, 3, 6 and 12 months for all studies. So if, for example, a study had a measurement at 6 weeks, this was assigned to the 1 month slot, being the nearest standard time. If additional measurements were made over and above the standard times e.g. at 20 weeks, then these were used if the nearest standard time was missing e.g. if a 6 month reading was missing, the 20 week (~ 5 month) reading was imputed as the 6 month reading.

Measurement scales

The scale of each of the measurements for each of the studies was checked. For example, most studies reported the Barthel index on a scale of 0-20, but some reported on a scale of 0-100, with each point of the 0-20 scale worth 5 points. For this example re-scaling the 0-100 to the 0-20 scale is a simple division by 5. There was one study that appeared to be on the 0-100 scale - it had values of 88 and 99 - but on closer inspection the distribution was entirely within the range 0-20, with 88 and 99 appearing to be special codes (e.g. not done, or lost). The Action Research Arm Test (ARAT) values were more difficult: the usual range is 0-57, with 4 subscales - two each with a total of 18 points, one at 12 and one at 9 (Lyle 1981).

Missing values

Missing values are an important issue. As in the example given above, if an impossible value has been reserved for the missing data, there is usually not a problem - it can be identified quite readily and changed to missing in the analysis database. The example above does however illustrate that when combining studies, an impossible value on one scale (88 and 99 on a scale 0-20) can become a legitimate value on another scale for the same measurement (0-100). The most difficult situation to spot is when a legitimate value is used as a missing value, most commonly, particularly when using Excel as the datafile, the value zero. We have assumed throughout that the zeroes on the file are all legitimate values, unless the context clearly indicates otherwise. It should be noted that the appearance of zero as a missing value can happen unexpectedly, for example, if data are transferred from one version to an update, or to another platform via an import tool, or a database translation tool.

Missing data - analysis issues

There is a further issue of the handling of missing data in the analysis. The analyses presented here are on the basis of all available information. That is, we have not attempted to fill in any of the missing data, with the exception of the 'near adjacent values' algorithm stated above.

Take for example the Barthel index scores. There will have been subjects in probably all of the studies that will have missing Barthel index scores for a definite reason - at one extreme, they are so independent that they have stopped participating in the study, at the

other extreme, they died early in the trial e.g. after 2 weeks. Somewhere in-between may be the subjects who suffered a setback (e.g. a further stroke) that meant they were not receiving physiotherapy or fit to be assessed. All of these subjects have missing data that may be informative (in a statistical sense) i.e. it is not missing at random, or missing completely at random. If there were any difference in this "missingness" down to the randomised treatment, then there is a potential problem of bias. If augmented physiotherapy had a propensity to kill people (an extreme example), and further to kill people who were more severely disabled, or to hospitalise people, or even to cause people to withdraw more often than on standard treatment, the current analysis would potentially be biased in favour of augmented physiotherapy by excluding these subjects.

Barthel index scores were censured at death to avoid zero scores being recorded in further analyses.

The duration of in-patient rehabilitation time was measured in days. There were a variety of possible definitions of inpatient rehabilitation. Some say that rehabilitation starts on first entering hospital after acute stroke, alternatively we could take the date of transfer to an area designated as a rehabilitation or stroke unit, alternatively we could look just at the date of randomisation or the date of commencing the intervention. We decided to compare the groups from the date the patient was admitted to hospital until they were either discharged home or to another institution for continuing care. This was chosen based on availability and clarity of definition.

Exploring thresholds of improvement in Barthel Index scores

One feature of using the mean change in Barthel index score is that if there are subjects who do worse on treatment, they tend to cancel out the subjects who do better on treatment. This may or may not be a desirable feature for an outcome measure. If for example, those who did worse on treatment (either augmented or standard) would be taken out and treated differently e.g. physiotherapy was suspended, then it might be better to use an outcome that focussed on treatment successes.

Tables A8.1 and A8.2 show the results for just such an approach based on 3 month and 6 month follow up data respectively. There were no differences at any threshold at 1 month follow up (data not shown).

We defined as a treatment success a subject who either (a) has a change over baseline is greater than or equal to the stated threshold change over baseline Barthel index score or (b), or a subject who has achieved the maximum score on the measure (and so cannot improve further). Treatment success is than modelled as a binary outcome in a logistic regression using study, age, gender, and treatment group as covariates. These logistic regressions were fitted separately for months 3 and 6 (See Figure A8.1). The data for month 12 were so sparse that no analysis was done for this time.

Table A8.1 Defining treatment success at different stated thresholds of change in Barthel index score at 3 month follow up

Threshold	Month 3			
	N(ST)	N(AU)	OR(95%CI)	P
≥ 7	137(45%)	213(52%)	1.33(0.96, 1.85)	0.086
≥ 8	122(40%)	184(45%)	1.24(0.89, 1.72)	0.20
≥ 9	99(32%)	163(40%)	1.47(1.04, 2.06)	0.027
≥ 10	86(28%)	143(35%)	1.47(1.03, 2.08)	0.033

ST = Standard physiotherapy, AU = Augmented physiotherapy, OR = Odds ratio, CI = Confidence interval

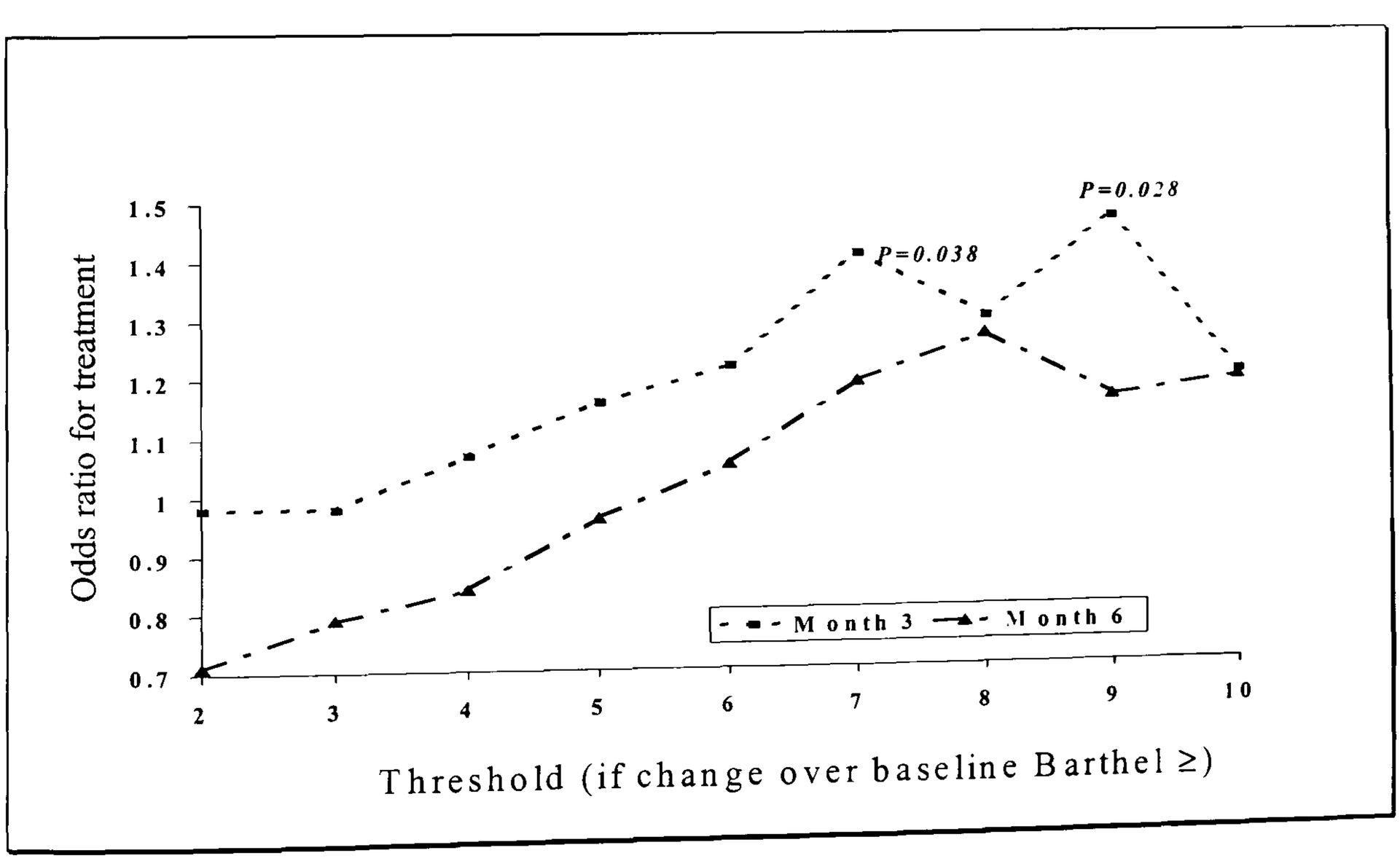
Table A8.2 Defining treatment success at different stated thresholds of change in Barthel index score at 6 month follow up

Threshold	Month 6			
	N(ST)	N(AU)	OR(95%CI)	P
≥ 7	144(54%)	223(63%)	1.40(0.99, 2.00)	0.062
≥ 8	130(49%)	200(56%)	1.37(0.97, 1.94)	0.079
≥ 9	117(44%)	185(52%)	1.41(0.99, 1.99)	0.054
≥ 10	101(38%)	165(46%)	1.44(1.01, 2.05)	0.043

ST = Standard physiotherapy, AU = Augmented physiotherapy, OR = Odds ratio, CI = Confidence interval

The data shown are the number of subjects (%) in each randomised treatment group who have a change over baseline Barthel index score at least as great as the stated threshold, and the Odds Ratio (OR), adjusted for study, age and gender, with 95% confidence interval and associated P-value for augmented vs. standard physiotherapy.

Figure A8.1 Exploration of threshold of change in Barthel index score in PINTAS database in order to define "Treatment success"



We focussed only on large treatment effects of a change over baseline of ~ units of Barthel index or greater. At the earlier time of 3 months there appears an advantage for augmented over standard physiotherapy at very large treatment effects of 9 units of Barthel index or higher, with an increase in odds of almost 50% (Odds Ratio [OR] 1.47, 95% confidence interval 1.04 to 2.06, P=0.027 for a change ≥9, P=0.033 for a change ≥10).

"Clinically significant" change in Barthel index score

Following the Collaborators' meeting and in order to aid interpretation of our results for the Barthel index analyses, we wanted to find the Collaborative group members' opinion of what might be a "clinically" significant change in BI score.

Before they were aware of the above results we sent a short questionnaire to all members of the collaborative group, asking their opinion on the following questions:

What do you consider to be a "clinically significant" change in the BI score?

e.g. a change in score,

percentage improvement over baseline

or give a clinical cut off point e.g. 10/20 or 16/20 for categorizing patients.

We also asked for comments and for the group to identify which items on the BI were most likely to be influenced by physiotherapy intervention, which might reflect overall impairment, which might reflect upper limb impairment and which might reflect lower limb impairment.

All but one collaborator responded and there were a wide variety of comments from this small group.

Changes in score varied from 1 to 10 points with "significant clinical thresholds" e.g. the difference between dependent and independent living, varying from 15 – 18 points on the Barthel index.

It was difficult to generalize from the groups' open comments, but all were looking for far greater change than we saw in results from our analyses. It was acknowledged that small changes may still be clinically significant for individual patients especially where these took them from dependence to independence even in one item on the BI.

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It was difficult to generalize from the groups' open comments, but all were looking for far greater change than we saw in results from our analyses. It was acknowledged that small changes may still be clinically significant for individual patients especially where these took them from dependence to independence even in one item on the BI.

Additional data summaries for "Change in outcome score" analyses in Chapter 5.

Additional data are given from the available trials for change in ARAT score, walking speed and change in Barthel index score.

Table A8.3 Mean (SD) Action Research Arm Test (ARAT) scores in PINTAS meta-analysis

Study	Time	Standard		Augmented		Total	
		N	Mean(SD)	N	Mean(SD)	N	Mean(SD)
GAPS	0	-					
	1	35	25.0(22.9)	34	27.7(20.5)	69	26.3(21.6)
	3	33	28.9(23.0)	32	31.5(21.0)	65	30.2(21.9)
	6	33	28.2(24.2)	28	30.3(20.6)	61	29.2(22.5)
	12	-					
Kwakkel	0	37	1.3(3.1)	64	4.1(10.1)	101	3.0(8.3)
	1	35	7.3(15.4)	59	13.7(20.0)	94	11.3(18.6)
	3	35	8.7(17.7)	53	19.4(22.9)	88	15.1(21.6)
	6	37	10.2(19.5)	59	21.7(23.9)	96	17.3(22.9)
	12	34	12.2(20.7)	57	20.6(23.2)	91	17.5(22.6)
Lincoln	0	95	7.2(13.6)	187	5.9(12.3)	282	6.4(12.7)
	1	89	17.4(20.3)	166	17.6(21.0)	255	17.5(20.7)
	3	61	22.9(22.7)	128	22.7(23.0)	189	22.8(22.9)
	6	-					
	12	-					
Rodgers	0	61	18.5(22.8)	62	19.1(22.0)	123	18.8(22.3)
	1	-					
	3	51	36.5(25.3)	54	38.3(22.6)	105	37.4(23.8)
	6	48	40.8(22.9)	48	38.6(23.5)	96	39.7(23.1)
	12	-					
TOTAL	0	193	9.6(17.2)	313	8.2(15.4)	506	8.7(16.1)
	1	159	16.9(20.7)	259	18.0(21.0)	418	17.6(20.9)
	3	119	26.2(25.4)	139	29.5(23.7)	258	28.0(24.5)
	6	179	26.1(24.7)	263	26.2(23.8)	442	26.2(24.1)
	12	34	12.2(20.7)	57	20.6(23.3)	91	17.5(22.6)

SD = Standard deviation

Table A8.4 Mean walking speed in PINTAS meta-analysis

Study	Time	Standard		Augmented		Difference A-S	
		n	Mean(SD)	n	Mean(SD)	Mean(95% CI)	P-value
GAPS	0	-	-	-	-	-	-
	1	35	0.36(0.37)	34	0.45(0.43)	0.09 (-0.10, 0.28)	0.36
	3	35	0.49(0.37)	32	0.54(0.34)	0.06 (-0.12, 0.23)	0.52
	6	34	0.48(0.36)	29	0.59(0.36)	0.11 (-0.08, 0.29)	0.24
	12	-	-	-	-	-	-
Kwakkel	0	37	0.05(0.22)	64	0.04(0.14)	-	-
	1	35	0.28(0.54)	57	0.42(0.63)	0.13 (-0.12, 0.39)	0.30
	3	32	0.50(0.58)	56	0.64(0.66)	0.14 (-0.14, 0.42)	0.31
	6	36	0.66(0.59)	59	0.73(0.65)	0.08 (-0.18, 0.34)	0.54
	12	33	0.70(0.58)	53	0.81(0.67)	0.11 (-0.17, 0.39)	0.43
Partridge	0	60	0.01(0.06)	54	0(0)	-	-
	1	56	0.15(0.22)	52	0.15(0.19)	0.00 (-0.07, 0,08)	0.92
	3	-	-	-	-	-	-
	6	-	-	-	-	-	-
	12	-	-	-	-	-	-
Richards	0	-	-	-	-	-	-
	1	7	0.24(0.15)	15	0.28(0.17)	0.04 (-0.12, 0.19)	0.60
	3	7	0.34(0.22)	15	0.32(0.18)	-0.02 (-0.21, 0.17)	0.84
	6	-	-	-	-	-	-
	12	-	-	-	-	-	-
Sunderland	0	-	-	-	-	-	-
	1	55	0.33(0.38)	57	0.33(0.37)	0.00 (-0.14, 0.14)	0.96
	3	59	0.36(0.38)	54	0.39(0.41)	0.03 (-0.12, 0.18)	0.68
	6	54	0.35(0.40)	55	0.45(0.44)	0.09 (-0.07, 0.25)	0.25
	12	39	0.44(0.41)	36	0.50(0.48)	0.06 (-0.15, 0.26)	0.58
TOTAL	0	97	0.02(0.14)	118	0.02(0.11)	-	-
	1	188	0.27(0.38)	215	0.33(0.44)	0.05 (-0.03, 0.13)	0.23
	3	133	0.42(0.43)	157	0.50(0.56)	0.07 (-0.04, 0.17)	0.23
	6	124	0.48(0.47)	143	0.59(0.54)	0.09 (-0.03, 0.21)	0.13
	12	72	0.56(0.51)	89	0.69(0.62)	0.09 (-0.09, 0.26)	0.32

SD = Standard deviation, CI = Confidence interval

Table A8.5. PINTAS meta-analysis: Change over baseline in Barthel index score. By randomised treatment group, and difference in change over baseline between randomised treatment groups

Study	Time	Standard		Augmented		Augmented – Standard*	
		n	Mean(SD)	n	Mean(SD)	Difference (95% CI)	P-value
GAPS	1	34	4.0(3.0)	33	2.9(2.6)	-1.1(-2.5,0.3)	0.12
	3	33	5.7(4.0)	32	5.1(3.3)	-0.6(-2.4,1.2)	0.51
	6	34	5.9(4.1)	31	5.1(3.7)	-0.9(-2.8,-1.1)	0.37
	12	-	-	-	-	-	-
Kwakkel	1	36	4.8(3.1)	60	6.0(4.4)	1.2(-0.4,2.8)	0.15
	3	35	7.4(3.9)	56	9.5(3.8)	2.2(0.5,3.8)	0.0097
	6	37	9.7(4.1)	58	11.1(3.9)	1.4(-0.3,3.0)	0.10
	12	34	10.1(3.9)	54	10.7(4.0)	0.6(-1.2,2.3)	0.51
Lincoln	1	89	5.1(4.4)	168	5.1(3.9)	0(-1.1,1.0)	0.98
	3	83	6.6(4.0)	157	6.1(3.9)	-0.5(-1.5,0.6)	0.35
	6	79	7.3(4.6)	151	7.1(4.2)	-0.2(-1.4,-1.0)	0.73
	12	-	-	-	-	-	-
Richards	1	7	8.9(5.8)	15	7.5(4.9)	-1.4(-6.3,3.6)	0.57
	3	7	10.5(5.0)	15	10.7(4.1)	0.2(-4.0,4.4)	0.93
	6	-	-	-	-	-	-
	12	-	-	-	-	-	-
Rodgers	1	-	-	-	-	-	-
	3	51	4.5(5.6)	51	4.0(5.5)	-0.5(-2.7,1.6)	0.62
	6	48	4.7(5.5)	45	5.5(4.8)	0.8(-1.3,2.9)	0.47
	12	-	-	-	-	-	-
Slade	1	39	1.7(2.0)	40	2.0(2.0)	0.3(-0.6,1.2)	0.46
	3	28	1.3(2.2)	37	2.6(3.1)	1.3(-0.1,2.6)	0.072
	6	7	0.3(0.7)	9	0.9(1.6)	0.6(-0.8,2.0)	0.40
	12	2	1.9(1.8)	1	0(-)	-1.9(-20,20)	0.55
Sunderland	1	65	3.4(3.9)	65	4.0(4.1)	0.6(-0.8, 2.0)	0.38
	3	68	5.3(3.8)	63	6.2(4.9)	0.9(-0.6,2.4)	0.24
	6	61	6.5(3.6)	61	6.9(5.2)	0.4(-1.2,2.0)	0.63
	12	44	6.5(3.5)	34	8.1(4.9)	1.6(-0.3,3.5)	0.10
TOTAL*	1	270	4.1(3.9)	381	4.6(4.0)	0.2(-0.4, 0.8)	0.55
	3	305	5.6(4.4)	411	6.1(4.6)	0.3(-0.3,0.9)	0.40
	6	266	6.6(4.7)	355	7.2(4.8)	0.3(-0.4,1.0)	0.47
	12	80	7.9(4.1)	89	9.6(4.6)	1.0(-0.3,2.2)	0.12

SD = Standard deviation, CI = Confidence interval

* For the TOTAL, from a separate linear model for each time point that adjusts for study. Otherwise, for each individual study, from a separate linear model for each time point.

Shortened versions of the Barthel index

There is a suggestion that some of the 10 elements of the Barthel index are not likely to be clinically relevant to post stroke physiotherapy intervention. Following the investigations of Hobart and Thompson (Hobart and Thompson 2001), we adopted two shortened versions of the Barthel index: first, a score using just 3 categories (the transfer, stairs and mobility questions), and then a score using 6 categories (the 3 previously listed plus dressing, toilet use, and bathing). Results for these versions are given in table A8.6 and table A8.7 respectively.

Table A8.6 PINTAS meta-analysis. Using a 3-item shortened Barthel index (transfer, stairs, mobility) – number of subjects, mean and standard deviation over time

Time	Standard			Augmented		
	N	Mean	SD	N	Mean	SD
Baseline	226	2.02	1.84	345	1.86	1.77
1-month	198	4.00	2.70	301	3.83	2.72
3-month	232	4.67	2.58	336	4.85	2.63
6-month	205	5.37	2.47	297	5.51	2.55

SD = Standard deviation

There was no statistical evidence of a development of the change over baseline in the 3-category shortened Barthel index between augmented and standard physiotherapy groups: P=0.92 in a test for interaction from a repeated measures model as previously specified for the full 10 category Barthel index. The estimated treatment effect due to augmented physiotherapy compared with standard physiotherapy was 0.16 (95% confidence interval -0.23 to 0.56, P=0.41).

Table A8.7 PINTAS meta-analysis – Using a 6-item shortened Barthel index (transfer, stairs, mobility, dressing, toilet use, bathing) – number of subjects, mean and standard deviation over time

Time	Standard			Augmented		
	N	Mean	SD	N	Mean	SD
Baseline	226	3.11	2.86	345	2.80	2.84
1-month	198	6.37	4.11	301	6.06	4.06
3-month	232	7.87	4.12	336	7.99	4.25
6-month	205	8.77	3.99	297	8.79	4.05

SD = Standard deviation

There was no statistical evidence of a development of the change over baseline in the 6-category shortened Barthel index between augmented and standard physiotherapy groups: P=0.87 in a test for interaction from a repeated measures model as previously specified for the full 10 category Barthel index. The estimated treatment effect due to augmented physiotherapy compared with standard physiotherapy was 0.23 (95% confidence interval -0.40 to 0.85, P=0.48).

Additional analysis of walking speed, excluding subjects who were not observed to walk at any time during the study

An additional analysis of the walking speed data was undertaken, in which subjects who did not show any evidence of walking at any point in the study were excluded. The aim here was to take out any effect of subjects for whom no amount of physiotherapy, augmented or standard, was having an effect, and so allow a more precise estimate of what the possible advantage of intensive physiotherapy might have in the subset of subjects for whom an improvement through the use of physiotherapy might be anticipated. This analysis therefore attempts to mirror what might happen in practice in the management of a patient, with those for whom physiotherapy is inappropriate or impossible, and/or for those who physiotherapy is showing consistently no progress from a start point of not walking not considered for further physiotherapy until an improvement occurs.

This strategy of excluding subjects who never showed any evidence of a non-zero walking speed resulted in the omission of n=63 subjects receiving standard physiotherapy and n=58 subjects receiving augmented physiotherapy. That similar numbers were excluded from each group is encouraging in that we can be somewhat reassured that the resulting comparison is not likely to be seriously biased either for or against augmented physiotherapy. If, for example, augmented physiotherapy worked well for some but was damaging for others, one might expect to see the latter type of subjects contributing to more exclusions from the augmented physiotherapy group. If on the other hand augmented physiotherapy was particularly beneficial for getting the non-walkers started again at walking, one might expect to see fewer patients excluded from the augmented group than the comparison group.

Results are given in Table A8.8 below.

Table A8. 8 PINTAS meta-analysis: Walking speed (with subjects who never walked excluded) by month and treatment group.

Time	Standard		Augmented		Difference A-S	
	N	Mean(SD)	N	Mean(SD)	Mean(95% CI)	P-value
0	54	0.04(0.19)	78	0.03(0.13)	-	-
1	131	0.39(0.40)	164	0.43(0.45)	0.05 (-0.05, 0.15)	0.35
3	105	0.54(0.42)	132	0.60(0.49)	0.06 (-0.06, 0.18)	0.33
6	99	0.60(0.45)	114	0.75(0.50)	0.12 (-0.01, 0.25)	0.061
12	59	0.68(0.48)	72	0.85(0.57)	0.13 (-0.06, 0.32)	0.17

SD = Standard deviation, CI = Confidence interval

There was no evidence of a treatment by time interaction (P=0.41). The estimated effect of augmented compared with standard physiotherapy on walking speed amongst the subjects who walked at some point in the study was 0.07 ms-1 (95% CI –0.02 to 0.16, P=0.12).

For the pre-specified subgroups of age, disability severity, target of treatment, and baseline severity of arm impairment there was no evidence of any treatment by time interactions, nor of any formally significant differences in treatment effect between the levels of the subgroups. Table A8.9 below summarises these results:

Table A8.9 PINTAS meta-analysis: Walking speed (with subjects who never walked excluded) by subgroup.

Subgroup	Level	Augmented-Standard (95% CI)	P-value
Barthel	≤10	0.11 (-0.03 to 0.24)	0.12
	>10	0.01 (-0.13 to 0.16)	0.86
Target	Arm Only	0.05 (-0.12 to 0.23)	0.23
	Leg or Mixed	0.08 (-0.03 to 0.19)	0.16
Age	<70 years	0.11 (-0.03 to 0.25)	0.13
	>70 years	0.04 (-0.07 to 0.15)	0.51
Arm impairment	Moderate	0.11 (-0.01 to 0.24)	0.079
	Severe	0.14 (-0.03 to 0.31)	0.095

CI = Confidence interval